Published in final edited form as:
Annu Rev Biochem. 2014 ; 83: 671–696. doi:10.1146/annurev-biochem-051810-093157.

Regulating the Chromatin Landscape: Structural and Mechanistic Perspectives

Blaine Bartholomew
University of Texas M.D. Anderson Cancer Center, Department of Molecular Carcinogenesis, Smithville, Texas 78957

Blaine Bartholomew: bbartholomew@mdanderson.org

Abstract

A large family of chromatin remodelers that noncovalently modify chromatin are crucial in cell development and differentiation. They are often the targets of cancer, neurological disorders, and other human diseases. These complexes alter nucleosome positioning, higher-order chromatin structure, and nuclear organization. They also assemble chromatin, exchange out histone variants, and disassemble chromatin at defined locations. We review aspects of the structural organization of these complexes, the functional properties of their protein domains, and variation between complexes. We also address the mechanistic details of these complexes in mobilizing nucleosomes and altering chromatin structure. A better understanding of these issues will be vital for further analyses of subunits of these chromatin remodelers, which are being identified as targets in human diseases by NGS (next-generation sequencing).

Keywords

epigenetics; histone; nucleosome; SWI/SNF; ISWI; CHD; ATRX; INO80; SWR1; cancer; differentiation; transcription

INTRODUCTION

Although the genetic information in DNA determines a cell's identity, other underlying factors have long been considered crucial for the determination of developmental fate and can be as important as the genetic information. The effects of these factors, although distinct from the coding sequence of DNA, can nonetheless be inherited from one generation to the next, like patterns of DNA sequence. They control the regions of DNA that are "read" by the transcriptional machinery. One family of chromain regulators that is important in regulating the epigenome uses ATP to change the physical state of chromatin without modifying histones. These remodelers can change the position of nucleosomes on DNA or the histone variants present in nucleosomes, or they may entirely disassemble nucleosomes in an ATP-dependent manner.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, membership, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

MULTIPLICITY OF CHROMATIN REMODELERS: COMPOSITION AND FUNCTION

ATP-dependent chromatin remodelers belong to the SF2 superfamily and the Snf2 family of ATP-dependent DNA and RNA helicases. Each subfamily of Snf2 is generally named after the first complex discovered in that subfamily. The different subfamilies can be distinguished on the basis of the sequence homology of the ATPase domain and the presence of other domains within the catalytic subunit (Figure 1*a*). Sequence analysis of the helicase domain alone is sufficient to classify remodelers appropriately and illustrates that the helicase domain of these different chromatin remodeler complexes is specifically tuned for its varied functional roles (1). The five major subfamilies of chromatin remodelers are SWI/SNF, ISWI, INO80 or SWR1, CHD, and α-thalassemia mental retardation syndrome X-linked (ATRX) (Figure 1*a*). In addition to the five major subfamilies of ATP-dependent chromatin remodelers, at least 20 more subfamilies belong to the Snf2 family. Some of them probably do not target chromatin but instead function to remove different factors from DNA (as observed for example with Mot1 and Rad54). The number of complexes belonging to a single subfamily multiplies with increased organism complexity. For example, in *Saccharomyces cerevisiae* there exist only the SWI/SNF and RSC complexes, which belong to the SWI/SNF subfamily, but in humans there are an estimated 100 or more different versions of SWI/SNF that vary in one of two catalytic subunits and in the assortment of accessory subunits assembled into the complex (2, 3). In the CHD subfamily in *Saccharomyces cerevisiae* there is only one type of CHD complexes, namely CHD1, but in humans there are nine different CHD catalytic subunits that exist either as single subunits or as large multisubunit complexes (4). This additional diversity in chromatin remodelers tends to correlate to the existence of tissue-specific forms of these complexes. Particular remodeler subunits are expressed in specific cell types and probably confer a unique property to the complex needed in that cell type (5–7). As investigators identify tissue-specific subunits and mutations of particular subunits associated with different diseases, it will be crucial to understand how changes in subunit function and composition alter the biological activities of these complexes.

α-Thalassemia mental retardation syndrome X-linked (ATRX): a Snf2-related protein that binds to DAXX and, together with DAXX, catalyses the deposition of H3.3-containing nucleosomes

There are fundamental differences in the basic enzymology of the various subfamilies. Most remodelers change the position of nucleosomes on DNA in an ATP-dependent manner, referred to as mobilizing nucleosomes; however the outcomes of nucleosome mobilization can be varied depending on the type of remodeler. A remodeler can move nucleosomes until the length of linker DNA separating it from the adjacent nucleosome is too short to support further movement and is referred to as nucleosome spacing (Figure 1*b*). In this case, the remodeler can sense the length of DNA between the nucleosomes to determine when to stop mobilizing nucleosomes and is typical of members of the ISWI and CHD subfamilies. Some remodelers do not require a minimal length of linker DNA to move nucleosomes and displace adjacent nucleosomes when moved into their vicinity (Figure 1*b*). The SWI/SNF subfamily can disassemble nucleosomes in this manner and create nucleosome-deficient

regions (8–10). Another possibility is the preferential exchange of particular H2A histone variants without disrupting or mobilizing nucleosomes as seen with INO80/SWRI complexes and H2A (H2AZ)/H2B dimers (11–13). Some remodelers facilitate the de novo assembly of nucleosomes onto DNA and may be involved in the formation of specialized chromatin structures. **ATRX** and members of the ISWI and CHD families assemble nucleosomes with histone chaperones or without any additional factors (14–21). These remodelers are important for genomic stability and are involved in chromatin formation at telomeric and centromeric regions (22–25).

STRUCTURE OF REMODELERS AND THEIR INTERACTIONS WITH NUCLEOSOMES

Because of the size and complexity of these complexes, determining their structural properties and the physical interactions between remodelers and chromatin can be daunting. Frequently, it is important to dissect the complex and look at individual components separately. In the following sections, we describe the functional characteristics of the parts of the complex separately, but first we discuss ways to examine the fully assembled native complex.

Figure 2 shows a select combination of ensemble and single-molecule techniques that are effective for examining the interactions of remodelers and the dynamics of chromatin remodeling. The four single-molecule approaches depicted in Figure 2*a–d* have revealed important mechanistic details of nucleosome dynamics and movement, which is discussed further below. A combination of three site-directed cross-linking techniques has tracked changes in histone--DNA interactions that occur during remodeling and has mapped remodeler interactions with DNA and histones (Figure 2*e–g*).

Cross-linking specific sites in DNA to the remodeler has revealed the binding locations of the helicase domain and the C terminus of Isw2, the catalytic subunit of the ISW2 complex, when the entire complex was recruited to nucleosomes (26). The sequence homology between the helicase domains of Isw2 and Rad54, and that of the C-terminus of Isw2 and ISWI from Drosophila, enabled investigators to create a model of the helicase, HAND, **SANT**, and SLIDE domains engaging nucleosomes based on the crystal structures of Rad54 and ISWI (Figure 3*a*). Certain detailed interactions (e.g., that of the SLIDE domain), as predicted from this model, have been proven correct (27). Cryo--electron microscopy (cryo-EM) in combination with site-directed cross-linking and peptide mapping can also provide specific details at a larger scale. The low-resolution structure of yeast SWI/SNF obtained by cryo-EM revealed large-scale features such as a trough roughly the size of a single nucleosome (Figure 3*c*). DNA footprinting of nucleosome-bound SWI/SNF showed that one DNA gyre of the nucleosome was protected by SWI/SNF. Together, these data indicate that the nucleosome probably binds in the trough region and leans against one side of the trough (Figure 3*d–f*) (28). This model, in combination with site-directed DNA and histone cross-linking, implicates a region in the cryo-EM structure as the likely location of the helicase domain, as well as the high-wall region of SWI/SNF as the probable location of different subunits of SWI/SNF (Figure 3*g–h*).

SANT domain: a domain named after Swi3/Ada2/N-Cor/TFIIIB, where the SANT domain was first identified. It is structurally similar to the Myb DNA binding domain

THE HELICASE DOMAIN OF CHROMATIN REMODELERS

X-ray crystallography of helicase domains from several Snf2-type enzymes has identified two lobes that resemble the RecA protein structure and is similar to that observed for other ATP-dependent DNA and RNA helicases (Figure 1*a*) (29–32). Both lobes in the Snf2 family have additional extensions protruding (protrusions 1 and 2) from each lobe that consist of two antiparallel α-helices and a structured linker connecting the two lobes. A triangular shaped brace binding to lobe 2 is located at the C terminus of the ATPase domain.

The helicase domain has signature motifs that are typical of the Snf2 family and SF2 superfamily. The seven helicase SF2 motifs found in all chromatin remodelers and which appear primarily in the RecA-like regions are motifs I, Ia, II, and III (in lobe 1) and motifs IV, V, and VI (in lobe 2) (1, 33–35). The Q motif binds to the surface of lobe 1 and is the eighth helicase motif. Additional motifs that are unique to the Snf2 family are motifs A--N. The Snf2 motifs in the RecA-like regions are generally closely juxtaposed to the helicase motifs and appear to extend them further. Several of the Snf2-specific motifs are in protrusions 1 and 2 proximal to sites where insertions are commonly found in Snf2 family members. Much of the subfamily-specific variation observed between Snf2 subfamilies resides in the protrusion regions and suggests that these regions play important roles. A major insertion of 280 to 484 amino acids is in the helicase domains of INO80 and SWR1 between motifs C and K (Figure 1*a*). The insertions in Ino80 and Swr1 probably add extra structure to the opposite side of the helicase domain from that of the DNA binding site. Changes at a minor insertion site are predicted to retain and extend this α-helical region (1). The protrusions are relatively conserved in sequence and length among subfamily members but vary between different subfamilies. The conservative nature of the protrusions suggests that they have an important role in fine-tuning the enzyme for its particular functional specificity. Genetic and biochemical data suggest that protrusion 1 regulates the ATPase activity of RSC, a SWI/SNF-type remodeler found in yeast (36).

Chromatin remodelers move on DNA a specific distance as one molecule of ATP is hydrolyzed and released; and this distance is known as the step size. SF2 helicases unwind DNA or RNA duplexes several base pairs at a time while translocating 1 bp along an oligonucleotide (37–39). The translocation step size of SF1 helicases is 1 bp (40–42). Experiments performed with the RSC chromatin remodeler have identified a step size of ~ 2 bp on free DNA. ACF, an ISWI-type remodeler, moves DNA out of nucleosomes in ~3-and ~7-bp steps. The 1-bp discrepancy between the step sizes of DNA and RNA helicases and those of chromatin remodelers may be due to the difference between an inherent step size and a kinetic step size. Kinetic step sizes are generally caused by inherent pauses or specific steps being rate-limiting in translocation. Recent experiments performed with ISW2, another ISWI-type chromatin remodeler, with higher resolution than previous experiments suggest the kinetic step sizes of ~3 and ~7 bp are composed of faster single-nucleotide translocations (43).

Structural analyses of the SF1 helicases PcrA and Rep with DNA, in the presence and absence of a nonhydrolyzable ATP analog and ADP, have provided insights into the potential mechanism of single-nucleotide translocation on a polynucleotide chain. The two RecA portions of lobes 1 and 2 constitute the ATP binding pocket, and the non-RecA portion of lobe 2 moves when DNA is present to create a DNA binding interface composed of both lobes (44). Binding of ATP further closes the RecA regions around DNA and causes a conformational change that flips the binding of one nucleotide to another position in lobe 1, essentially twisting the DNA (45, 46). In Figure 1*c*, the model with single stranded-DNA has been adapted to one with double-stranded DNA in order to better reflect the likely events occurring in nucleosome remodeling. New contacts between the RecA region of lobe 2 and DNA occurred with ATP binding thereby further tightening binding of the RecA regions to DNA (Figure 1*c*). The release of ADP and inorganic phosphate relaxed the contacts with key nucleotides, thereby allowing the release of DNA torsional strain by the movement of DNA toward the site of DNA twist. This mechanism is an inchworm-type model for DNA translocation that may readily explain the observed 1-bp translocation steps that are typical of chromatin remodelers and of DNA and RNA helicases.

NUCLEOSOME RECOGNITION: HISTONE BINDING DOMAINS

The helicase domains in ISWI and SWI/SNF complexes dock onto nucleosomal DNA at superhelical location 2 (SHL2), located two helical turns from the dyad axis (47–51). Binding of the helicase domain requires a multiprong interface between the remodeler complex and nucleosomes that involves other domains. Generally, recognition modules can be divided into those that bind histones and those that bind DNA. Some histone recognition modules bind to particular modified histone tails and are found within the catalytic subunit which include such examples like the **bromodomain** for the SWI/SNF family and the **chromodomain** in the CHD family (Figure 2*b*). Other histone recognition modules, such as the plant homeodomain (PHD) finger in the bromodomain PHD finger transcription factor (BPTF) subunit of NURF (52, 53), a member of the ISWI subfamily, and the PBRM1 (BAF180) subunit of human SWI/SNF, with its multiple bromodomains (54–56), are found in the auxiliary subunits. These recognition modules are “readers” of histone modifications such as acetylated or methylated lysines. Much has been written about the modules that recognize histone modifications (57, 58), so we provide only a few examples of how these recognition domains contribute to nucleosome remodeling.

Bromodomain: a protein domain that binds acetylated lysines often located in histone tails

Chromodomain: a chromatin organization modifier; a structural domain of ~40 to 50 amino acids used to bind methylated lysines

Plant homedomain (PHD) finger: binds to trimethylated lysine at position 4 in histone H3 and is often associated with active transcription

Bromodomain PHD finger transcription factor (BPTF): the largest subunit of the NURF chromatin remodeling complex

Remodelers with appropriate histone recognition modules are recruited by binding to genomic sites containing the correct corresponding modified histones. For example, the mammalian NURF complex has, in addition to the ISWI catalytic subunit SNF2L, a large auxiliary subunit termed BPTF. The **PHD** finger in BPTF promotes binding of the NURF complex to chromatin with trimethylation of histone H3 lysine 4 or H3K4me3 (52, 53). The binding of NURF is adversely affected when global levels of H3K4me3 are reduced by loss of the histone methyltransferase WDR5. The bromodomain of BPTF binds to acetylated lysine 16 in histone H4, which together with the PHD finger helps selectively target BPTF to chromatin that contains both markers. **BPTF** increases its selectivity in a combinatorial manner. **ATRX** has a similar dual-readout mechanism in the ADD domain, which has two pockets: one that binds unmodified Lys4 and the other that binds di- or trimethylated Lys9 in histone H3 (59, 60). HP1, which also binds H3K9me3, interacts with ATRX through the HP1 ID domain shown in Figure 1*a* and can form a multivalent interaction to recruit the complex, presumably through HP1 binding to either the other H3 histone tail or an adjacent nucleosome. Efficient recruitment of ATRX in vivo requires HP1, unmodified H3K4, and H3K9me3. The yeast ISW1b complex is recruited to the coding regions of actively transcribed genes by a recognition domain in its auxiliary subunit Ioc4 that binds to trimethylated lysine 36 in histone H3 or H3K36me3 (61, 62). The **PWWP** domain of Ioc4 binds to H3K36me3 both in vitro and in vivo and helps ISW1b maintain nucleosomes over the coding region and prevent histone exchange.

> PWWP: named after a conserved Pro/Trp/Trp/Pro motif, this structural motif is composed of 100 to 130 amino acids and may be involved in protein--protein interactions

The bromodomains in SWI/SNF-type complexes contribute to the selective binding of SWI/SNF to acetylated regions of chromatin, as well as to the efficiency of the remodeling reaction. Acetylation of histone H3 tails increases the affinity of SWI/SNF and RSC for nucleosomes by a factor of seven to nine and enhances recruitment of SWI/SNF in combination with transcription activators (63). Multiple bromodomains such as those in RSC do not enhance the affinity further than that of SWI/SNF with a single bromodomain, and the extra bromodomains in RSC may directly enhance nucleosome movement. The rate of nucleosome movement by SWI/SNF and RSC is accelerated by H3 tail acetylation under conditions in which binding is not limiting (63). This rate increase is not caused merely by histone acetylation helping to loosen the histone--DNA interactions in the nucleosome so that it can move more freely; rather, it specifically requires the bromodomain in conjunction with H3 acetylation. Even more compelling evidence is that the number of bromodomains determines the degree to which H3 acetylation increases the rate of nucleosome movement. Thus, nucleosome movement by RSC is enhanced more by acetylation than is nucleosome movement by SWI/SNF. Preliminary data suggest that these interactions cause significant changes in remodeler conformations (64). Site-directed cross-linking of specific sites in acetylated and unacetylated histone H3 tails of nucleosomes with SWI/SNF are consistent with important structural changes in the interactions of SWI/SNF with H3 tails that are induced by acetylation (63). Histone acetylation also stabilizes the interactions between SWI/SNF and nucleosomes, making it more difficult for them to dissociate from their bound sites (65, 66).

The crystal structure of truncated Chd1 revealed that a histone recognition domain such as the chromodomain may regulate the activity of the helicase domain. The tandem chromodomains of Chd1 in the crystal structure bind to the two helicase lobes of Chd1 in a way that precludes DNA binding (29). These findings suggest that chromodomains may act as gatekeepers of the helicase domain and block its binding to DNA until chromodomains switch to binding to H3K9me3. The interplay among histone recognition domains can be quite involved, with various competing reactions, and may serve as a regulatory control in remodeling. Rsc4, an auxiliary subunit of RSC that belongs to the SWI/SNF subfamily, has two bromodomains that bind acetylated histone H3 lysine 14 or H3K14ac (67). The second tandem bromodomain directly binds to H3K14ac; the first bromodomain does not bind to histones at all, but rather to an acetylated lysine at residue 25 within Rsc4 (68). Acetylation of lysine 25 of Rsc4 inhibits binding of the second bromodomain to H3K14ac and implicates an autoregulatory mechanism for Rsc4 activity.

Some histone recognition modules in remodelers [e.g., the Snf2 ATP coupling (SnAC) domain in the catalytic subunit of SWI/SNF (Figure 2*b*)] may bind more globular regions of the nucleosome and have roles other than recruitment, such as actively promoting nucleosome remodeling. Deletion of the SnAC domain does not alter complex assembly, the affinity of SWI/SNF for nucleosomes, SWI/SNF recruitment by transcription activators, or binding to nucleosomal DNA (69). The SnAC domain is not required for efficient DNA translocation, as observed in single-molecule experiments with magnetic tweezers (Figure 2*b*) (70), yet SWI/SNF nucleosome remodeling activity strongly depends on the SnAC domain. The SnAC domain interacts with histones as shown by mapping the contacts of the catalytic subunit with histones when SWI/SNF is bound to nucleosomes (70). Three contact sites, two in the helicase domain and a third within the SnAC domain, have been observed. Other data from mammalian SWI/SNF studies suggest that the SnAC domain probably binds to histone H3 in GST (glutathione *S*-transferase) pulldown experiments (71). The SnAC domain enhances the ATPase activity of the helicase domain, but the effect of the SnAC domain on nucleosome mobilization is an order of magnitude greater than that of ATP hydrolysis(70). The most crucial role for the SnAC domain is facilitating the movement of nucleosomal DNA and is separate from effects on ATP hydrolysis. The SnAC domain is presently considered to be a critical histone anchor requires to adequately anchor the helicase domain to nucleosomes and prevent it from slipping when translocating on DNA.

> Snf2 ATP coupling (SnAC) domain: an evolutionarily conserved domain found in the catalytic subunit of SWI/SNF that is believed to anchor the helicase domain to histones

Histone interactions are also mediated through accessory subunits for the **ATRX** and SWR1 complexes to assemble new chromatin or exchange histone dimers of specific histone variants. ATRX binds to the histone chaperone death domain--associated protein (DAXX) and associates with chromatin containing the histone H3.3 variant (20, 21). Recombinant DAXX alone assembles H3.3/H4 tetramers onto DNA, and the DAXX/ATRX complex can deposit and remodel H3.3 nucleosomes. The highly conserved N terminus of DAXX is the region responsible for binding the globular region of histone H3.3 (21). In the SWR1

complex, the Swc2 subunit and the N terminus of Swr1 bind to H2AZ and suggest that SWR1 might bind two H2AZ/H2B dimers (72, 73).

Death domain--associated protein (DAXX): a histone chaperone responsible for replication-independent incorporation of histone H3.3 variant

NUCLEOSOME RECOGNITION: DNA BINDING DOMAINS

Nucleosome recognition by remodelers entails interactions not only with histones but also with DNA. Several domains in different remodelers are known to bind DNA, but in general, we do not know much about their roles in remodeling. ISW2 and ISW1a make extensive contact with extranucleosomal DNA, as demonstrated by DNA footprinting with hydroxyl radical and exonuclease III (74, 75). The large accessory subunits of these two complexes are extensively engaged with extranucleosomal DNA and, in the case of ISW2, reach at least as far as 50 to 60 bp from the entry site of nucleosomes. The C terminus of Isw2 contains three well-conserved domains (**SANT**, SLIDE, and HAND). The ~50--amino acid SANT domain is found in many chromatin regulators, such as SWI/SNF and SAGA, as well as in some transcription factors, such as TFIIIB and N-Cor (76). DNA cross-linking studies performed with ISW2 found that the SLIDE domain binds near DNA that is 19 bp from the entry side of nucleosomes and that the the HAND domain binds to DNA that is ~10 bp inside nucleosomes (Figures 2*e* and 3*a*) (26). The crystal structure of the C terminus of ISWI from *Drosophila* (dIswi) revealed that SLIDE and SANT domains are structurally related to one another and resemble the DNA binding module of c-Myb (77). The SANT and SLIDE domains have three α-helices that are organized in a manner that is spatially similar to c-Myb. The SLIDE domain alone binds DNA, a finding that is consistent with the positively charged residues on the presumed recognition helix, but the SANT domain does not bind, presumably because of a lack of positively charged residues in the recognition helix.

The crystal structure of Ioc3 and the C terminus of Isw1 with 48 bp of DNA and of the DNA binding domain of CHD1 with DNA showed the SLIDE domain bound to DNA (Figure 3*b*) (78) (79, 80). Two distinct regions of Ioc3, referred to as the CLB (coil-linker-DNA-binding) and the HLB (helical-linker-DNA-binding) domains, were found to contact DNA. The CLB domain is made from two random coils, one at the N terminus (amino acids 160–167) and the other at the C terminus (amino acids 691–696), which contacts primarily the DNA phosphate backbone. The HLB domain contacts DNA upstream of the SLIDE and SANT domains' binding sites. In a current model of ISW1a binding to a dinucleosome, the CLB binds to the flanking extranucleosomal DNA, while the HLB, SANT, and SLIDE domains bind to the linker DNA connecting the two nucleosomes (78).

One role of the SLIDE domain is to recruit the complex by binding linker DNA, and deletion of the C termini of dIswi and Chd1 reduces the remodeling activities of these catalytic subunits (79, 81, 82). Investigators restored the activity of Chd1 in the absence of the SLIDE and SANT domains by substituting it with another DNA binding domain(83, 84). This finding suggests the SLIDE and SANT domains recruit the complex by binding to linker DNA. One study showed that the C terminus confers primarily increased affinity and specificity of the helicase domain for nucleosomes (81). Another study indicated that the C

terminus of dIswi is required for efficient DNA translocation by the helicase domain but not for ATP hydrolysis (82). These studies are limited because the catalytic subunit in isolation was used, rather than in association with its accessory subunit(s), and is considerably less active than the intact complex. Also, deleting the entire C terminus may not be an effective way to decipher the different functions of the SLIDE, SANT, and HAND domains. Toward this objective, others have studied the SLIDE domain in the ISW2 complex by mutating several of the basic residues that are important for DNA binding to alanine. Reduced binding of the SLIDE domain did not interfere with normal recruitment of the complex or binding of the helicase domain to the correct location inside of nucleosomes, but it did negatively affect the nucleosome remodeling activities of ISW2. These data suggest that the SLIDE domain does more than merely recruit the complex to DNA, because its binding to DNA has an important role in the mobilization of nucleosomal DNA (discussed in more detail below in the Operation of the Helicase Domain Inside Nucleosomes Section).

INO80 binds to linker DNA, spaces nucleosomes, and requires an optimal length of 70 bp of extranucleosomal DNA to mobilize nucleosomes similar to ISWI (85). In yeast, INO80 and SWR1 are unique among chromatin remodelers because they contain actin as a subunit. Unlike cytoplasmic actin, the nuclear actin associated with INO80 is monomeric and does not associate with actin filaments (86). Investigators recently showed that actin has an important role in the interactions between INO80 and extranucleosomal DNA (86). Although actin alone has no particular affinity for DNA, actin in complex with two actin-related proteins (Arp4 and Arp8) binds DNA and forms part of the INO80 complex (87, 88).

The known DNA binding domains residing in SWI/SNF are (*a*) one (in higher eukaryotes) or two (in yeast) AT hook domains in its catalytic subunit (89, 90) and (*b*) ARID (AT-rich interaction domain) (91–94) and SWIRM (95–97) domains in the accessory subunits. ARID, a conserved feature of SWI/SNF, can be found in the Swi1 subunit of yeast SWI/SNF and in the ARID1a and ARID1b subunits of human SWI/SNF or BAF complexes. Recent data showed that ARID in human SWI/SNF is required for binding to promoters (98). Although the SWIRM domain in SWI/SNF binds to DNA, some SWIRM domains in other complexes appear to have lost this ability (99). The functional role of the AT hook, ARID, and the SWIRM domain in SWI/SNF recruitment and remodeling have not yet been well defined.

PROTEIN--PROTEIN INTERACTIONS INVOLVED IN COMPLEX ASSEMBLY AND REMODELING

Some domains are important for complex assembly and are involved in subunit-subunit interactions. The SLIDE and SWIRM domains have a dual role, because they bind DNA and are also required for complex integrity. The ~75--amino acid helicase/SANT-associated (HSA) domain is found associated with **bromo-**, SANT, and helicase domains and is located next to the N terminus of the helicase domains of INO80, SWR1, and SWI/SNF (100). The protein targets for the HSA domain are actin and actin-related proteins (ARPs). Specific pairs or triplets of ARPs and actin associate with the HSA domain, and the particular set varies depending on the specific HSA domain. The HSA domain of Snf2 and Sth1, the two catalytic subunits of yeast SWI/SNF and RSC, binds to a dimer of Arp7 and Arp9 (36). The HSA domain in Ino80 binds to subcomplex of Arp4, Arp8, and actin (101), and in Swr1, the

HSA domain binds only Arp4 and actin. Deletion of HSA from Sth1 and the subsequent loss of Arp7 and Arp9 only slightly reduced the ATPase activity of RSC (36). Gain-of-function mutation studies have demonstrated that the Arps and the HSA domain, appear to have a modest role in regulating the activity of the helicase domain, presumably in concert with protusion region 1 and a region next to the HSA domain, termed the post-HSA domain. The structures have recently been solved of Arp8 and Arp4 in their ATP-bound form found in INO80 and SWR1, and the subcomplex of Arp7, Arp9, the HSA domain, and Rtt102 in SWI/SNF (87, 102, 103). The actin fold regions of Arp4 and Arp8 contain large insertions that block the polymerization domains of these proteins and prevents them from polymerizing like free actin. Arp7 and Arp9 do not have the conserved actin active site and cannot bind or hydrolyze ATP, whereas Arp4 and Arp8 do have an active ATPase site (104). The HSA domain forms a 95--amino acid--long helix that Arp7 and Arp9 straddle as a heterodimer, and a highly extended form of Rtt102 interacts with and stabilizes the association of both ARPs. The Arp7/Arp9/HSA/Rtt102 complex binds to free DNA but not to a 147-bp core nucleosome particle and resembles the DNA binding properties of the Arp8/Arp4/actin complex (87, 102).

> Helicase/SANT-associated (HSA) domain: 75--amino acid domain predicted to bind DNA

The large insertion located in the helicase domains of INO80 and SWR1 between protusion 2 and the second recA-like domain is another interaction module that recruits Rvb1 and Rvb2 (in yeast) or Tip49a and Tip49b (in humans) into these complexes. Rvb1 and Rvb2 are ATP-dependent DNA helicases that belong to the AAA^+ superfamily and are highly conserved in archaea and eukaryotes (105, 106). The role of DNA helicase activity in nucleosome remodeling is unclear, but Rvb1 and Rvb2 also bind Arp5, thereby bringing a third distinct Arp member into the INO80 complex (107). Arp5 is required for the remodeling activity of INO80; consequently, deletion of this insertion and loss of Rvb1/Rvb2/Arp5 inactivate the INO80 complex (101).

Protein--protein interactions are probably involved in regulation of the helicase domain, as has been observed with the **HSA** and **SnAC** domains of SWI/SNF and the **chromodomains** of CHD1. Two additional domains, known as AutoN and NegC, are found in the catalytic subunit of dIswi that regulate the activity of the helicase domain (Figure 1*a*). The AutoN motif negatively regulates the ATPase activity of ISWI and at the protein sequence level resembles the histone H4 N-terminal tail and its basic patch (82). The explanation for this finding is tied to the addition of the H4 tail peptide to ISWI and DNA enhancing both the ATPase and DNA tranlocation activities of ISWI. The AutoN motif appears to block or interfere with the helicase domain, and AutoN is probably competed from its binding target by the H4 tail. This model is supported by the observation that the ATPase activity of ISWI increases after two arginines in the AutoN region are changed to alanine that could mimic the basic patch of H4. The increased activity of the mutant is not stimulated further by the addition of the H4 peptide. ISWI with mutated AutoN also translocates along DNA and mobilizes nucleosomes more efficiently than does wild-type ISWI. Investigators identified the NegC domain by serially truncating dIswi from its C terminus. The NegC domain is located near the C-terminal end of the helicase domain. Deletion of NegC restored most of

the DNA translocation activity of dIswi that was lost when the HAND, **SANT**, and SLIDE domains were removed. Modeling of the NegC domain suggests that it may traverse both lobes of the helicase domain and interfere with the DNA binding surface of the helicase domain.

MECHANISM OF NUCLEOSOME MOVEMENT: NUCLEOSOME DYNAMICS

An important question is how translocation by the helicase domain is converted into nucleosome movement and nucleosome rearrangements, such as displacement and histone exchange. Many histone--DNA interactions contribute to the stability of nucleosomes and present a considerable barrier to the movement of DNA through nucleosomes (108, 109). Fourteen distinct helical turns of DNA contact the histone octamer, and the most central position is referred to as the dyad axis or superhelical location 0 (SHL0). Each helical turn from the dyad axis is numbered based on the number of helical turns from the dyad axis; superhelical location 1/−1, 2/−2 (SHL1/−1, 2/−2), and so on. One hundred twenty-one histone--DNA interactions in the nucleosome are mediated through hydrogen bounding with water molecules, and 116 hydrogen bonds are formed directly between histones and DNA. The two types of interactions should equally contribute to the stability of nucleosomes. Two basic models of nucleosome remodeling have dominated investigations into this process during the past decade: the DNA twist model and the bulge propagation model (110–112).

The DNA twist model requires the least amount of energy with a proposed 1-bp twist in DNA propagating through the entire nucleosome thereby changing the nucleosome translational position by 1 bp. This model is more energetically favorable because it requires only minor changes in the nucleosome structure. Some of these changes seem to be readily accommodated, as seen in the nucleosome crystal structure, where overwound DNA has been observed (109, 113). Experimental data tend to rule out twist diffusion as the exclusive mechanism of nucleosome mobilization because DNA hairpins and biotin cross-links do not inhibit remodeling even though they do not allow rotation of the DNA duplex caused by twisting (114, 115). Also DNA nicks which would interfere with propagation of DNA twist have been shown not to interfere with nucleosome remodeling by RSC (116) and ISWI (117), The DNA bulge propagation model initially requires a greater expenditure of energy to displace a segment of DNA from the surface of the nucleosome and a different segment of DNA rebinds the site to create a bulge on the surface of the nucleosome. The bulge should be able to move around the histone octamer in a wavelike fashion until it exits. Consistent with the bulge propagation model, restriction enzyme and DNase I cleavage patterns of nucleosomes remodeled with SWI/SNF suggest that transient DNA displacement occurs from histone octamer during remodeling (118, 119). Other evidence comes from the use of nucleosomes of which both molecules of H2A are covalently linked through a disulfide bond to constrain DNA near the dyad axis. DNA is trapped near the dyad axis and presumably a DNA bulge would not be able to move through this location. In these modified nucleosomes, the bulge on the surface was apparently able to form but, because of the cross-link, was unable to propagate efficiently through the dyad axis region and around the histone octamer to promote nucleosome movement (120).

MECHANISM OF NUCLEOSOME MOVEMENT: HELICASE DOMAIN WORKING FROM INSIDE

The helicase domain does not start translocating at the more vulnerable entry site of nucleosomes as first postulated; but rather initiates inside of nucleosomes at SHL2, ~50 bp from the entry site (49–51). The earliest evidence that remodelers contact DNA at SHL2 came from DNA footprinting of the yeast ISW2 complex. The catalytic subunit Isw2 was found by site-directed DNA cross-linking to be bound near the SHL2 site (75). RSC appears to bind to SHL2 and SHL–2 sites as shown by the creation of two DNase I hypersensitivity sites following binding, presumably due to two populations of bound RSC at alternative positions on nucleosomes (49). Investigators observed a similar effect with NURF by DNA footprinting with hydroxyl radical (50).

The role of DNA translocation in nucleosome remodeling has been investigated by blocking translocation with DNA gaps. The location where DNA translocation is required in the first stages of remodeling was identified by placing gaps at random positions in nucleosomes and finding which gaps blocked the start of remodeling. DNA gaps at SHL2 interfered with the mobilization of nucleosomes by NURF, ISW2, and SWI/SNF (Figure 4*a*) (50, 51). Besides blocking translocation, DNA gaps could also interfere with binding of particular domains of the remodeler to DNA and gaps at SHL2 could interfere with binding of the helicase domain. For ISW2, there were also gaps in one strand ~10 bp outside the ISW2 protection site near SHL3. These gaps interfered with the movement of the nucleosomes and are likely to be independent of interferring with binding (Figure 4*a*) (51). The gaps near SHL3 probably preferentially interfered with DNA translocation and suggests the helicase domain tracks on DNA away from the dyad axis, toward the entry site, and pulls DNA into nucleosomes, which would be consistent with the known direction of nucleosome movement. The gaps that interfered with nucleosome mobilization by SWI/SNF were in only 1 strand at the SHL2 position and in an additional 20 bp from SHL2 toward the entry site (Figure 4*a*). Most of these gaps probably interfere with DNA translocation rather than with SWI/SNF binding. Other experiments have directly shown the helicase domains of ISW2 and SWI/SNF are bound to DNA at SHL2 by finding them cross-linked to DNA 17 and 18 bp from the dyad axis (26, 47).

OPERATION OF THE HELICASE DOMAIN INSIDE NUCLEOSOMES

The pulling force of the helicase domain should be dependent on how the helicase domain is tethered to the nucleosomes. The helicase domain tether has to be strong enough to counter the resistance to DNA being moved due to the histone-DNA contacts and prevent the helicase domain from slipping on DNA. In the face of opposing forces like that found in nucleosomes, RSC and SWI/SNF tend to slip on DNA and cannot processively translocate on DNA (121). RSC translocation on free DNA was found in magnetic tweezer experiments to shorten DNA and was eliminated when an opposing force greater than 1 pN was applied, which is considerably lower than the 10–30 pN force required to disrupt the nucleosome structure (122). A minimal version of the RSC complex, containing Arp7 and Arp9 and a truncated Sth1 catalytic subunit with the helicase domain fused to a Tet repressor dimer, moved along DNA against opposing forces of up to 30 pN(123). The Tet repressor protein

provided the necessary strong anchor by binding to a Tet site engineered into the DNA template. This artificial remodeler demonstrates a tightly fixed anchor is required in addition to the helicase domain to create a pulling force that would be sufficient to disrupt histone--DNA interactions.

Anchors for the helicase domain can be contacts with the histone octamer and extranucleosomal and nucleosomal DNA. **SnAC** domain in the catalytic subunit of SWI/SNF seems to be a histone anchor required for nucleosome movement. Nucleosome movement is down regulated more than a factor of 100 by the absence of the SnAC domain under conditions in which both WT and SnAC minus SWI/SNF hydrolyze ATP equally (70). The anchor activity of the SnAC domain is not required for the efficient translocation of SWI/SNF on free DNA as seen in molecular tweezer experiments. Consistent with these data, studies with optical tweezers have found that the pulling force of RSC and SWI/SNF increases dramatically when remodeling nucleosomes compared to free DNA (124).

Not only do SWI/SNF and RSC mobilize nucleosomes, they tend to partially unravel mononucleosomes by pushing them off the ends of DNA and induce changes in the nucleosome canonical structure that are retained after remodeling (125 126). After changing nucleosome translational positions on DNA, ISWI retains more of the canonical nucleosome structure than does SWI/SNF type complexes (127). This difference may be connected to differences in the binding of the helicase domains of yeast SWI/SNF and ISW2 to nucleosomal DNA (47). The region of the helicase domain of Isw2 that is cross-linked to DNA 17 and 18 bp from the dyad axis coincides with the region of the helicase domain that is expected to contact DNA on the basis of sequence similarity with the Rad54 and its crystal structure when bound to DNA (26, 31). The region of the helicase domain of Snf2 switches from the same conserved cleft region as ISW2 when binding free DNA to a region orthogonal to the cleft region when bound to nucleosomes (47). Isw2 binds to the exposed part of DNA that faces away from the histone octamer at SHL2, whereas Snf2 wedges itself between the histone octamer and DNA gyre, as shown by studies that track their rotational positioning on DNA by site-directed cross-linking (47). Snf2 wedged between the octamer and DNA is expected to have a greater tendency to disrupt the DNA-octamer interface than ISW2 when it starts to translocate on DNA (pull and wedge) (Figure 4*b*). Isw2 bound on the outside (pull only) will not have the same strategic advantage for working as a wedge to pry off histone--DNA interactions.

Another variation of how helicase domains might engage nucleosomes comes from the human ACF complex potentially acting as dimer. Investigators have suggested that an ACF dimer binds to nucleosomes in which two helicase domains are bound at opposing sites on nucleosomes and are attempting to move nucleosomes in opposite directions (127–130). The dominant or more stably bound helicase domain is on the side with the longer linker DNA. As linker DNA is shortened by remodeling on the active side and lengthened on the other, the other helicase domain becomes the dominant one and reverses the direction of nucleosome movement (Figure 4*c*). The dimer model provides one explanation of how ISWI can center nucleosomes on DNA and space nucleosomal arrays in a linker DNA--dependent manner.

The binding of the helicase domain at SHL2 is advantageous because it begins at one of the weaker histone--DNA contact regions in the nucleosome surrounded by higher energy barriers at the dyad axis and SHL4. As the DNA begins to move through the helicase domain, it underwinds, tries to pull DNA in on the SHL4 side, and pushes DNA through the dyad axis side. Single-molecule studies performed with ISW2 show that DNA begins to exit the nucleosome before there is significant movement at the entry side (Figure 4*d*) (43). Such movement strains the DNA between the helicase domain and the entry site of the nucleosomes. This strain persists and increases while the helicase domain takes seven consecutive 1-bp, steps pushing the DNA out through the exit site (Figure 4*d*). When a sufficient DNA strain is generated, approximately 3 bp of DNA is drawn into the space between the entry site and the helicase domain. This process repeats after an additional 3 bp of DNA are pushed through the exit site, again triggering events at the entry site. Additional evidence for the requirement of torsional strain between the helicase domain and the entry site for remodeling is seen with DNA nicks ~10 bp to the side of the helicase binding site interfering (Figure 4*a*). The break in the DNA phosphate backbone can prematurely release the DNA torsional strain and avoid formation of significant torsional strain.

Other domains in remodelers may have active roles in mobilizing nucleosomes in addition to being anchors for the helicase domain, as illustrated by the case of ISW2. Interactions between ISW2 and nucleosomes expand on ATP hydrolysis, protecting an additional ~40 bp of nucleosomal DNA, and form a template-committed complex that is resistant to competitor DNA (131). The additional contacts occur between the helicase domain at SHL2 and the HAND domain at SHL6 and may facilitate the entry of DNA into nucleosomes (Figure 4*e*). The SLIDE domain contributes significantly to pushing DNA into the entry site. If SLIDE binding to linker DNA is reduced through mutation, then DNA moving into nucleosomes by ISW2 is uncoupled from DNA moving out the exit side (27). Part of ISW2 binds to linker DNA and, through a conformational switch, may push DNA into nucleosomes. This model would require the domain(s) involved to release and reset on a new position of linker DNA to perform multiple steps of pushing DNA into nucleosomes as needed (Figure 4*e*).

NUCLEOSOME SPACING VERSUS DISASSEMBLY

The linker DNA length--dependent regulation of nucleosome movement by ISWI to evenly space nucleosomes has several possible explanations. One is that the affinity of ISWI is reduced as the linker DNA length is shortened, causing the complex to fall off and search for new substrates with more appropriate lengths of linker DNA. This model is supported by measurements showing that ISWI binding affinity varies with linker DNA length and transiently samples nucleosomes (75, 132, 133). The interactions between the remodeler and linker DNA largely contribute to the affinity and stability of the complex with nucleosomes. Another explanation is that the rate at which the helicase domain translocates along nucleosomal DNA is regulated by the length of the linker DNA (134). This model accords with the ACF dimer model, in which the helicase domain that is most engaged with nucleosomal DNA is on the side with the longer linker DNA. In other studies in which ISW2 behaves as a monomer, DNA footprinting demonstrated that the stable binding of the helicase domain to SHL2 varied with the length of extranucleosomal DNA (135). Although

ISW2 binds to nucleosomes with 20 bp of extranucleosomal DNA, there is no protection at the SHL2 site, in contrast to the situation with 30 bp of extranucleosomal DNA. It seems plausible that the parts of the complex interacting with linker DNA (C terminus of ISWI/ auxiliary subunit--like Itc1) can stimulate or inhibit the helicase domain depending on the extent of their interactions with linker DNA (82). Not only do the interactions between the C terminus of ISWI and linker DNA regulate the activity of the helicase domain; they may also push DNA from the linker DNA into nucleosomes (27). In vitro ISW2 does not appear to space nucleosomes in arrays as uniformly as does ISW1a, a finding that suggests that ISW1a senses linker DNA length in a manner different than ISW2 (136, 137). Structural studies of Isw1 and Ioc3 suggest that the enhanced ability to uniformly space nucleosomes may be tied to simultaneous binding to both linker DNA (78). More research is needed to understand how these two interactions could regulate the activities of the helicase domain and nucleosome mobilization, which may be mediated through the C terminus of Isw1 and the auxiliary subunit Ioc3.

The discovery of nucleosome disassembly by SWI/SNF requiring a minimum of two nucleosomes on the same DNA template (8) highlights the importance of dinucleosome substrates. This study revealed that one nucleosome is retained and the other displaced and that the nucleosome retained is bound by SWI/SNF. As the SWI/SNF complex moves one nucleosome on DNA toward the second nucleosome, it pushes against the second nucleosome until the DNA is displaced and spooled into the mobilized nucleosome. The second nucleosome is eventually displaced as more DNA is actively displaced from its surface and spooled into the other. As might be expected, the temporal changes are first a rapid release of one H2A/H2B dimer and a second slower release of the remaining hexasome. Another study showed that RSC tends to form overlapping nucleosomes, a finding that is consistent with this model (138). Structural aspects of RSC binding to nucleosomes had prompted suggestions of RSC being able to disassemble nucleosomes (139, 140). In vivo data support the idea that the SWI/SNF and RSC complexes displace nucleosomes, thereby creating nucleosome-deficient regions often at promoter regions which may potentially be assisted by histone chaperones such as Asf1 (9, 10, 141, 142, 143, 144). [3, 4] The situation may be more complicated, given that data suggest RSC may have a major role in determining the in vivo spacing pattern of nucleosomes and have other functions than displacing nucleosomes (145).

REGULATION OF ATP-DEPENDENT CHROMATIN REMODELERS

Three ways to regulate the activity of an ATP-dependent chromatin remodeler are by (*a*) recruiting to the correct target site, (*b*) adjusting the activities of the helicase and other crucial domains, and (*c*) changing the subunits associated with the catalytic subunit to confer different activities onto the complex. One can regulate targeting by changing the degree to which certain histone modifications occur and targeting is discussed above in terms of known histone readers. Other than targeting, histone modification can regulate the activities of remodelers such as the example of the N-terminal tail of H4 and ISWI. Although the H4 tail does not necessarily target ISW2 to particular genomic sites, the H4 tail does promote the stable binding of the helicase domain to the SHL2 position (135). Acetylation of the H4

tail inhibits the stimulatory activity of H4 tails (146, 147) probably by destabilizing the binding of the helicase domain to nucleosomal DNA.

Other ways of regulating the activity of the helicase domain is to affect the affinity for DNA and consequently the enzyme's processivity or directly change the instrinsic ATPase activity. The ATPase activity can be reduced by altering the orientation of the two lobes such that the critical residues are not in close proximity for proper binding and catalysis of ATP. Alternatively DNA binding that enhances the proper placement of the two lobes can be blocked by other domains (e.g., the **chromodomain**) to negatively regulate the ATPase activity. The DNA affinity of the helicase domain is reduced by mutations within the STRAGGLG amino acid sequence of motif V of Snf2, which decreases the DNA translocation properties of SWI/SNF without adversely affecting ATP hydrolysis (148). Similar effects of mutations in motif V have been observed in other DNA helicases (149, 150). Other domains or elements outside the helicase domain, such as that identified in Chd1, may also be important for effective DNA translocation (151).

The particular accessory subunits associated with the catalytic subunit can strongly influence the remodeling activity and recruitment of the complex. The accessory subunits have been shown biochemically to be required for targeting, enhancing nucleosome affinity and remodeling activities of the catalytic subunits Brg1 (152, 153), human SNF2H (154, 155), and ISW2 (27). ISW1a and ISW1b, which both have the same catalytic subunit, show the importance of the accessory subunit because (*a*) ISW1a spaces nucleosomes and ISW1b does not and (*b*) ISW1b, but not ISW1a, is recruited to chromatin with H3K36me3 present (61, 62, 137). Human SWI/SNF has a great deal of compositional variation that gives rise to different functional properties and tissue specificity (2). As neuronal progenitor cells differentiate into neurons SWI/SNF switches out two subunits (BAF45a and BAF53a) for neuron-specific subunits (BAF45b/c and BAF53b) (5, 6, 156, 157). Clearly, in human SWI/SNF a frequently used method for regulating the complex in a tissue-specific manner is to switch particular subunits. Recent cancer genomic surveys have also demonstrated that certain subunits of human SWI/SNF are associated with different cancers. The Polybromo/PBRM1/BAF180 subunit of the pBAF or human SWI/SNF complex is a frequent target associated with pancreatic, kidney, and breast cancer, whereas mutations in ARID1a, a subunit of BAF or another form of human SWI/SNF, is found in many other cancers, such as gastric cancer, medulloblastoma, and lung cancer (158, 159). The increasing number of publications showing particular diseases linked to different mutated subunits of the human SWI/SNF is compelling evidence that complex specificity strongly depends on the accessory subunits assembled into the complex.

Posttranslational modifications of domains or accessory subunits may be important switches for regulating the activities of these complexes. Most of the evidence for this hypothesis comes from the SWI/SNF family of remodelers, (*a*) the first shown was inactivation of the catalytic subunits Brg1 and hBRM by phosphorylation, and (*b*) later phosphorylation of the human homolog of Swi3 upon mitosis (160, 161). In addition to the autoregulation of Rsc4 by acetylation (mentioned above), acetylation also targets the catalytic subunit of SWI/SNF. In yeast SWI/SNF, two lysine residues between the two AT hooks are acetylated which can bind to the **bromodomain** in Snf2 and in turn compete for binding to acetylated

nucleosomes (162). Interferon-γ activation causes hBRM to be acetylated by p300 and causes hBRM to dissociate from the mSin3/HDAC corepressor (163). Although Gcn5 is known to acetylate the HAND domain in ISWI, the effect of this modification on the activity of the ISWI complex is unknown (164).

CONCLUSIONS

ATP-dependent chromatin remodelers are vital gatekeepers of the epigenome, and as such, they are often the targets in many human diseases or developmental disorders. We are only beginning to find evidence of the importance of these chromatin regulators in differentiation and developmental control. Although the particular subunits involved in various diseases will continue to be identified by NGS-based approaches, it will become increasingly important to better understand the structural and functional properties not only of the helicase domain but also of the other domains involved in remodeling and the various roles of the accessory subunits in reorganizing chromatin.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

My research was supported by funds from the National Institutes of Health, General Medicine Division.

LITERATURE CITED

1. Flaus A, Martin DMA, Barton GJ, Owen-Hughes T. Identification of multiple distinct Snf2 subfamilies with conserved structural motifs. Nucleic Acids Res. 2006; 34:2887–905. [PubMed: 16738128]
2. Ho L, Crabtree GR. Chromatin remodelling during development. Nature. 2010; 463:474–84. [PubMed: 20110991]
3. Ronan JL, Wu W, Crabtree GR. From neural development to cognition: unexpected roles for chromatin. Nat Rev Genet. 2013; 14:347–59. [PubMed: 23568486]
4. Sims JK, Wade PA. SnapShot. Chromatin remodeling: CHD. Cell. 2011; 144:626, e1. [PubMed: 21335242]
5. Yoo AS, Crabtree GR. ATP-dependent chromatin remodeling in neural development. Curr Opin Neurobiol. 2009; 19:120–26. [PubMed: 19442513]
6. Lessard J, Wu JI, Ranish JA, Wan M, Windlow MM, et al. An essential switch in subunit composition of a chromatin remodeling complex during neural development. Neuron. 2007; 55:201–15. [PubMed: 17640523]
7. Yoo AS, Staahl BT, Chen L, Crabtree GR. MicroRNA-mediated switching of chromatin-remodelling complexes in neural development. Nature. 2009; 460:642–46. [PubMed: 19561591]
8. Dechassa ML, Sabri A, Pondugula S, Kassabov SR, Chatterjee N, et al. SWI/SNF has intrinsic nucleosome disassembly activity that is dependent on adjacent nucleosomes. Mol Cell. 2010; 38:590–602. [PubMed: 20513433]
9. Boeger H, Griesenbeck J, Kornberg RD. Nucleosome retention and the stochastic nature of promoter chromatin remodeling for transcription. Cell. 2008; 133:716–26. [PubMed: 18485878]
10. Boeger H, Griesenbech J, Strattan JS, Kornberg RD. Removal of promoter nucleosomes by disassembly rather than sliding in vivo. Mol Cell. 2004; 14:667–73. [PubMed: 15175161]

11. Luk E, Ranjan A, Fitzgerald PC, Mizuguchi G, Huang Y, et al. Stepwise histone replacement by SWR1 requires dual activation with histone H2A.Z and canonical nucleosome. Cell. 2010; 143:725–36. [PubMed: 21111233]
12. Mizuguchi G, Shen X, Landry J, Wu WH, Sen S, Wu C. ATP-driven exchange of histone H2AZ variant catalyzed by SWR1 chromatin remodeling complex. Science. 2004; 303:343–48. [PubMed: 14645854]
13. Papamichos-Chronakis M, Watanabe S, Rando OJ, Peterson CL. Global regulation of H2A.Z localization by the INO80 chromatin-remodeling enzyme is essential for genome integrity. Cell. 2011; 144:200–13. [PubMed: 21241891]
14. Loyola A, LeRoy G, Wang YH, Reinberg D. Reconstitution of recombinant chromatin establishes a requirement for histone-tail modifications during chromatin assembly and transcription. Genes Dev. 2001; 15:2837–51. [PubMed: 11691835]
15. Walfridsson J, Bjerling P, Thalen M, Yoo E-J, Park SD, Ekwall K. The CHD remodeling factor Hrp1 stimulates CENP-A loading to centromeres. Nucleic Acids Res. 2005; 33:2868–79. [PubMed: 15908586]
16. Robinson KM, Schultz MC. Replication-independent assembly of nucleosome arrays in a novel yeast chromatin reconstitution system involves antisilencing factor Asf1p and chromodomain protein Chd1p. Mol Cell Biol. 2003; 23:7937–46. [PubMed: 14585955]
17. Konev AY, Tribus M, Park SY, Lim CY, Emelyanov AV, et al. CHD1 motor protein is required for deposition of histone variant H3.3 into chromatin in vivo. Science. 2007; 317:1087–90. [PubMed: 17717186]
18. Lusser A, Urwin DL, Kadonaga JT. Distinct activities of CHD1 and ACF in ATP-dependent chromatin assembly. Nat Struct Mol Biol. 2005; 12:160–66. [PubMed: 15643425]
19. Drané P, Ouararhni K, Depaux A, Shuaib M, Hamiche A. The death-associated protein DAXX is a novel histone chaperone involved in the replication-independent deposition of H3.3. Genes Dev. 2010; 24:1253–65. [PubMed: 20504901]
20. Goldberg AD, Banaszynski LA, Noh KM, Lewis PW, Elsässer SJ, et al. Distinct factors control histone variant H3.3 localization at specific genomic regions. Cell. 2010; 140:678–91. [PubMed: 20211137]
21. Lewis PW, Elsässer SJ, Noh KM, Stadler SC, Allis CD. Daxx is an H3.3-specific histone chaperone and cooperates with ATRX in replication-independent chromatin assembly at telomeres. Proc Natl Acad Sci USA. 2010; 107:14075–80. [PubMed: 20651253]
22. Baumann C, Viveiros MM, De La Fuente R. Loss of maternal ATRX results in centromere instability and aneuploidy in the mammalian oocyte and pre-implantation embryo. PLoS Genet. 2010; 6:e1001137. [PubMed: 20885787]
23. Heaphy CM, de Wilde RF, Jiao Y, Edil BH, Shi C, et al. Altered telomeres in tumors with ATRX and DAXX mutations. Science. 2011; 333:425. [PubMed: 21719641]
24. Bower K, Napier CE, Cole SL, Dagg RA, Lau LMS, et al. Loss of wild-type ATRX expression in somatic cell hybrids segregates with activation of alternative lengthening of telomeres. PLoS ONE. 2012; 7:e50062. [PubMed: 23185534]
25. Perpelescu M, Nozaki N, Obuse C, Yang H, Yoda K. Active establishment of centromeric CENP-A chromatin by RSF complex. J Cell Biol. 2009; 185:397–407. [PubMed: 19398759]
26. Dang W, Bartholomew B. Domain architecture of the catalytic subunit in the ISW2--nucleosome complex. Mol Cell Biol. 2007; 27:8306–17. [PubMed: 17908792]
27. Hota SK, Bhardwaj SK, Deindl S, Lin YC, Zhuang X, Bartholomew B. Nucleosome mobilization by ISW2 requires the concerted action of the ATPase and SLIDE domains. Nat Struct Mol Biol. 2013; 20:222–29. [PubMed: 23334290]
28. Dechassa ML, Zhang B, Horowitz-Scherer R, Persinger J, Woodcock CL, et al. Architecture of the SWI/SNF--nucleosome complex. Mol Cell Biol. 2008; 28:6010–21. [PubMed: 18644858]
29. Hauk G, McKnight JN, Nodelman IN, Bowman GD. The chromodomains of the Chd1 chromatin remodeler regulate DNA access to the ATPase motor. Mol Cell. 2010; 39:711–23. [PubMed: 20832723]

30. Thoma NH, Czyzewski BK, Alexeev AA, Mazin AV, Kowalczykowski SC, Pavletich NP. Structure of the SWI2/SNF2 chromatin-remodeling domain of eukaryotic Rad54. Nat Struct Mol Biol. 2005; 12:350–56. [PubMed: 15806108]
31. Durr H, Körner C, Müller M, Hickmann V, Hopfner KP. X-ray structures of the *Sulfolobus solfataricus* SWI2/SNF2 ATPase core and its complex with DNA. Cell. 2005; 121:363–73. [PubMed: 15882619]
32. Wollmann P, Cui S, Viswanathan R, Berninghausen O, Wells MN, et al. Structure and mechanism of the Swi2/Snf2 remodeller Mot1 in complex with its substrate TBP. Nature. 2011; 475:403–7. [PubMed: 21734658]
33. Gorbalenya AE, Koonin EV, Donchenko AP, Blinov VM. A conserved NTP motif in putative helicases. Nature. 1988; 333:22. [PubMed: 2834648]
34. Gorbalenya AE, Koonin EV. Helicases: amino acid sequence comparisons and structure--function relationship. Curr Opin Struct Biol. 1993; 3:419–29.
35. Eisen JA, Sweder KS, Hanawalt PC. Evolution of the SNF2 family of proteins: subfamilies with distinct sequences and functions. Nucleic Acids Res. 1995; 23:2715–23. [PubMed: 7651832]
36. Szerlong H, Hinata K, Viswanathan R, Erdjument-Bromage H, Tempst P, Cairns BR. The HSA domain binds nuclear actin-related proteins to regulate chromatin-remodeling ATPases. Nat Struct Mol Biol. 2008; 15:469–76. [PubMed: 18408732]
37. Dumont S, Cheng W, Serebrov V, Beran RJ, Tinoco I Jr, et al. RNA translocation and unwinding mechanism of HCV NS3 helicase and its coordination by ATP. Nature. 2006; 439:105–8. [PubMed: 16397502]
38. Myong S, Bruno MM, Pyle AM, Ha T. Spring-loaded mechanism of DNA unwinding by hepatitis C virus NS3 helicase. Science. 2007; 317:513–16. [PubMed: 17656723]
39. Cheng W, Arunajadai SG, Moffitt JR, Tinoco I Jr, Bustamante C. Single--base pair unwinding and asynchronous RNA release by the hepatitis C virus NS3 helicase. Science. 2011; 333:1746–49. [PubMed: 21940894]
40. Dillingham MS, Wigley DB, Webb MR. Demonstration of unidirectional single-stranded DNA translocation by PcrA helicase: measurement of step size and translocation speed. Biochemistry. 2000; 39:205–12. [PubMed: 10625495]
41. Lee JY, Yang W. UvrD helicase unwinds DNA one base pair at a time by a two-part power stroke. Cell. 2006; 127:1349–60. [PubMed: 17190599]
42. Park J, Myong S, Niedziela-Majka A, Lee KS, Yu J, et al. PcrA helicase dismantles RecA filaments by reeling in DNA in uniform steps. Cell. 2010; 142:544–55. [PubMed: 20723756]
43. Deindl S, Hwang WL, Hota SK, Blosser TR, Prasad P, et al. ISWI remodelers slide nucleosomes with coordinated multi-base-pair entry steps and single-base-pair exit steps. Cell. 2013; 152:442–52. [PubMed: 23374341]
44. Korolev S, Hsieh J, Gauss GH, Lohman TM, Waksman G. Major domain swiveling revealed by the crystal structures of complexes of *E. coli* Rep helicase bound to single-stranded DNA and ADP. Cell. 1997; 90:635–47. [PubMed: 9288744]
45. Velankar SS, Soultanas P, Dillingham MS, Subramanya HS, Wigley DB. Crystal structures of complexes of PcrA DNA helicase with a DNA substrate indicate an inchworm mechanism. Cell. 1999; 97:75–84. [PubMed: 10199404]
46. Singleton MR, Dillingham MS, Wigley DB. Structure and mechanism of helicases and nucleic acid translocases. Annu Rev Biochem. 2007; 76:23–50. [PubMed: 17506634]
47. Dechassa ML, Hota SK, Sen P, Chatterjee N, Prasad P, Bartholomew B. Disparity in the DNA translocase domains of SWI/SNF and ISW2. Nucleic Acids Res. 2012; 40:4412–21. [PubMed: 22298509]
48. Elsässer SJ, Huang H, Lewis PW, Chin JW, Allis CD, Patel DJ. DAXX envelops a histone H3.3–H4 dimer for H3.3-specific recognition. Nature. 2012; 491:560–65. [PubMed: 23075851]
49. Saha A, Wittmeyer J, Cairns BR. Chromatin remodeling through directional DNA translocation from an internal nucleosomal site. Nat Struct Mol Biol. 2005; 12:747–55. [PubMed: 16086025]
50. Schwanbeck R, Xiao H, Wu C. Spatial contacts and nucleosome step movements induced by the NURF chromatin remodeling complex. J Biol Chem. 2004; 279:39933–41. [PubMed: 15262970]

51. Zofall M, Persinger J, Kassabov SR, Bartholomew B. Chromatin remodeling by ISW2 and SWI/SNF requires DNA translocation inside the nucleosome. Nat Struct Mol Biol. 2006; 13:339–46. [PubMed: 16518397]
52. Wysocka J, Swigut T, Xiao H, Milne TA, Kwon SY, et al. A PHD finger of NURF couples histone H3 lysine 4 trimethylation with chromatin remodelling. Nature. 2006; 442:86–90. [PubMed: 16728976]
53. Li H, Ilin S, Wang W, Duncan EM, Wysocka J, et al. Molecular basis for site-specific read-out of histone H3K4me3 by the BPTF PHD finger of NURF. Nature. 2006; 442:91–95. [PubMed: 16728978]
54. Thompson M. Polybromo-1: the chromatin targeting subunit of the PBAF complex. Biochimie. 2009; 91:309–19. [PubMed: 19084573]
55. Chandrasekaran R, Thompson M. Polybromo-L-bromodomains bind histone H3 at specific acetyl-lysine positions. Biochem Biophys Res Commun. 2007; 355:661–66. [PubMed: 17320048]
56. Goodwin GH, Nicolas RH. The BAH domain, polybromo and the RSC chromatin remodelling complex. Gene. 2001; 268:1–7. [PubMed: 11368894]
57. Taverna SD, Li H, Ruthenburg AJ, Allis CD, Patel DJ. How chromatin-binding modules interpret histone modifications: lessons from professional pocket pickers. Nat Struct Mol Biol. 2007; 14:1025–40. [PubMed: 17984965]
58. Patel DJ, Wang Z. Readout of epigenetic modifications. Annu Rev Biochem. 2013; 82:81–118. [PubMed: 23642229]
59. Eustermann S, Yang JC, Amos R, Chapman LM, Jelinska C, et al. Combinatorial readout of histone H3 modifications specifies localization of ATRX to heterochromatin. Nat Struct Mol Biol. 2011; 18:777–82. [PubMed: 21666677]
60. Argentaro A, Chang J-C, Chapman LM, Kowalczyk MS, Gibbons RJ, et al. Structural consequences of disease-causing mutations in the ATRX-DNMT3-DNMT3L (ADD) domain of the chromatin-associated protein ATRX. Proc Natl Acad Sci USA. 2007; 104:11939–44. [PubMed: 17609377]
61. Smolle M, Venkatesh S, Gogol MM, Li H, Zhang Y, et al. Chromatin remodelers Isw1 and Chd1 maintain chromatin structure during transcription by preventing histone exchange. Nat Struct Mol Biol. 2012; 19:884–92. [PubMed: 22922743]
62. Maltby VE, Martin BJ, Schultze JM, Johnson I, Hentrich T, et al. Histone H3 lysine 36 methylation targets the Isw1b remodeling complex to chromatin. Mol Cell Biol. 2012; 32:3479–85. [PubMed: 22751925]
63. Chatterjee N, Sinha D, Lemma-Dechassa M, Tan S, Shogren-Knaak MA, Bartholomew B. Histone H3 tail acetylation modulates ATP-dependent remodeling through multiple mechanisms. Nucleic Acids Res. 2011; 39(21):9155–66. [PubMed: 21835776]
64. Skiniotis G, Moazed D, Walz T. Acetylated histone tail peptides induce structural rearrangements in the RSC chromatin remodeling complex. J Biol Chem. 2007; 282:20804–8. [PubMed: 17535815]
65. Hassan AH, Neely KE, Workman JL. Histone acetyltransferase complexes stabilize swi/snf binding to promoter nucleosomes. Cell. 2001; 104:817–27. [PubMed: 11290320]
66. Hassan AH, Prochasson P, Neely KE, Galasinski SC, Chandy M, et al. Function and selectivity of bromodomains in anchoring chromatin-modifying complexes to promoter nucleosomes. Cell. 2002; 111:369–79. [PubMed: 12419247]
67. Kasten M, Szerlong H, Erdjument-Bromage H, Tempst P, Werner M, Cairns BR. Tandem bromodomains in the chromatin remodeler RSC recognize acetylated histone H3 Lys14. EMBO J. 2004; 23:1348–59. [PubMed: 15014446]
68. VanDemark AP, Kasten MM, Ferris E, Heroux A, Hill CP, Cairns BR. Autoregulation of the rsc4 tandem bromodomain by gcn5 acetylation. Mol Cell. 2007; 27:817–28. [PubMed: 17803945]
69. Sen P, Ghosh P, Pugh BF, Bartholomew B. A new, highly conserved domain in Swi2/Snf2 is required for SWI/SNF remodeling. Nucleic Acids Res. 2011; 39:9155–66. [PubMed: 21835776]
70. Sen P, Vivas P, Dechassa ML, Mooney AM, Poirier MG, Bartholomew B. The SnAC domain of SWI/SNF is a histone anchor required for remodeling. Mol Cell Biol. 2013; 33:360–70. [PubMed: 23149935]

71. Lavigne M, Eskeland R, Azebi S, Saint-André V, Jang SM, et al. Interaction of HP1 and Brg1/Brm with the globular domain of histone H3 is required for HP1-mediated repression. PLoS Genet. 2009; 5:e1000769. [PubMed: 20011120]
72. Wu WH, Alami S, Luk E, Wu CH, Sen S, et al. Swc2 is a widely conserved H2AZ-binding module essential for ATP-dependent histone exchange. Nat Struct Mol Biol. 2005; 12:1064–71. [PubMed: 16299513]
73. Wu WH, Wu CH, Ladurner A, Mizuguchi G, Wei D, et al. N terminus of Swr1 binds to histone H2AZ and provides a platform for subunit assembly in the chromatin remodeling complex. J Biol Chem. 2009; 284:6200–7. [PubMed: 19088068]
74. Gangaraju VK, Bartholomew B. Dependency of ISW1a chromatin remodeling on extranucleosomal DNA. Mol Cell Biol. 2007; 27:3217–25. [PubMed: 17283061]
75. Kagalwala MN, Glaus BJ, Dang W, Zofall M, Bartholomew B. Topography of the ISW2-nucleosome complex: insights into nucleosome spacing and chromatin remodeling. EMBO J. 2004; 23:2092–104. [PubMed: 15131696]
76. Boyer LA, Latek RR, Peterson CL. The SANT domain: a unique histone-tail-binding module? Nat Rev Mol Cell Biol. 2004; 5:158–63. [PubMed: 15040448]
77. Grüne T, Brzeski J, Eberharter A, Clapier CR, Corona DF, et al. Crystal structure and functional analysis of a nucleosome recognition module of the remodeling factor ISWI. Mol Cell. 2003; 12:449–60. [PubMed: 14536084]
78. Yamada K, Frouws TD, Angst B, Fitzgerald DJ, DeLuca C, et al. Structure and mechanism of the chromatin remodelling factor ISW1a. Nature. 2011; 472:448–53. [PubMed: 21525927]
79. Ryan DP, Sundramoorthy R, Martin D, Singh V, Owen-Hughes T. The DNA-binding domain of the Chd1 chromatin-remodelling enzyme contains SANT and SLIDE domains. EMBO J. 2011; 30:2596–609. [PubMed: 21623345]
80. Sharma A, Jenkins KR, Heroux A, Bowman GD. Crystal structure of the chromo-helicase DNA-binding protein 1 (Chd1) DNA-binding domain in complex with DNA. J Biol Chem. 2011; 286(49):42099–104. [PubMed: 22033927]
81. Mueller-Planitz F, Klinker H, Ludwigsen J, Becker PB. The ATPase domain of ISWI is an autonomous nucleosome remodeling machine. Nat Struct Mol Biol. 2013; 20:82–89. [PubMed: 23202585]
82. Clapier CR, Cairns BR. Regulation of ISWI involves inhibitory modules antagonized by nucleosomal epitopes. Nature. 2012; 492:280–84. [PubMed: 23143334]
83. McKnight JN, Jenkins KR, Nodelman IM, Escobar T, Bowman GD. Extranucleosomal DNA binding directs nucleosome sliding by Chd1. Mol Cell Biol. 2011; 31:4746–59. [PubMed: 21969605]
84. Patel A, Chakravarthy S, Morrone S, Nodelman IM, McKnight JM, Bowman GD. Decoupling nucleosome recognition from DNA binding dramatically alters the properties of the Chd1 chromatin remodeler. Nucleic Acids Res. 2013; 41:1637–48. [PubMed: 23275572]
85. Udugama M, Sabri A, Bartholomew B. The INO80 ATP-dependent chromatin remodeling complex is a nucleosome spacing factor. Mol Cell Biol. 2010; 31:662–73. [PubMed: 21135121]
86. Kapoor P, Chen M, Winkler DD, Luger K, Shen X. Evidence for monomeric actin function in INO80 chromatin remodeling. Nat Struct Mol Biol. 2013; 20:426–32. [PubMed: 23524535]
87. Gerhold CB, Winkler DD, Lakomek K, Seifert FU, Fenn S, et al. Structure of actin-related protein 8 and its contribution to nucleosome binding. Nucleic Acids Res. 2012; 40:11036–46. [PubMed: 22977180]
88. Bartholomew B. Monomeric actin required for INO80 remodeling. Nat Struct Mol Biol. 2013; 20:405–7. [PubMed: 23552289]
89. Singh M, D'Silva L, Holak TA. DNA-binding properties of the recombinant high-mobility-group-like AT-hook-containing region from human BRG1 protein. Biol Chem. 2006; 387:1469–78. [PubMed: 17081121]
90. Aravind L, Landsman D. AT-hook motifs identified in a wide variety of DNA-binding proteins. Nucleic Acids Res. 1998; 26:4413–21. [PubMed: 9742243]

91. Wilsker D, Patsialou A, Dallas PB, Moran E. ARID proteins: a diverse family of DNA binding proteins implicated in the control of cell growth, differentiation, and development. Cell Growth Differ. 2002; 13:95–106. [PubMed: 11959810]
92. Wilsker D, Probst L, Wain HM, Maltais L, Tucker PW, Moran E. Nomenclature of the ARID family of DNA-binding proteins. Genomics. 2005; 86:242–51. [PubMed: 15922553]
93. Wang T, Zhang J, Zhang X, Tu X. Solution structure of SWI1 AT-rich interaction domain from *Saccharomyces cerevisiae* and its nonspecific binding to DNA. Proteins. 2012; 80:1911–17. [PubMed: 22488857]
94. Wilsker D, Patsialou A, Zumbrun SD, Kim S, Chen Y, et al. The DNA-binding properties of the ARID-containing subunits of yeast and mammalian SWI/SNF complexes. Nucleic Acids Res. 2004; 32:1345–53. [PubMed: 14982958]
95. Aravind L, Iyer LM. The SWIRM domain: A conserved module found in chromosomal proteins points to novel chromatin-modifying activities. Genome Biol. 2002; 3:research0039. [PubMed: 12186646]
96. Da G, Lenkart J, Zhao K, Shiekhattar R, Cairns BR, Marmorstein R. Structure and function of the SWIRM domain, a conserved protein module found in chromatin regulatory complexes. Proc Natl Acad Sci USA. 2006; 103:2057–62. [PubMed: 16461455]
97. Qian C, Zhang Q, Li S, Zeng L, Walsh MJ, Zhou MM. Structure and chromosomal DNA binding of the SWIRM domain. Nat Struct Mol Biol. 2005; 12:1078–85. [PubMed: 16299514]
98. Chandler RL, Brennan J, Schisler JC, Serber D, Patterson C, Magnuson T. ARID1a--DNA interactions are required for promoter occupancy by SWI/SNF. Mol Cell Biol. 2013; 33:265–80. [PubMed: 23129809]
99. Yoneyama M, Tochio N, Umehara T, Koshiba S, Inoue M, et al. Structural and functional differences of SWIRM domain subtypes. J Mol Biol. 2007; 369:222–38. [PubMed: 17428495]
100. Doerks T, Copley RR, Schultz J, Ponting CP, Bork P. Systematic identification of novel protein domain families associated with nuclear functions. Genome Res. 2002; 12:47–56. [PubMed: 11779830]
101. Shen X, Ranallo R, Choi C, Wu C. Involvement of actin-related proteins in ATP-dependent chromatin remodeling. Mol Cell. 2003; 12:147–55. [PubMed: 12887900]
102. Schubert HL, Wittmeyer J, Kasten MM, Hinata K, Rawling DC, et al. Structure of an actin-related subcomplex of the SWI/SNF chromatin remodeler. Proc Natl Acad Sci USA. 2013; 110:3345–50. [PubMed: 23401505]
103. Fenn S, Breitsprecher D, Gerhold CB, Witte G, Faix J, Hopfner KP. Structural biochemistry of nuclear actin-related proteins 4 and 8 reveals their interaction with actin. EMBO J. 2011; 30:2153–66. [PubMed: 21499228]
104. Cairns BR, Erdjument-Bromage H, Tempst P, Winston F, Kornberg RD. Two actin-related proteins are shared functional components of the chromatin-remodeling complexes RSC and SWI/SNF. Mol Cell. 1998; 2:639–51. [PubMed: 9844636]
105. Jha S, Dutta A. RVB1/RVB2: running rings around molecular biology. Mol Cell. 2009; 34:521–33. [PubMed: 19524533]
106. Nano N, Houry WA. Chaperone-like activity of the AAA^+ proteins Rvb1 and Rvb2 in the assembly of various complexes. Philos Trans R Soc B. 2013; 368:20110399.
107. Jónsson ZO, Jha S, Wohlschlegel JA, Dutta A. Rvb1p/Rvb2p recruit Arp5p and assemble a functional Ino80 chromatin remodeling complex. Mol Cell. 2004; 16:465–77. [PubMed: 15525518]
108. Davey CA, Sargent DF, Luger J, Mäder AW, Richmond TJ. Solvent mediated interactions in the structure of the nucleosome core particle at 1.9 Å resolution. J Mol Biol. 2002; 319:1097–113. [PubMed: 12079350]
109. Luger K, Mäder AW, Richmond RK, Sargent DF, Richmond TJ. Crystal structure of the nucleosome core particle at 2.8 Å resolution. Nature. 1997; 389:251–60. [PubMed: 9305837]
110. Flaus A, Owen-Hughes T. Mechanisms for ATP-dependent chromatin remodelling: farewell to the tuna-can octamer? Curr Opin Genet Dev. 2004; 14:165–73. [PubMed: 15196463]
111. Bowman GD. Mechanisms of ATP-dependent nucleosome sliding. Curr Opin Struct Biol. 2010; 20:73–81. [PubMed: 20060707]

112. Flaus A, Owen-Hughes T. Mechanisms for nucleosome mobilization. Biopolymers. 2003; 68:563–78. [PubMed: 12666181]
113. Ong MS, Richmond TJ, Davey CA. DNA stretching and extreme kinking in the nucleosome core. J Mol Biol. 2007; 368:1067–74. [PubMed: 17379244]
114. Aoyagi S, Hayes JJ. hSWI/SNF-catalyzed nucleosome sliding does not occur solely via a twist-diffusion mechanism. Mol Cell Biol. 2002; 22:7484–90. [PubMed: 12370295]
115. Strohner R, Wachsmuth M, Dachauer K, Mazurkiewicz J, Hochstadter J, et al. A “loop recapture” mechanism for ACF-dependent nucleosome remodeling. Nat Struct Mol Biol. 2005; 12:683–90. [PubMed: 16025127]
116. Lorch Y, Davis B, Kornberg RD. Chromatin remodeling by DNA bending, not twisting. Proc Natl Acad Sci U S A. 2005; 102(5):1329–32. [PubMed: 15677336]
117. Langst G, Becker PB. ISWI induces nucleosome sliding on nicked DNA. Mol Cell. 2001; 8(5): 1085–92. [PubMed: 11741543]
118. Narlikar GJ, Phelan ML, Kingston RE. Generation and interconversion of multiple distinct nucleosomal states as a mechanism for catalyzing chromatin fluidity. Mol Cell. 2001; 8:1219–30. [PubMed: 11779498]
119. Fan HY, He X, Kingson RE, Narlikar GJ. Distinct strategies to make nucleosomal DNA accessible. Mol Cell. 2003; 11:1311–22. [PubMed: 12769854]
120. Liu N, Peterson CL, Hayes JJ. SWI/SNF- and RSC-catalyzed nucleosome mobilization requires internal DNA loop translocation within nucleosomes. Mol Cell Biol. 2011; 31:4165–75. [PubMed: 21859889]
121. Narlikar GJ, Sundaramoorthy R, Owen-Hughes T. Mechanisms and functions of ATP-dependent chromatin-remodeling enzymes. Cell. 2013; 154:490–503. [PubMed: 23911317]
122. Lia G, Praly E, Ferreira H, Stockdale C, Tse-Dinh YC, et al. Direct observation of DNA distortion by the RSC complex. Mol Cell. 2006; 21:417–25. [PubMed: 16455496]
123. Sirinakis G, Clapier CR, Gao Y, Viswanathan R, Cairns BR, Zhang Y. The RSC chromatin remodelling ATPase translocates DNA with high force and small step size. EMBO J. 2011; 30:2364–72. [PubMed: 21552204]
124. Zhang Y, Smith CL, Saha A, Grill SW, Mihardja S, et al. DNA translocation and loop formation mechanism of chromatin remodeling by SWI/SNF and RSC. Mol Cell. 2006; 24:559–68. [PubMed: 17188033]
125. Kassabov SR, Zhang B, Persinger J, Bartholomew B. SWI/SNF unwraps, slides, and rewraps the nucleosome. Mol Cell. 2003; 11:391–403. [PubMed: 12620227]
126. Cote J, Peterson CL, Workman JL. Perturbation of nucleosome core structure by the SWI/SNF complex persists after its detachment, enhancing subsequent transcription factor binding. Proc Natl Acad Sci USA. 1998; 95:4947–52. [PubMed: 9560208]
127. Kassabov SR, Henry NM, Zofall M, Tsukiyama T, Bartholomew B. High-resolution mapping of changes in histone--DNA contacts of nucleosomes remodeled by ISW2. Mol Cell Biol. 2002; 22:7524–34. [PubMed: 12370299]
128. Simon MD, Chu F, Racki LR, de la Cruz CC, Burlingame AL, et al. The site-specific installation of methyl-lysine analogs into recombinant histones. Cell. 2007; 128:1003–12. [PubMed: 17350582]
129. Racki LR, Narlikar GJ. ATP-dependent chromatin remodeling enzymes: Two heads are not better, just different. Curr Opin Genet Dev. 2008; 18:137–44. [PubMed: 18339542]
130. Racki LR, Yang JG, Naber N, Partensky PD, Acevedo A, et al. The chromatin remodeller ACF acts as a dimeric motor to space nucleosomes. Nature. 2009; 462:1016–21. [PubMed: 20033039]
131. Gangaraju VK, Prasad P, Srour A, Kagalwala MN, Bartholomew B. Conformational changes associated with template commitment in ATP-dependent chromatin remodeling by ISW2. Mol Cell. 2009; 35:58–69. [PubMed: 19595716]
132. Erdel F, Schubert T, Marth C, Längst G, Rippe K. Human ISWI chromatin-remodeling complexes sample nucleosomes via transient binding reactions and become immobilized at active sites. Proc Natl Acad Sci USA. 2010; 107:19873–78. [PubMed: 20974961]

133. Rippe K, Schrader A, Riede P, Strohner R, Lehmann E, Längst G. DNA sequence-and conformation-directed positioning of nucleosomes by chromatin-remodeling complexes. Proc Natl Acad Sci USA. 2007; 104:15635–40. [PubMed: 17893337]

134. Yang JG, Madrid TS, Sevastopoulos E, Narlihar GJ. The chromatin-remodeling enzyme ACF is an ATP-dependent DNA length sensor that regulates nucleosome spacing. Nat Struct Mol Biol. 2006; 13:1078–83. [PubMed: 17099699]

135. Dang W, Kagalwala MN, Bartholomew B. Regulation of ISW2 by concerted action of histone H4 tail and extranucleosomal DNA. Mol Cell Biol. 2006; 26:7388–96. [PubMed: 17015471]

136. Tsukiyama T, Palmer J, Landel CC, Shiloach J, Wu C. Characterization of the imitation switch subfamily of ATP-dependent chromatin-remodeling factors in *Saccharomyces cerevisiae*. Genes Dev. 1999; 13:686–97. [PubMed: 10090725]

137. Vary JC Jr, Gangaraju VJ, Qin J, Landel CC, Kooperberg C, et al. Yeast Isw1p forms two separable complexes in vivo. Mol Cell Biol. 2003; 23:80–91. [PubMed: 12482963]

138. Engeholm M, de Jager M, Flaus A, Brenk R, van Noort J, Owen-Hughes T. Nucleosomes can invade DNA territories occupied by their neighbors. Nat Struct Mol Biol. 2009; 16:151–58. [PubMed: 19182801]

139. Chaban Y, et al. Structure of a RSC-nucleosome complex and insights into chromatin remodeling. Nat Struct Mol Biol. 2008; 15(12):1272–7. [PubMed: 19029894]

140. Leschziner AE, et al. Conformational flexibility in the chromatin remodeler RSC observed by electron microscopy and the orthogonal tilt reconstruction method. Proc Natl Acad Sci U S A. 2007; 104(12):4913–8. [PubMed: 17360331]

141. Gkikopoulos T, Havas KM, Dewar J, Owen-Hughes T. SWI/SNF and Asf1p cooperate to displace histones during induction of the *Saccharomyces cerevisiae* HO promoter. Mol Cell Biol. 2009; 29:4057–66. [PubMed: 19470759]

142. Boeger H, Griesenbeck J, Strattan JS, Kornberg RD. Nucleosomes unfold completely at a transcriptionally active promoter. Mol Cell. 2003; 11:1587–98. [PubMed: 12820971]

143. Garcia JF, et al. Combinatorial, site-specific requirement for heterochromatic silencing factors in the elimination of nucleosome-free regions. Genes Dev. 2010; 24(16):1758–71. [PubMed: 20675407]

144. Lorch Y, Maier-Davis B, Kornberg RD. Chromatin remodeling by nucleosome disassembly in vitro. Proc Natl Acad Sci U S A. 2006; 103(9):3090–3. [PubMed: 16492771]

145. Wippo CJ, Israel L, Watanabe S, Hochheimer A, Peterson CL, Korber P. The RSC chromatin remodelling enzyme has a unique role in directing the accurate positioning of nucleosomes. EMBO J. 2011; 30:1277–88. [PubMed: 21343911]

146. Corona DF, Clapier CR, Becker PB, Tamkun JW. Modulation of ISWI function by site-specific histone acetylation. EMBO Rep. 2002; 3:242–47. [PubMed: 11882543]

147. Shogren-Knaak M, Ishii H, Sun JM, Pazin MJ, Davie JR, Peterson CL. Histone H4-K16 acetylation controls chromatin structure and protein interactions. Science. 2006; 311:844–47. [PubMed: 16469925]

148. Smith CL, Peterson CL. A conserved Swi2/Snf2 ATPase motif couples ATP hydrolysis to chromatin remodeling. Mol Cell Biol. 2005; 25:5880–92. [PubMed: 15988005]

149. Hsu DS, Kim ST, Sun Q, Sancar A. Structure and function of the UvrB protein. J Biol Chem. 1995; 270:8319–27. [PubMed: 7713940]

150. Moolenaar GF, Visse R, Ortiz-Buysse M, Goosen N, van de Putte P. Helicase motifs V and VI of the *Escherichia coli* UvrB protein of the UvrABC endonuclease are essential for the formation of the preincision complex. J Mol Biol. 1994; 240:294–307. [PubMed: 8035457]

151. Patel A, McKnight JN, Genzor P, Bowman GD. Identification of residues in chromo-helicase DNA-binding protein 1 (Chd1) required for coupling ATP hydrolysis to nucleosome sliding. J Biol Chem. 2011; 286:43984–93. [PubMed: 22039057]

152. Kadam S, McAlpine GS, Phelan ML, Kingson RE, Jones KA, Emerson BM. Functional selectivity of recombinant mammalian SWI/SNF subunits. Genes Dev. 2000; 14:2441–51. [PubMed: 11018012]

153. Phelan ML, Sif S, Narlikar GJ, Kingson RE. Reconstitution of a core chromatin remodeling complex from SWI/SNF subunits. Mol Cell. 1999; 3:247–53. [PubMed: 10078207]

154. He X, Fan HY, Narlikar GJ, Kingson RE. Human ACF1 alters the remodeling strategy of SNF2h. J Biol Chem. 2006; 281:28636–47. [PubMed: 16877760]

155. He X, Fan HY, Garlick JD, Kingston RE. Diverse regulation of SNF2h chromatin remodeling by noncatalytic subunits. Biochemistry. 2008; 47:7025–33. [PubMed: 18553938]

156. Staahl BT, Tiang J, Wu W, Sun A, Gitler AD. Kinetic analysis of npBAF to nBAF switching reveals exchange of SS18 with CREST and integration with neural developmental pathways. J Neurosci. 2013; 33:10348–61. [PubMed: 23785148]

157. Vogel-Ciernia A, Matheos DP, Barrett RM, Kramár EA, Azzawi S, et al. The neuron-specific chromatin regulatory subunit BAF53b is necessary for synaptic plasticity and memory. Nat Neurosci. 2013; 16:552–61. [PubMed: 23525042]

158. Romero OA, Sanchez-Cespedes M. The SWI/SNF genetic blockade: effects in cell differentiation, cancer and developmental diseases. Oncogene. 2013 In press.

159. Shain AH, Pollack JR. The spectrum of SWI/SNF mutations, ubiquitous in human cancers. PLoS ONE. 2013; 8:e55119. [PubMed: 23355908]

160. Sif S, Stukenberg PT, Kirschner MW, Kingson RE. Mitotic inactivation of a human SWI/SNF chromatin remodeling complex. Genes Dev. 1998; 12:2842–51. [PubMed: 9744861]

161. Muchardt C, Reyes JC, Bourachot B, Leguoy E, Yaniv M. The hbrm and BRG-1 proteins, components of the human SNF/SWI complex, are phosphorylated and excluded from the condensed chromosomes during mitosis. EMBO J. 1996; 15:3394–402. [PubMed: 8670841]

162. Kim JH, Saraf A, Florens L, Washburn M, Workman JL. Gcn5 regulates the dissociation of SWI/SNF from chromatin by acetylation of Swi2/Snf2. Genes Dev. 2010; 24:2766–71. [PubMed: 21159817]

163. Zhang Y, Cheng MB, Zhang YJ, Zhong X, Dai H, et al. A switch from hBrm to Brg1 at IFNγ-activated sequences mediates the activation of human genes. Cell Res. 2010; 20:1345–60. [PubMed: 21079652]

164. Ferreira R, Eberharter A, Bonaldi T, Chioda M, Imhof A, Becker PB. Site-specific acetylation of ISWI by GCN5. BMC Mol Biol. 2007; 8:73. [PubMed: 17760996]

165. Hall MA, Shundrovsky A, Bai L, Fulbright RM, Lis JT, Wang MD. High-resolution dynamic mapping of histone-DNA interactions in a nucleosome. Nat Struct Mol Biol. 2009; 16:124–29. [PubMed: 19136959]

Related Resources

1. http://www.lifesci.dundee.ac.uk/groups/tom_owen-hughes/showcase/worming.mov
2. http://www.lifesci.dundee.ac.uk/groups/tom_owen-hughes/showcase/bulging.mov

Summary Points

1. The helicase domains in chromatin remodelers are distinct between one subfamily and another and probably reflect the finely tuned properties that are unique to each subfamily. Many subfamily-specific features reside in the protusion regions of the helicase domain.
2. Helicase domains of several remodelers begin to translocate on DNA near the center of nucleosomes, and their orientation on nucleosomes can help determine their effects on nucleosome structure.
3. Many remodelers are recruited to chromatin by domains that recognize histone modifications and can be combined to target their binding. The interactions of the histone recognition domain also appear to contribute to the catalytic efficiency of remodeling, independently of recruitment effects such as those observed with H3 tail acetylation, RSC and SWI/SNF. Domains that bind to globular histone regions can serve as crucial anchors for the helicase domain and probably help create a sufficient pulling force to disrupt histone--DNA interactions (one example is the SnAC domain).
4. Protein--protein interactions with the helicase domain regulate substrate binding, ATP hydrolysis, and/or DNA translocation. An example of this is the two domains in the catalytic subunit of ISWI (AutoN and NegC).
5. In addition to structural determination by X-ray crystallography, cryo-EM, and modeling, site-directed cross-linking approaches effectively map the subunits and domains of remodelers that are associated with specific sites in DNA and histone octamer when remodelers are bound to nucleosomes.
6. Some protein domains such as SLIDE in Isw2 can be important for complex assembly, binding to linker DNA, and facilitating DNA entering into nucleosomes during remodeling. Some amount of DNA torsional strain is required to trigger the entry of DNA into nucleosomes and accounts for the ~7- and ~3-bp kinetic step sizes of the ISW2 and ACF complexes.
7. The combinatorial arrangement of accessory subunits can have significant effects on the remodeling activities of these complexes and their diverse operations. The accessory subunits may have histone or DNA recognition modules for changing recruitment patterns or may modify the ability to mobilize or space nucleosomes.
8. Mutations in accessory subunits or in conserved domains of the catalytic subunits of chromatin remodelers are often associated with neurological and development disorders and diseases such as cancer.

Future Issues

1. We need a better understanding of the functional roles of many accessory subunits and proteins domains in reorganizing chromatin. Investigators should focus on their effects on recruitment, regulation of the helicase domain activities, mobilization of nucleosomes, exchange of histone variants, and displacement.
2. Further research with a combination of ensemble and single-molecule techniques will be crucial to improving our understanding of the mechanics of chromatin remodeling. Nucleosome mobilization is a complex process, and there are more autoregulation and feedback mechanisms than originally envisioned.
3. It will be important to investigate the effects of chromatin structure on nucleosome remodeling at a higher level than that of mononucleosomes, as has been done in a few studies of model dinucleosome substrates. More research is needed to understand how subunit interactions with different linker DNAs in a dinucleosome can contribute to the remodeling and spacing activities of such complexes as ISW1a.
4. The contributions of ATP-dependent chromatin remodelers to nucleosome assembly, and how they collaborate with histone chaperones, should be further studied. It will be imperative to understand the interplay between remodelers and histone chaperones, the balance between them, and the potential importance of context. In particular, the role of chromatin remodelers in heterochromatin formation at centromeres and telomeres needs to be further investigated.
5. Recent genomic studies that have found mutations in chromatin remodeler subunits to be potential drivers in various cancers and neurological disorders have highlighted the need to understand (*a*) the roles of subunits such as PBRM1/polybromo1 and ARID1a/1b in SWI/SNF remodeling and (*b*) how mutations in these subunits could alter their functions.

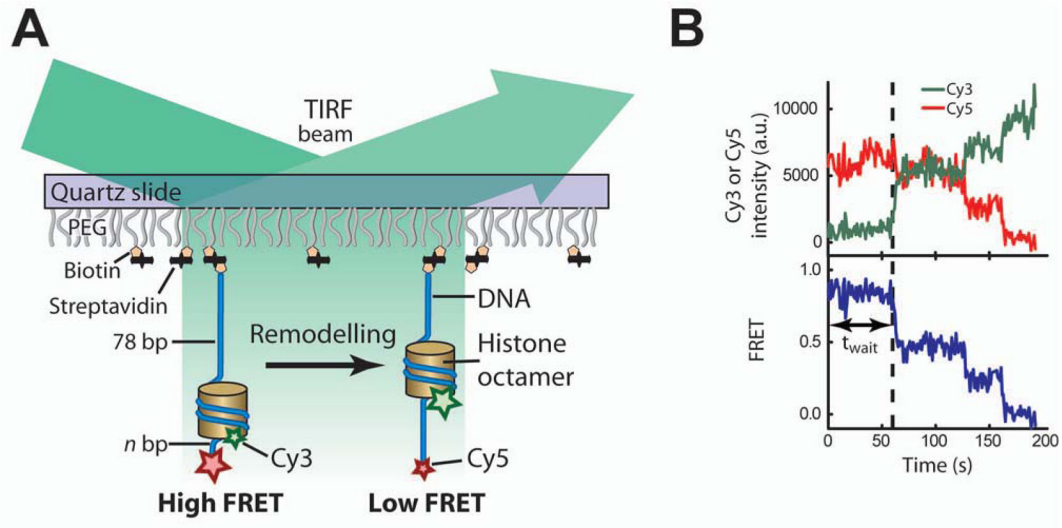

Figure 1.

Properties and domain organization of ATP-dependent chromatin remodelers. (*a*) The SF2 (*top*) and Snf2 (*bottom*) motifs found in the helicase domain, along with the insertion sites. The purple and light blue regions correspond to the two RecA-like regions, and the magenta regions correspond to the protusion and linker regions. The domain organization of the catalytic subunit for each of the five major classes of remodelers is shown. (*b*) Remodelers have four distinct properties. In the exchange reaction, the different H2A variant containing dimers are represented in gold and blue. The red oval in the assembly reaction represents the newly assembled nucleosome. (*c*) This model for the ATP-dependent movement of the helicase domain along DNA is based on crystal structures of PcrA. The purple and blue ovals represent the protein contacts with DNA from lobes 1 and 2, respectively.
Abbreviations: ATRX, α-thalassemia mental retardation syndrome X-linked; HSA, helicase/SANT-associated; PHD, plant homeodomain; Pi, inorganic phosphate; SnAC, SNF ATP coupling.

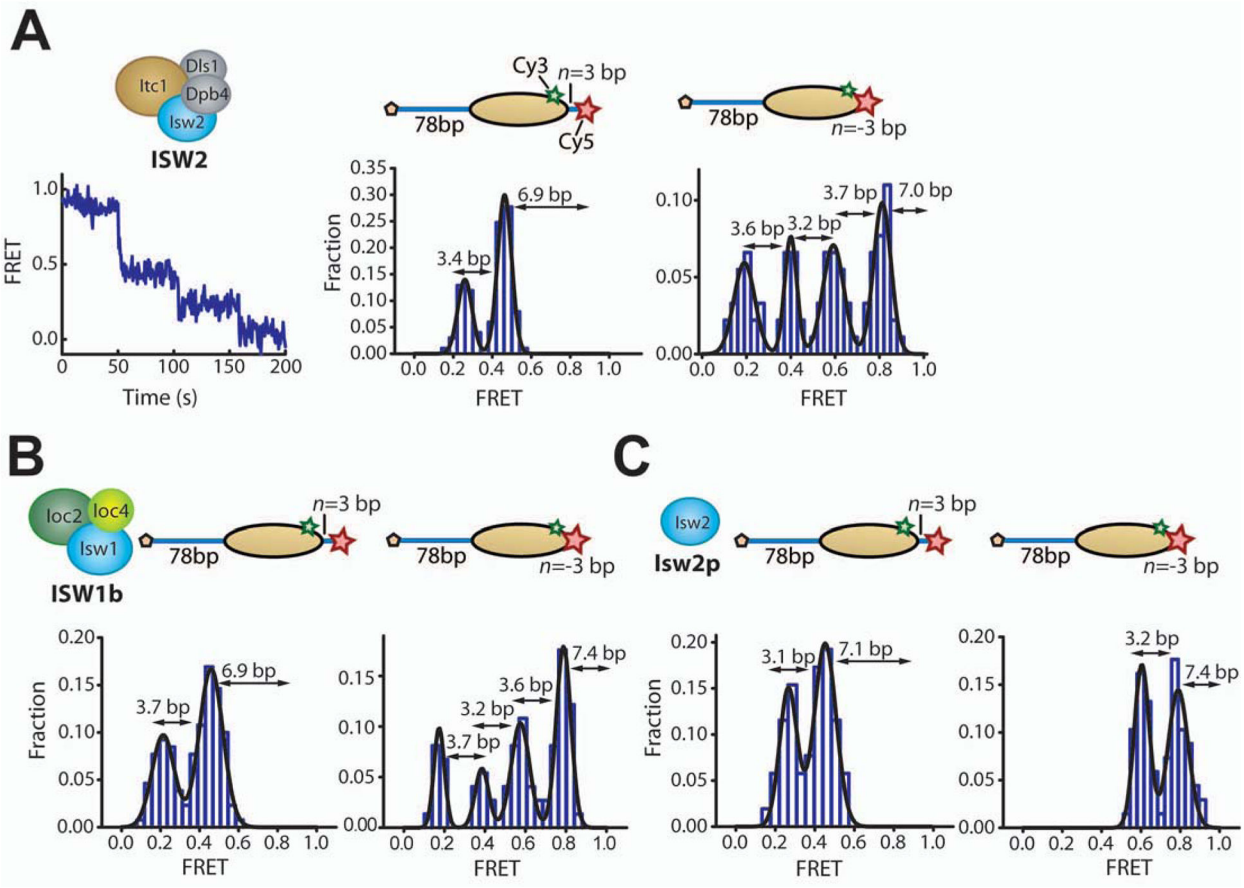

Figure 2.

Approaches for studying the dynamics of nucleosome remodeling and the interactions of remodelers with nucleosomes. (*a–d*) Single-molecule approaches. (*a*) DNA unzipping is used to precisely measure the strength of histone--DNA interactions throughout nucleosomes with near-base-pair resolution (159). (*b*) The magnetic tweezer and (*c*) dual optical trap techniques are used to measure the DNA translocation properties of nucleosome remodelers such as rates, processivity, and the ability to move against an opposing force. (*d*) Single-molecule fluorescence resonance energy transfer (smFRET) tracks the movement of DNA relative to the histone octamer by measuring the rate at which a modified site in the histone octamer (Cy3) is moved from a different modified site in DNA (Cy5) by changes in FRET efficiencies. Individual nucleosomes are observed through the technique of total internal reflection fluorescence (TIRF). (*e–g*) Site-directed cross-linking approaches. (*e*) In the first approach, photoreactive groups are incorporated at specific locations in DNA through either a nucleotide base or the phosphate backbone, and a DNA radiolabel is transferred to its protein target following cross-linking. The two other approaches incorporate different types of photoreactive groups into the histone octamer. (*f*) The photoreactive group is radioiodinated and is designed to cleave and transfer the radiolabel to the target by disulfide bond reduction. (*g*) This approach incorporates the photoreactive group at a histone site that is close to DNA and is intended to covalently link histone to

DNA. Such cross-links can be used to cleave the DNA at the cross-linked site to determine the location of the cross-link. Abbreviation: PEG, polyethylene glycol.

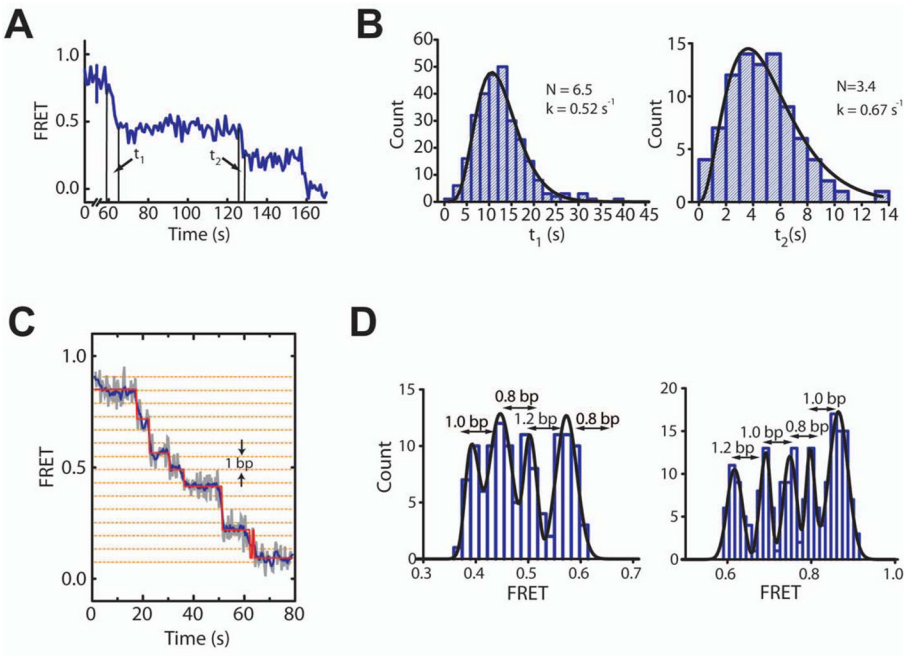

Figure 3.

Structural aspects of the ISW2, ISW1a, and SWI/SNF complexes. (*a*) This model of the interactions between the C terminus (gray) and helicase domain (blue) of Isw2 and the nucleosome is based on site-directed cross-linking between DNA and a remodeler, as depicted in Figure 2*e* (26). The HAND, SLIDE, and helicase domains are cross-linked to three regions in DNA. The cross-linked regions are colored magneta, and the red dots in the DNA indicate the sites of the DNA cross-linker. Because of the orientation, the region of the helicase domain cross-linked to DNA 17 and 18 bp from the dyad axis is not visible. (*b*) Two DNA molecules bind Ioc3 (*purple*) and the C terminus of Isw1 (*pink*). This binding is the basis for the suggestions that ISW1a binds external and internal linker DNA in a dinucleosome. (*c*) As demonstrated by cryo--electron microscopy yeast SWI/SNF contains a trough region (TB) flanked by a high wall (HW) and a low wall (LW), and blocked at one end by another wall (BW). (*d–f*) This model of a nucleosome bound into the trough region of SWI/SNF is based in part on the finding that SWI/SNF protects nearly one gyre of DNA (*red*) when bound (*f*). The SWI/SNF/nucleosome complex (*d–e*). (*g*) Four different subunits of SWI/SNF cross-link to different parts of the histone octamer when SWI/SNF binds to nucleosomes. (*h*) The interactions between specific subunits of SWI/SNF and nucleosomes in terms of the DNA gyre (*red dotted line*) and the histone octamer face (*green circle*). The colored dots represent specific sites that were probed by site-directed cross-linking (28). Panel *h* is based on the model depicted in panels *e* and *f*.

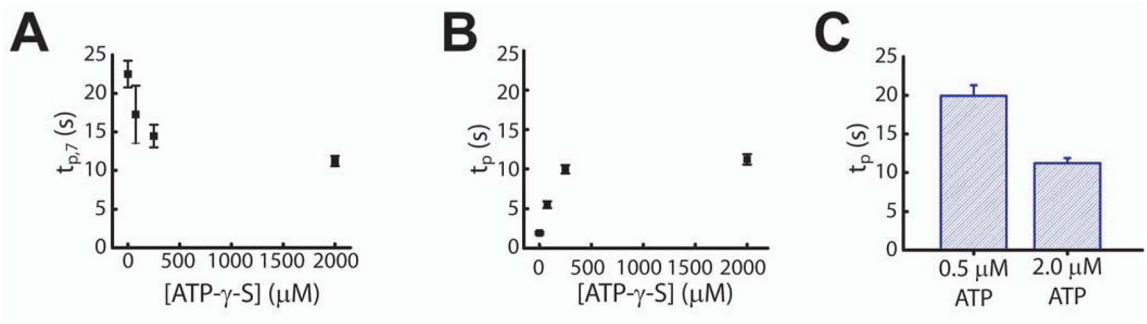

Figure 4.

Mechanisms for mobilizing nucleosomes. (*a*) The nucleosomal region where DNA gaps interfere. Two black lines represent DNA and the breaks in the black line represent the single—base pair gaps that interfere with NURF, ISW2 and SWI/SNF remodeling. The green box represents the location of the helicase domain. (*b*) The orientation of the helicase domain on nucleosomes is either on the exposed side of nucleosomal DNA (pull only) or between the DNA gyre and the histone octamer (pull and wedge). When the helicase domain tracks through DNA, there are two expected outcomes. (*c*) The dual helicase model, in which only one of the two helicases (*blue*) is bound at a time, depending on the linker DNA available at either side of the nucleosome. The arrows indicate the direction in which DNA moves. (*d*) The two strands of DNA are colored gold and blue, and the helicase domain is colored pink. First, the helicase domain moves DNA out of the exit side in 1-bp increments until a total of 7 bp has been moved. This movement causes a DNA strain between the helicase domain and the entry site, as demonstrated by underwinding DNA. The next step is the passage of 3 bp of DNA from the entry site, which releases some of the torsional strain. (*e*) The SLIDE domain is colored green, the helicase domain is colored blue, and additional protein--DNA contacts are colored gray. The movements of the helicase domain and the SLIDE domain are coordinated by two actions; the helicase domain pulling DNA and the SLIDE domain pushing DNA into nucleosomes. Abbreviation: SHL2, superhelical location 2.

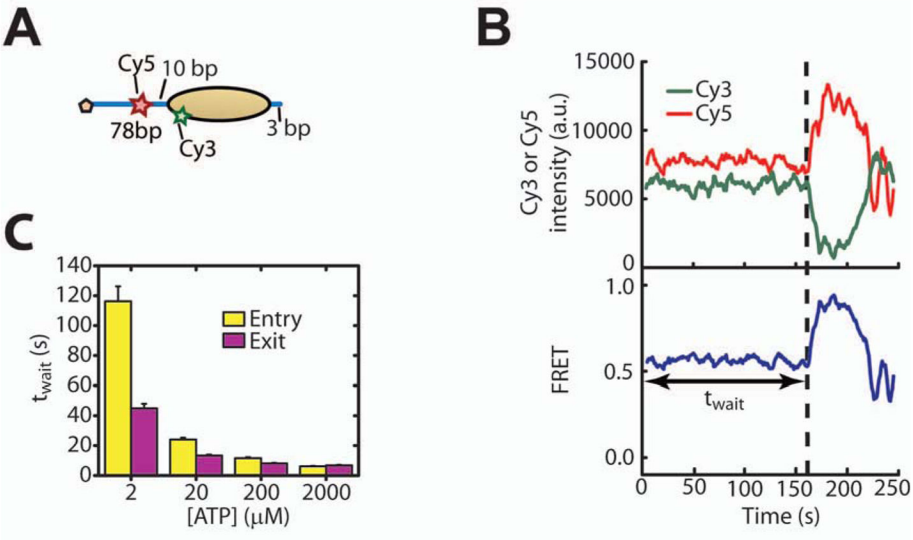

Figure 5.

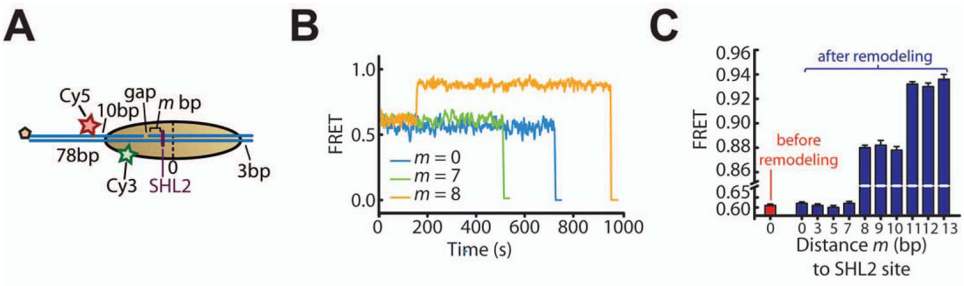

Figure 6.

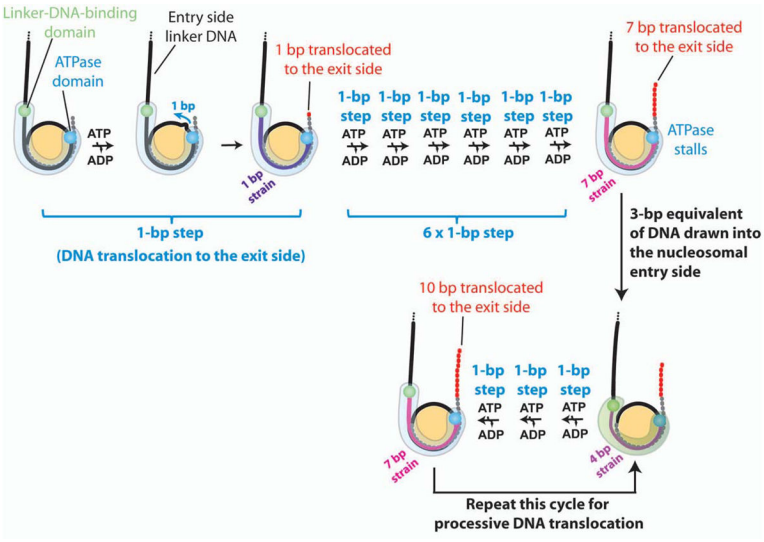

Figure 7.