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Mechanisms of ATP Dependent Chromatin Remodeling

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Abstract

The inter-relationship between DNA repair and ATP dependent chromatin remodeling has begun to become very apparent with recent discoveries. ATP dependent remodeling complexes mobilize nucleosomes along DNA, promote the exchange of histones, or completely displace nucleosomes from DNA. These remodeling complexes are often categorized based on the domain organization of their catalytic subunit. The biochemical properties and structural information of several of these remodeling complexes are reviewed. The different models for how these complexes are able to mobilize nucleosomes and alter nucleosome structure are presented incorporating several recent findings. Finally the role of histone tails and their respective modifications in ATP-dependent remodeling are discussed.

Keywords

chromatin remodeling; nucleosome; SWI/SNF; ISWI; CHD; INO80; SWR1; twist diffusion; bulge propagation; nucleosome spacing

Introduction

Nucleosomes are the fundamental unit of chromatin that are a highly compact and yet dynamic nucleoprotein complex. Nucleosomes are formed by wrapping ~147 bp of DNA around a histone octamer[1]. All DNA related processes in eukaryotes have to overcome the compaction of DNA by chromatin. Histone octamers which were long considered to be just a structural backbone or molecular spools have recently been found to be more dynamic and to have a regulatory role. The dynamic nature of chromatin is caused by two distinct mechanisms. The first kind involves covalent modifications of the histone N-terminal tails and occurs without the hydrolysis of ATP [2]. The second mode requires the hydrolysis of ATP and involves the movement of histone octamers relative to DNA in order to make the DNA accessible[3]. Even though these mechanisms are distinct, they are functionally interconnected inside the cell. In certain cases these two functions co-exist in the same complex or they exist in separate complexes that are both required for maximum opening of chromatin and activation of transcription, DNA replication and repair.

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Movement of nucleosomes along DNA has to overcome at least 100 contacts between the histone octamer and DNA[4]. A wide variety of nucleosome remodeling complexes exists inside the cell and hence it is possible to have a wide variety of mechanisms for nucleosome mobilization. Recent discoveries have shown that different chromatin remodeling complexes share a common mechanism for remodeling chromatin. First, we review the general properties of several of the different ATP remodeling families and second, examine the emerging view of the underlying mechanism of remodeling that is in common with these different remodelers.

Nucleosome remodeling complexes

SWI/SNF family

The discovery of chromatin remodeling factors started with that of SWI/SNF which is a ~11-subunit complex. It was originally identified as a regulator of mating type switching (SWI) or as a requirement for growth on energy sources other than sucrose (SNF – sucrose nonfermenting)[5-7]. In *S.cerevisiae*, as in *Drosophila* and humans, there appears to be two versions (SWI/SNF and RSC) of the SWI/SNF complex (Figures 1 and 2). RSC is more abundant in the cell than SWI/SNF and RSC is essential for cell growth while SWI/SNF is not. SWI/SNF and RSC have been shown to have distinct, non-overlapping roles. The catalytic subunit of yeast SWI/SNF is the Swi2 or Snf2 protein and its paralog in RSC is the Sth1 subunit [8]. RSC has also been shown to exist in two functionally distinct complexes that differ by containing either Rsc1 or 2 [9]. In *Drosophila* the two forms of SWI/SNF called BAP (Brahma associated proteins) and PBAP (Polybromo-associated BAP) both contain the same catalytic subunit (Brahma), but are distinguished by BAP containing the OSA subunit and PBAF containing the Polybromo and BAP170 subunits[10]. Although human SWI/SNF can be characterized as being of two forms, namely BAF (BRG1/hBRM-Associated Factors) and PBAF (Polybromo-associated BAF), there are many forms of human SWI/SNF that acquire tissue-specific subunits[11] or additional sub-complexes in which the SWI/SNF-type remodelers are associated with other factors such as BRCA1 [12,13], components of the histone deacetylase Sin3 complex [14] and histone methylases [15,16]. Recently, Rtt102p was identified as the newest subunit of both SWI/SNF and RSC complexes by MudPIT or mass spectrometry analysis[17]. The loss of RTT102 created similar phenotypes consistent with the loss of other SWI/SNF subunits[18]. The role of SWI/SNF by all indications is far reaching. In mammals it is involved in many developmental programs such as muscle [19-22], heart [23], blood[24], skeletal[25], neuron[26-29], adipocyte [30], liver[31] and immune system/T-cell development[32,33]. Yeast SWI/SNF has been shown to be involved in an early step in homologous recombination (HR) while RSC promotes HR at the stage of strand invasion [34,35]. RSC is involved in sister chromatid cohesion and chromosome segregation[36-38]. SWI/SNF has an impact on alternative splicing as BRM has been shown to regulate the crosstalk of RNA polymerase II (Pol II) with RNA processing enzymes by reducing the rate of Pol II elongation to promote splicing of less than optimal splice sites [39]. Telomeric silencing and silencing transcription of rRNA genes by RNA polymerase II also requires yeast SWI/SNF[40].

Several structural domains have been identified for the subunits of SWI/SNF that have been indicated to have either DNA or histone binding activity and could conceivably help SWI/SNF to grip the nucleosome for efficient restructuring of the nucleosome[10] (Figure 3). The ATPase domain consists of seven subdomains that structurally forms two lobes referred to as the DEXD and helicase motifs that form a cleft to which DNA binds based on X-ray crystal structure from the related Rad54 ATPase domain[41,42]. In addition the Swi2/Snf2 protein contains at its C-terminus a bromo domain which has been shown to recognize specific acetylated lysines in histone tails[43-50]. The Swi1 contains an ARID domain (an AT-rich interaction domain) that is found in its orthologs OSA in Drosophila and BAF250 in mammals. It is also found in the Rsc9 subunit of RSC and BAP170 for mammals. The ARID domain, sometimes referred to as

the BRIGHT domain (B-cell-specific trans-activator of IgH transcription), has been demonstrated to have both sequence specific as well as sequence independent DNA binding activity[51-55]. The ARID domain forms a helix-turn helix structure that prefers to bind AT rich DNA. The ARID domain in the Dead ringer protein has been shown to have DNA-sequence specific binding; whereas ARID from OSA binds DNA with no sequence specificity [51,55-57]. The ARID domain from yeast Swi1 is not a typical member of the ARID family, because it likely has weaker DNA binding affinity due to changes in key residues that normally interact with the major groove of DNA[58]. Swi3 has two known domains that have affinity for nucleosomes and DNA that are called SWIRM and SANT. SWIRM is a conserved domain of about 85 residues that is found in Rsc8 and Moira, respectively the paralog and ortholog of Swi3, as well as in Ada2, a component of a histone acetyltransferase complex (HAT) and LSD1/BHC110, a histone demethylase[59-61]. The SWIRM domain of Swi3 is essential for proper assembly of Swi3 into SWI/SNF and is required in vivo for SWI/SNF activity. The SWIRM domain was shown to bind DNA and mononucleosomes with comparable high affinity. SANT domain is found in several ATP-dependent chromatin remodeling complexes such as RSC and ISWI, and in histone modifying enzymes Ada2, NCoR that interacts with HDAC and Sin3, and SPR1 from *C. elegans* that is part of the co-repressor complex that is essential for HDAC1 activation[62-67]. The SANT domain is also present in other repressor complexes such as MLL, SMRT and some members of the polycomb group of proteins and has been shown to stimulate binding to histone tails[68-70]. The SANT domain contains ~50 residues and is structurally related to the c-Myb DNA binding domain [71]. It has three alpha helices containing bulky aromatic residues in a helix-turn-helix arrangement. Structural and biochemical data of the SANT domain in ISWI from Drosophila indicates that the SANT domain may bind to histones[72].

ISWI family

The first members of this growing group of chromatin remodeling enzymes, dNURF and dCHRAC, were originally identified by biochemical characterization from *Drosophila* embryo extracts using an in vitro assay for activities allowing transcription factor access to sites in nucleosomal arrays [73,74]. Later multiple additional remodelers belonging to this group were identified in yeast[75], humans[76,77], mouse[78], and *Xenopus*[79] (Figure 2). The ATPase subunit of this group of chromatin remodeling enzymes has been named Imitation SWItch (ISWI) because of its similarity to the SWI2 ATPase in the SNF2 subfamily. Characteristic of the ISWI type ATPases is the presence of a SANT (SWI3, ADA2, N-CoR and TFIIIB B") domain and the absence of a bromodomain[80]. The SANT domain is similar to the putative DNA binding domains of the ADA HAT complexes, the transcriptional co-repressor N-CoR and the transcription factor TFIIIB [81]. This has prompted speculations that the SANT domain might be responsible for the nonspecific binding of ISWI complexes to DNA and their preferential binding to nucleosomes containing linker DNA over core nucleosomes [82]. The complexes in this group are relatively smaller (300-800 kDa) and contain fewer subunits ranging from 2-4 as compared with the larger complexes in the SNF2, CHD and INO80 subfamilies which contain up to 15 subunits and are often ~2 mDa.

In *Drosophila*, ISWI is assembled into three distinct complexes: NURF, ACF and CHRAC. NURF(Nucleosome Remodeling Factor) is a four subunit complex containing BPTF/Nurf301, ISWI, Nurf-55 and Nurf-38 [73]. NURF was first identified by its requirement for making the *hsp70* heat shock promoter accessible in the presence of the GAGA transcription factor [83]. This duo was also shown to activate the *fushi tarazu* gene[84]. The ATPase activity of this complex is specifically stimulated by nucleosomes and not DNA, in contrast to the SWI/SNF complex where DNA and nucleosomes equally stimulate the ATPase activity. NURF interacts with the histone H4 N-terminal tail and this interaction is essential for its ATPase and nucleosome mobilization activity [85]. Using alanine scanning mutagenesis, residues 16

through 19 (KRHR) in the N-terminal tail of histone H4 were shown to be important for nucleosome mobilization by NURF[86]. NURF has been shown to activate transcription in vitro[87] and in vivo. NURF also appears to have a role in X chromosome morphology[88] and steroid signaling during larval to pupal metamorphosis[89]. Transcriptional activation by NURF is brought about by mobilizing nucleosomes along the DNA [90] which requires the largest subunit of NURF, NURF 301[91]. The direction of nucleosome mobilization is modulated by transcription factor Gal4[92].

ISWI in *Drosophila* forms another multisubunit complex called ACF (ATP-utilizing chromatin factor) which can processively deposit histone octamers along the DNA to form long periodic arrays of nucleosomes[93,94]. ACF mediated chromatin assembly also requires the histone chaperone NAP1. Non-histone architectural protein HMGB1 was found to regulate ACF remodeling activity by acting as a DNA chaperone that can facilitate rate limiting distortion of DNA. ACF translocates along DNA in the process of chromatin assembly [95]. Acf1 plays an important role in development as Acf1 null mutants were found to die during larval to pupal transition[96]. Biochemical experiments have shown that ACF/CHRAC is a major chromatin assembly protein in *Drosophila*. Cells lacking ACF/CHRAC more rapidly proceed through S phase due to the lack of resistance from chromatin consistent with these complexes functioning in the formation of repressive chromatin.

CHRAC (chromatin accessibility complex) has ISWI, Acf1 and two small histone fold containing proteins CHRAC-14 and CHRAC-16[74]. CHRAC can also generate nucleosome arrays with regular spacing. The two small subunits, CHRAC-14 and CHRAC-16, were shown to be involved in early *Drosophila* development[97].

In *S.cerevisiae* there are two ISWI genes - *ISW1* and *ISW2* (reviewed in [98]) which were identified based on their extensive homology with dISWI [75]. Isw1p forms two distinct complexes inside the cell – ISW1a (contains Isw1p, Ioc3p) and ISW1b (Isw1p, Ioc2p and Ioc4p)[99]. ISW1a shows a strong nucleosome spacing activity while ISW1b does not. Isw2p was found to be associated with a 140 kDa protein referred to as Itc1p which appears to be partially related to the Acf1 protein sharing the structural domains WAC, WAKZ, PHD fingers, DDT and bromodomain motifs. ISW2 also has two additional smaller subunits Dpb4 and Dls1 that have histone fold domains and are homologs respectively of the hCHRAC 15/17 and the dCHRAC 14/16 histone fold of protein pairs from the human and *Drosophila* CHRAC complexes, respectively. ISW2 has a nucleosome spacing activity that is not as tightly regulated as ISW1a and ISW2 has no detectable nucleosome disruption activity [75,100]. These similarities suggest that ISW2may be viewed as a yeast CHRAC homolog underscoring the extensive organizational and functional conservation of chromatin remodeling complexes from divergent species.

A number of structural domains have been identified in both the catalytic subunit and accessory subunits of this class. Besides the conserved Swi2/Snf2 ATPase domain, ISWI contains the SANT, SLIDE (SANT-like ISWI *d*omain), HAND and AID (Acf1 interaction domain) domains [80]. The SANT and SLIDE domains are connected by a highly conserved spacer helix. The SLIDE domain was found to mediate the DNA binding activity of ISWI. Deletion of either the SANT or SLIDE domains did not affect binding to nucleosomes, while deletion of both adversely affected binding. The ‘C’ terminus of ISWI is therefore vital for nucleosome recognition. Deletion of SLIDE also largely abolished the ATPase activity of ISWI. Acf1 contains WAC (WSTF, Acf1, cbp146p), WAKZ (WSTF, Acf1, KIAA0314, ZK783.4), DDT (DNA binding homeobox and Different Transcription factors), BAZ , two PHD (Plant homeodomain) fingers and a bromodomain[101]. The two PHD fingers were found to increase the efficiency of nucleosome mobilization by ACF in Drosophila [102]. Isw1p and Isw2p of *S.cerevisiae* share the same domain organization as dISWI except that the AID domain is absent

in the yeast counterparts. Itc1p is partially related to Acf1 of ACF complex in Drosophila. Ioc3 (Imitation switch one complex 3) of ISW1a complex has no detectable domain organization, while Ioc2 and Ioc4 of ISW1b complex have PHD and PWWP domains respectively[99].

CHD family

CHD-1 (chromodomain-helicase DNA binding protein [103]) was first isolated from mouse as a protein which contains features of both the Swi2/Snf2 family of ATPases and the Polycomb/HP1 chromodomain family of proteins[104]. In contrast to polycomb/HP1, CHD1 is not localized to condensed chromatin but possesses a minor groove DNA binding motif found in H1, HMG I/Y, D1 and datin [105]. Consequently, the *Drosophila* CHD1 homolog was found to be localized to interbands (extended chromatin regions) and puffs (regions of high transcriptional activity) on polytene chromosomes[106]. The chromo- and helicase-domains of CHD1 are required for its association with chromatin. CHD1 isolated from yeast was shown to be an ATP dependent nucleosome remodeling factor which can reposition nucleosomes along the DNA. Unlike SWI/SNF, nucleosome mobilization mediated by CHD1 does not expose large regions of nucleosomal DNA[107].

INO80 and SWR1 family

INO80 and SWR1 are both large complexes containing 15 and 14 different subunits, respectively that are involved in transcription activation and DNA repair. Ino80p, the largest subunit of the INO80 complex, contains a conserved ATPase/helicase domain. While the ATPase/helicase domain of other members of the SNF2 superfamily, such as Swi2/Snf2 and ISWI, are continuous, the ATPase/helicase domain of Ino80 and Swr1 are split by a large spacer region. Comparison of INO80 and its orthologs from human (hINO80) and Drosophila (dINO80) reveal two conserved regions, the TELY motif at the amino terminus and the GTIE motif at the carboxy terminus [108]. Actin (Act1) and three actin-related proteins, Arp4, Arp5 and Arp8, are associated with the complex in addition to Ino80. Two other subunits are present as multiple copies per Ino80 are Rvb1 and Rvb2 that were previously identified as ‘RuvB-like’ proteins with homology to the bacterial RuvB protein or the Holliday junction DNA helicase [108]. Glycerol gradient sedimentation of the purified INO80 complex showed that all of the polypeptides sedimented together as a high molecular weight complex, consistent with all 15 proteins belonging to the same complex [108]. Coomassie blue staining of INO80 shows that Rvb1 and Rvb2 have about 6 copies to one of Ino80 in the complex, corresponding well to the double hexamer composition of bacterial RuvB [108]. INO80 exhibits ATP dependent 3'-5' helicase activity likely due to the presence of Rvb1 and Rvb2. The SWR1 complex has in common with INO80 for subunits namely Rvb1, Rvb2, Act1 and Arp4. Yeast strains lacking INO80 not only have mis-regulated transcription, but also are hypersensitive to DNA-damaging agents suggesting that INO80 may not only regulate transcription but also facilitate DNA repair [109,110].

One of the earliest events correlated with the cell's response to DNA damage is the rapid phosphorylation of histone H2AX adjacent to the DNA break site[111]. There are no H2A variants in yeast, but H2A is phosphorylated on the homologous serine that is located four residues from the carboxy terminus in response to DNA damage and the phosphorylated species is referred to as γ-H2AX. Interestingly, recent studies have shown that there is a strong interaction between the INO80 complex and γ-H2AX. This interaction was stable under harsh conditions and provides a potential mechanism for the recruitment of the INO80 complex to double strand breaks[110]. Further analyses have suggested that actin and the Arps are not required for the interaction between INO80 and γ-H2AX, but instead is the Nhp10 subunit [109].

The composition of INO80 suggests it has additional roles in DNA repair through homologous recombination. Since INO80 contains Rvb1/2 belonging to AAA+ family ATPases, they could use their DNA helicase/tracking function to disrupt nucleosomes proximal to the break. Rvb1/Rvb2 could promote the migration of the Holliday structure, while the remodeling function of INO80 slides or transfers nucleosomes encountered during migration[112].

The discovery of Swr1 (Swi2/Snf2 related) complex has defined a new mode of ATP dependent chromatin remodeling – histone variant exchange (reviewed in [113,114]). Almost at the same time three groups discovered the existence of this ~13 subunit complex that interacts with the histone variant H2A.Z[115-117]. The catalytic subunit of this complex is Swr1 which has an ATPase domain related to Snf2. In vitro, SWR1 can catalyze ATP dependent replacement of H2A/H2B dimers with the H2A.Z/H2B dimers independent of replication[117]. In vivo, SWR1 is required for incorporation of H2A.Z at approximately 25 chromosomal locations scattered across the yeast genome [118]. Htz1 has a role in transcription and can also act as a barrier inhibiting spread of silent telomeric and mating locus heterochromatin into transcriptionally active regions. SWR1 dependent deposition of Htz1 was observed at telomeres (which requires Yaf9 component) [119], centromeres[120] and other intergenic regions[121]. Biochemical analyses have shown that Swc2 component binds Htz1 physically and is needed for Htz1 deposition[122]. SWR1 complex shares four subunits with NuA4 HAT and have been shown to work together in efficient blockage of spreading heterochromatin [123,124].

Mechanisms of nucleosome remodeling

Different outcomes of nucleosome mobilization – differences in step sizes

Both ISWI and SWI/SNF were shown to change the translational position of nucleosomes [125,126], but they seem to differ in their ability to disrupt nucleosomes. This difference is made most evident using a restriction endonuclease accessibility assay. SWI/SNF has been shown to make nucleosomal DNA accessible to endonuclease cutting presumably by the creation of DNA loops on the surface[127]. The increased accessibility of nucleosomal DNA caused by SWI/SNF remodeling occurs without moving the entire nucleosome from the particular DNA site to a new distal translational position in which the site would be located in the linker DNA region. ISWI complexes on the other hand appear not to make nucleosomal DNA accessible through the process of remodeling itself, but only do so as the entire nucleosome is moved far enough to place the DNA site into the linker DNA region. These differences are likely reflected in their differing roles in the cell since SWI/SNF generally makes nucleosomal DNA sites accessible to either transcription activators or repressors, while ISWI appears to be generally involved in moving nucleosomes in order to establish a repressive chromatin environment.

Evidence suggests that both of these complexes mobilize nucleosomes using a loop recapture type mechanism and thus both appear to create DNA bulges on the surface of the nucleosome as discussed later. The differences in remodeling outcomes could therefore be due to differences in the size of the DNA bulge created by these complexes and would likely be reflected in the step size of DNA moving through the nucleosome. Two different reports suggest that ISWI complexes have a small DNA step size of ~10 bp which would likely cause the formation of a small bulge on the surface of the nucleosome that would not be readily cleaved by DNA endonucleases. One study mapped the translational positioning before and during remodeling by NURF with hydroxyl radical footprinting and found that NURF moved the nucleosome in ten base pair steps[128]. Hydroxyl radical footprinting shows all the regions that are protected by the nucleosome, but it was possible to tract the location of the dyad axis of the nucleosome because the dyad had a rather distinctive footprint pattern. The one difficulty in this study was that nucleosomes were reconstituted on a DNA that had a high affinity for the histone octamer and that preferentially positioned the nucleosome to a single translational

position. The DNA would then likely constrain the nucleosome to be offset from its original position in 10 bp increments in order to maintain the preferred rotational phasing of the nucleosome. Thus the 10 bp increments observed in these studies may not reflect the intrinsic step size of NURF, but rather the thermodynamically preferred positioning of the nucleosome on this particular DNA sequence.

Another approach to map the step size of another ISWI complex (i.e ISW2) was to use a DNA that did not bind the nucleosome as tightly[129]. Second, the movement of the nucleosome was rapidly tracked such that it was possible to observe nucleosome movement after hydrolysis of a single ATP by ISW2. Fortuitously, the new nucleosome position seen under these rapid conditions was not a position on the DNA that was thermodynamically preferred to be bound by the nucleosome, thus helping to avoid the potential confusion of the observed nucleosome movement being due to the intrinsic property of the DNA template rather than that of ISW2. Reaction conditions were slowed by lowering the temperature and the ATP concentration such that ISW2 hydrolyzed 0.52 ATP per second making it possible to examine the early events of ISW2 remodeling. ISW2 moved nucleosomes 9 and 11 bp in the time it took to hydrolyze one ATP. These movements were found not to be thermodynamically preferred and would slip a few more bp farther from the original position to move nucleosomes a total of 14 and 16 bp. There was no evidence for single bp movements by ISW2 which is often considered to be a trademark of the twist diffusion model.

Similar experiments were done with SWI/SNF in which the reaction was slowed down so that SWI/SNF hydrolyzed 0.36 ATP per second [129]. Using the same DNA template as for the ISW2 experiments, SWI/SNF was found to move nucleosomes 52 bp from their original position with no other intermediates evident. The approach used to map nucleosome mobilization by SWI/SNF and ISW2 monitored the DNA contact point of residue 53 of histone H2B[125,126]. The site-directed mapping showed that for SWI/SNF there were two steps, the first being the loss of the H2B contact with DNA and then shortly afterwards its reappearance with DNA at a distance of 52 bp from it prior position. These data suggest that SWI/SNF may first peel off a large segment of DNA from the nucleosome surface which could be used to form a large DNA bulge. After this bulge has migrated along the surface of the nucleosome the contact with histone H2B would be restored as observed. The different step sizes of SWI/SNF and ISW2 had a striking similarity to their respective footprints on the nucleosome. ISW2 contacts ~10bp of nucleosomal DNA at SHL2 [130] while SWI/SNF contacts ~60bp of nucleosomal DNA from the entry site to SHL2 (JP and BB, unpublished data).

A Common Unifying Characteristic of ISWI and SWI/SNF Remodeling

Translocation along DNA that is driven by ATP hydrolysis of these enzymes is believed to be required for nucleosome mobilization. Recent discoveries have revealed key aspects of how DNA translocation is used to disrupt some of the over 100 histone-DNA contacts involved in the nucleosome architecture. An approach that has provided vital insight into this problem has been the identification of nucleosomal regions contacted by the remodeler followed by determination of those regions the remodeler needs to translocate along for remodeling to occur. High-resolution DNA footprinting has shown that ISW2 contacts three distinct regions on the nucleosome – the linker DNA, a 10 bp region inside the nucleosome at the entry/exit site, and a 10 bp region two helical turns from the dyad axis (SHL-2)(Figure 4)[130]. The site where DNA translocation is required for remodeling was determined by blocking translocation through the placement of 1 nucleotide (nt) gaps into DNA. A scanning approach was used to identify the region(s) at which the 1 nt gap would interfere with ISW2 remodeling. A set of nucleosomes were constructed with gapped DNA containing the 1 nt gap at different positions. These nucleosomes were remodeled by ISW2 and the remodeled nucleosomes were electrophoretically separated from the unremodeled nucleosomes. The distribution of DNA

gaps in the remodeled and unremodeled nucleosomes were compared to find the gap location (s) that were enriched in the unremodeled nucleosomes and thus those gaps that interfered with ISW2 remodeling. The striking result was that there was only one region where the 1 nt gap interfered with ISW2 remodeling coinciding with the region two helical turns from the dyad. This result was unexpected as it is more difficult to translocate along DNA far inside the nucleosome in which the flanking regions of DNA are firmly secured by extensive histone-DNA interactions than DNA either at the entry/exit sites of the nucleosome or linker DNA region. Similarly, translocation of the remodeler near the dyad axis has been found to be required for nucleosome mobilization by NURF[128], SWI/SNF[131], and RSC[132]. Yeast SWI/SNF was shown to have 3'-5'strand-specific translocation activity[129]. Although these ATP-dependent remodeling complexes have different outcomes in terms of nucleosome accessibility, they all have in common the requirement for DNA translocation near the dyad for nucleosome remodeling. DNA photoaffinity labeling studies with ISW2 and SWI/SNF have shown that the catalytic subunit of these complexes contacts nucleosomal DNA two helical turns from the dyad consistent with DNA translocation occurring at this site[130].

Two Models

There are two models as to how DNA translocation inside the nucleosome causes nucleosome movement. The first model proposes that DNA moves in 1 bp waves from the translocation site to the edge of the nucleosome (Figure 5C). The advantage of this model is it allows movement of DNA to the outside of the nucleosome without causing any large changes of the core nucleosome structure and the ease in which DNA torsional strain created by translocation can be released. Nucleosome crystallographic studies have found that the nucleosome can readily accommodate overtwisted DNA on its surface. However, data not consistent with this model has already been mentioned of nucleosome movement occurring in increments much larger than 1 bp. This model would also not be consistent with the ISW2 data mentioned earlier as the 1 nt gaps that interfere with remodeling were only in a ~20 bp region encompassing the internal contact site and 10 nts to one side of this site. If the 1 bp wave was required to propagate from the internal translocation site to the entry/exit site of the nucleosome then 1 nt gaps anywhere between these sites spanning a range of ~60 bps should interfere rather than the observed highly localized region.

A second model proposes that translocation of the remodeler synergistically functions in conjunction with other parts of the remodeler-nucleosome complex to create a DNA bulge of at least 10 bp on the nucleosome surface. The two prong approach for mobilizing nucleosomes by ISW2 would involve ISW2 interactions with linker DNA and the entry site associated with a conformational shift of ISW2 to promote the entry of extra DNA to release the DNA torsional strain created by ISW2 at the internal site (Figure 5B). This small DNA bulge created between the entry site and the translocation site is trapped on the nucleosome surface until one of the two major ISW2 contacts is released. Due to the uniform direction of nucleosome movement observed for ISW2, it is evident a priori that the internal contact would need to be released for the subsequent passage of the bulge and proper movement of DNA in the nucleosome. The model would be essentially the same for SWI/SNF with a few adjustments. The interactions of SWI/SNF with nucleosomal DNA are much more extensive than ISW2 and thus have the potential for creating a larger DNA bulge. DNA translocation remains the catalysis that promotes release of DNA from the nucleosome surface and coordinated with the extensive binding of SWI/SNF to this DNA region creates a large DNA loop for propagation around the nucleosome as depicted in Figure 5A.

Further evidence for the loop recapture model with bulge propagation comes from incorporation of ethidium bromide during nucleosome sliding by ACF [133]. Ethidium bromide intercalates into free DNA better than nucleosomal DNA and if nucleosomal DNA is

made accessible during nucleosome mobilization, then site specific intercalation occurs followed by laser-induced crosslinking creating single-strand breaks at the intercalation sites [134,135]. Ethidium bromide incorporation was dependent on ACF but independent of ATP showing that the interaction of remodeler with the nucleosome generated free DNA on the surface of the nucleosome. Further, ACF can remodel nucleosomes with large biotin moieties attached to the DNA showing that 'loop recapture' could be the actual mechanism for nucleosome mobilization.

Directional nucleosome mobilization – Role of accessory subunits

While the translocation of the whole complex is brought about by the above mentioned mechanisms, what determines the direction in which the translocation happens has remained elusive until recently. The first insights into the directional mobilization came from studies in *Drosophila* where ISWI forms multiple complexes which share the same catalytic subunit, but differ in their subunit composition. ISWI forms NURF, ACF and CHRAC inside the cell. ISWI alone was able to reposition nucleosomes from the center to the end of a DNA fragment, while CHRAC complex containing Acf1 and two small histone fold proteins in addition to ISWI moved nucleosomes from the end to the center[136]. Acf1 appears to be responsible for the change in the direction of nucleosome mobilization, since addition of Acf1 and ISWI separately provided the same directional nucleosome mobilization properties as CHRAC. Topological studies of ISW2 provided vital functional aspects of accessory subunits[130]. Using site-specific photoaffinity labeling, Itc1p was shown to exclusively interact with linker DNA. Efficient interaction of ISW2 needs ~67bp of linker DNA and the majority of this linker DNA is contacted by Itc1p. Hence, it is most likely that Itc1 orients the complex by contacting the linker DNA (Figure 5). When a bulge is fed into the nucleosome, Itc1 helps in the directional propagation of the bulge by preventing the bulge from entering the linker DNA region so that the bulge can exit from the other side of the nucleosome resulting in directional nucleosome movement. Absence of the accessory subunits like Itc1p and Acf1 might compromise the orientation of the remodeling complex and hence directional preference for nucleosome mobilization.

Directional nucleosome mobilization and nucleosome spacing activity

Nucleosome spacing is defined as the arrangement of nucleosomes in an array with similar linker DNA lengths between nucleosomes. Only ISWI class of nucleosome remodeling factors has been shown to possess this property. *Drosophila* and human ACF and CHRAC, human RSF[93,137-139] and yeast ISW1a[99] and ISW2[75] complexes can space nucleosomes. ISW2 complex has nucleosome spacing activity that is not as uniform as that of ISW1a. The molecular basis for the nucleosome spacing activity of ISWI has not been clear. Interestingly, the ISWI complexes having a strong directional preference for nucleosome mobilization are all those that exhibit this spacing activity. For example, ISW1b which can remodel nucleosomes in both directions from the center to the end of DNA or visa versa does not exhibit this nucleosome spacing activity (VKG and BB, submitted). ISW1a which has the same catalytic subunit as ISW1b has a preferred direction for mobilizing nucleosomes and spaces nucleosomes[99].

ISW2 spaces nucleosomes every ~200bp (linker DNA length of 67bp) and ISW1a spaces nucleosomes every ~175bp (linker DNA length of 30bp). Nucleosome spacing by ISW2 is a function of its affinity to linker DNA which is predominantly dictated by its accessory subunit Itc1. Extensive binding of Itc1 with the linker region could prevent nucleosomes from moving too close to each other and hence the extent of linker DNA interaction determines the spacing of nucleosomes. Recent studies have shown that a concerted action between the length of the extranucleosomal DNA and that of the histone H4 tail regulates nucleosome sliding by ISW2 (paper in press). H4 tail helps recruit Isw2p and Itc1p to SHL2, but this is also dependent on

the length of extranucleosomal DNA. Optimal recruitment by H4 tail occurs when the length of the extranucleosomal DNA is 70-85 bp. ISW1a appears to have a distinct manner for regulating spacing. ISW1a interacts with both the entry/exit sites simultaneously when there is an optimal extranucleosomal DNA length of 30 bp ob both sides and this interaction in turn abrogates its interaction with the H4 tail.

Role of histone tails and their modification in chromatin remodeling

Initial evidence for the role of histone N-terminal tails came from studies on NURF where the removal of histone H4 N-terminal tail affected nucleosome remodeling[85,86]. Subsequently, this feature was found to be a characteristic feature of ISWI containing complexes in other organisms too. The basic patch of histone H4 tail $R_{17}H_{18}R_{19}$ is specifically recognized by ISWI containing complexes[140]. The presence of such an epitope was found to be essential in generating ATP-dependent regularly spaced nucleosome arrays by RSF[141]. Recent reports have shown that H3K9me3 mark can actively recruit the PHD domain of NURF[142,143]. Similarly, the same mark was also shown to recruit Isw1p ATPase to chromatin[144]. Interestingly, an essential requirement for the H4 N-terminal tail is not shared by other classes of chromatin remodelers. Histone modifications were however found to effect the interaction of SWI/SNF with nucleosomes. Acetylation by SAGA and NuA4 was found to stabilize SWI/SNF interaction with nucleosome in a bromodomain dependent manner [49,145]. Acetylation of lysine 8 of histone H4 has also been shown to facilitate recruitment of SWI/SNF[146]. Other studies in yeast and mammalian systems similarly demonstrate that histone acetylation mediates the in vivo binding of SWI/SNF to a variety of promoters[147-149]. Acetylation of histone H3 at a globular region instead of the flexible tail region was also recently shown to facilitate the in vivo recruitment of SWI/SNF[150]. It was suggested that this enhanced binding of SWI/SNF could be due to acetylation opening the nucleosome near the entry/exit site at the site of acetylation. The integrity of the globular domain of H3 seems to be important for SWI/SNF binding. The L61W change in H3 causes the binding of SWI/SNF to the *PHO84* and *SER3* promoters to be lowered and as shown for the *PHO84* promoter in a direct manner [151]. In biochemical assays, histone tails were found not to be essential for remodeling by SWI/SNF, but were required for the catalytic turnover of SWI/SNF on nucleosomal arrays [152]. Similarly, deacetylation of histone tails was found to have a similar effect.

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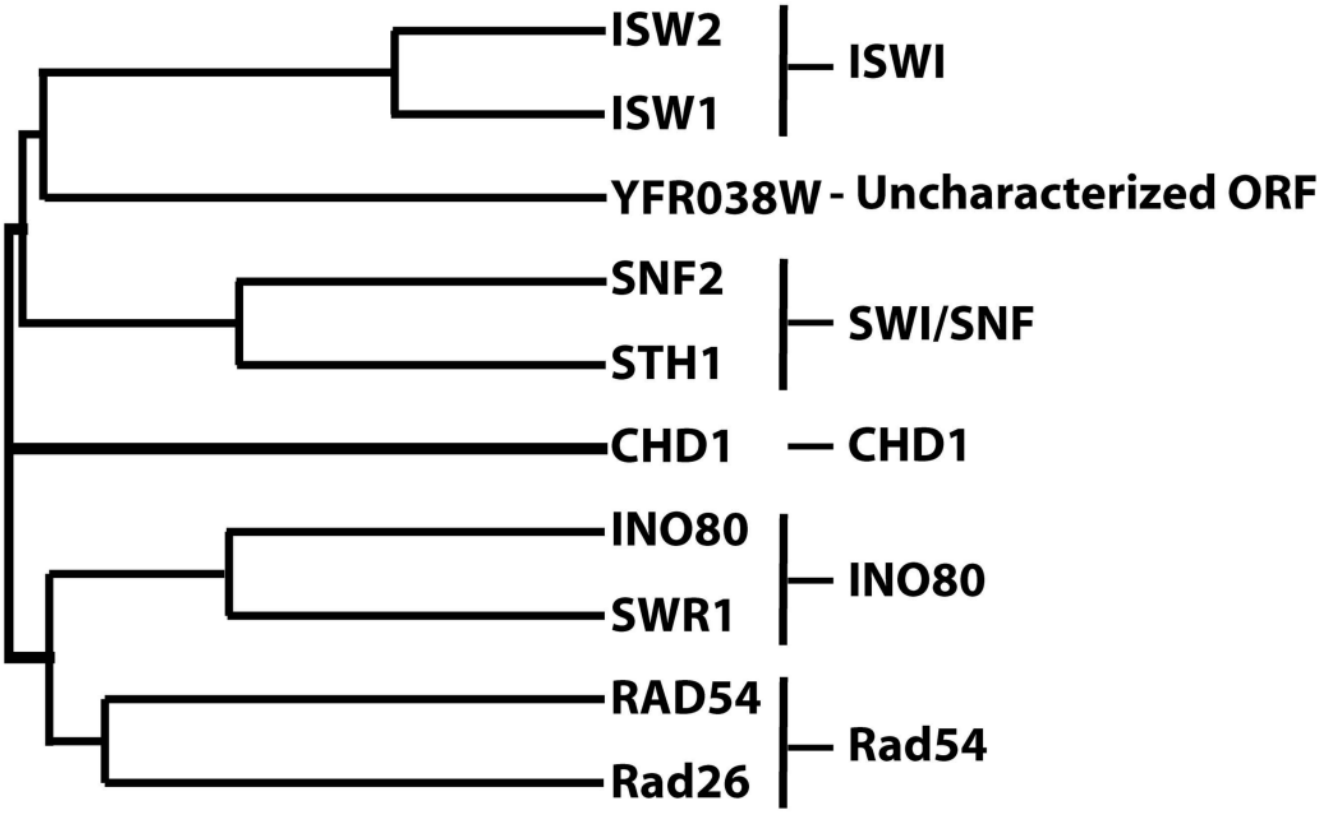

Figure 1.

Similarity of different ATP dependent remodeling complexes in *S.cerevisiae*. Clustering of complexes into different subfamilies is dependent on the sequence homology between the members of the subfamily.

SWI/SNF Subfamily -

S.cerevisiae		*D.melanogaster*		*H.sapiens*	
SWI/SNF	RSC	BAP	PBAP	BAF	PBAF
Swi2/Snf2	Sth1*	Brahma*	Brahma*	Brg1 or hBrm*	BRG1*
Swi1/Adr6		OSA	BAF250		
	Rsc 1,2&4		Polybromo		Polybromo/BAF 180
	Rsc9		BAP170		
Swi3	Rsc8	Moira	Moira	BAF170& 155	BAF170& 155
Snf5	Sfh1	Snr1	Snr1	hSNF5/INI1	hSNF5/INI1
Swp82/Yfl049w	Rsc7/ Npl6p				
Swp73/Snf12	Rsc6	BAP60	BAP60	BAF60a	BAF60aorb
Arp7/Swp61	Arp7/Rsc11	BAP55	BAP55	BAF53	BAF53
Arp9/Swp59	Arp9/Rsc12				
		Actin	Actin	Actin	Actin
Snf6					
Swp29/Tfg3/Taf14/Arc					
Rtt102	Rtt102				
Snf11					
	Rsc 5,10,13-15				

INO80 Subfamily -

S.cerevisae		*H.sapiens*
yINO80	ySWR1	hINO80
Ino80*	Swr1*	hIno80*
Arp8		Arp8
Arp5		Arp5
Arp4	Arp4	BAF53a/Arp4
Rvb1	Rvb1	Tip49a
Rvb2	Rvb2	Tip49b
Ies2		hIes2/PAPA-1
Ies6		hIes6/C18orf37
Act1	Act1	Amida
Taf14	Arp6	FLJ90652
Nhp10	Aor1/Swc5	NFRKB
Ies1	Vps71/Swc6	MCRS1
Ies3	Vps72/Swc2	FJL20309
Ies4	Yaf9	
Ies5	Bdf1	
	Swc1/Swc3	
	Swc4/God1	

ISWI Subfamily -

S.cerevisae			*D.melanogaster*		*H.sapiens*					*M.musculus*	
ISW1a	ISW1b	ISW2	ACF	CHRAC	NURF	WCRF/hACF	WICH	hCHRAC	RSF	SNF2h/Cohesin	NoRC	mWICH
Isw1*	Isw1*	Isw2*	ISWI*	ISWI*	ISWI*	hSNF2h*	hSNF2h*	hSNF2h*	hSNF2h*	hSNF2h*	mSNF2h*	mSNF2h*
Ioc3	Ioc2	Itc1	Acf1	Acf1		hAcf1		hAcf1		Mi2	Tip5/Baz2a	
	Ioc4						Wstf					mWstf
		Dpb4		Chrac16				hChrac17		Mta1 & 2	p50	
		Dls1		Chrac14				hChrac15		HDAC1 & 2	p80	
					Nurf301				p325	RbAp46		
					Nurf55					RbAp48		
					Nurf38					MBD2 & 3		
										Rad21		
										SA1 & 2		
										Smc1 & 3		

CHD Subfamily -

S.cerevisae	*D.melanogaster*		*M.musculus*		*H.sapiens*	
CHD1	Mi2	CHD1	CHD1	Mi2	NuRD	ATRX
Chd1*	Chd4*	Chd1*	Chd1*	Chd4/Chd3*	Chd3/Chd4*	ATRX*
	Rpd3			HDAC1 & 2	HDAC1 & 2	
				RbAp48	RbAp48	
				Icaros 1,2 & 7	RbAp46	
				Aiolos	MBD3	
					MTA2	

CHD Subfamily is the least characterized and can have uncharacterized proteins

Figure 2.

Subunit composition of members of each subfamily of remodeling complexes. The catalytic subunit is marked by an asterisk on the side. Subunits which are shared by multiple complexes in the same organism are underlined. Sub units which are homologous in different organisms by virtue of their sequence are shadowed in grey.

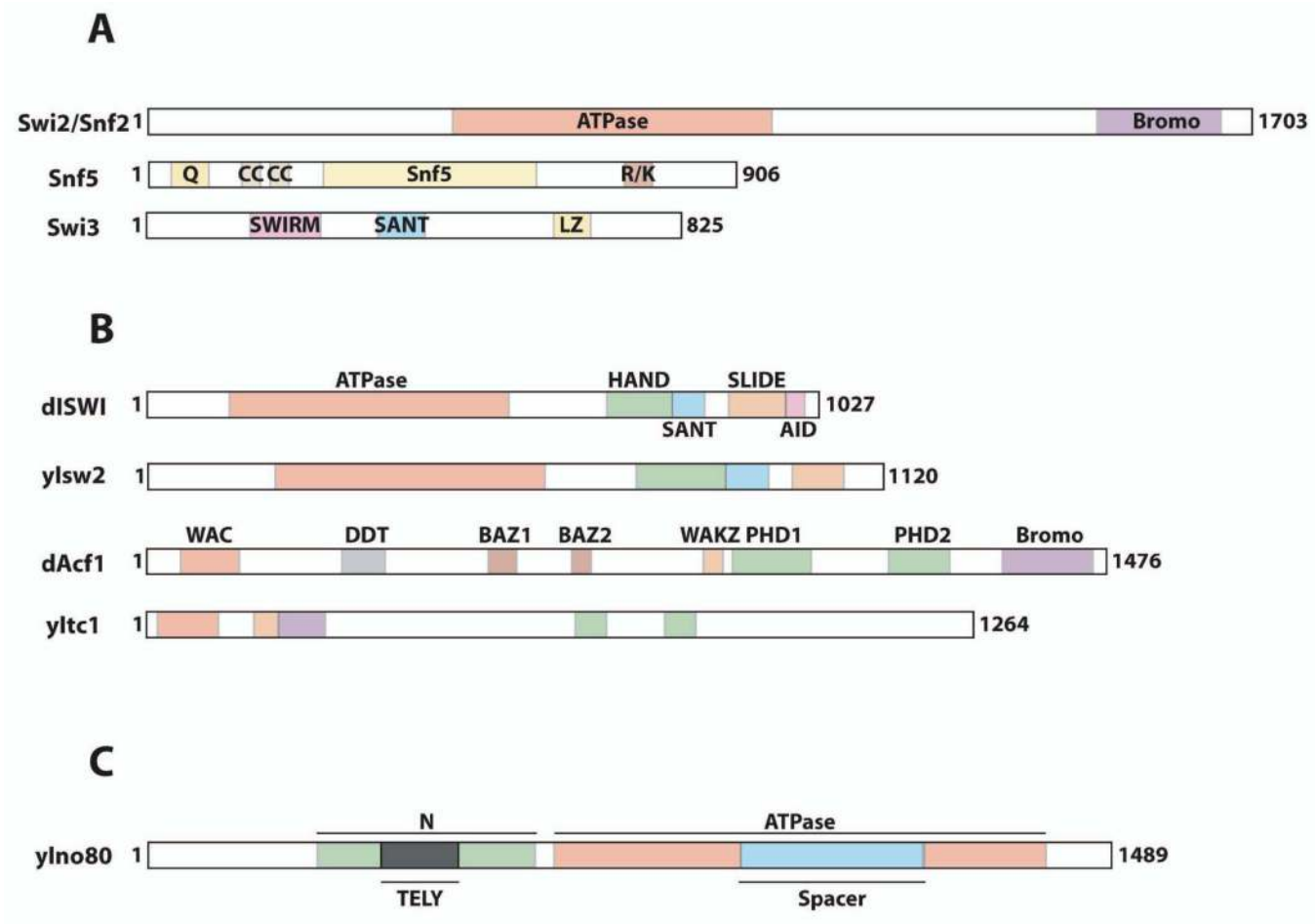

Figure 3.

Domain organization of the various subunits of different chromatin remodeling complexes. (A) Shown are the domains that have been found in three of the SWI/SNF subunits, namely Snf2, Snf5, and Swi3. (B) The catalytic subunit of the ISWI complexes from yeast and flies are compared, as well as that of the large accessory subunit of CHRAC/ACF and ISW2. (C) The domain organization of the catalytic subunit of the INO80 complex is shown. The abbreviations for the different domains are bromo for bromo domain, 'Q' represents the Q rich region, 'CC' for coiled coil region, 'R/K' for Arginine/Lysine rich basic region, and 'LZ' for Leucine Zipper.

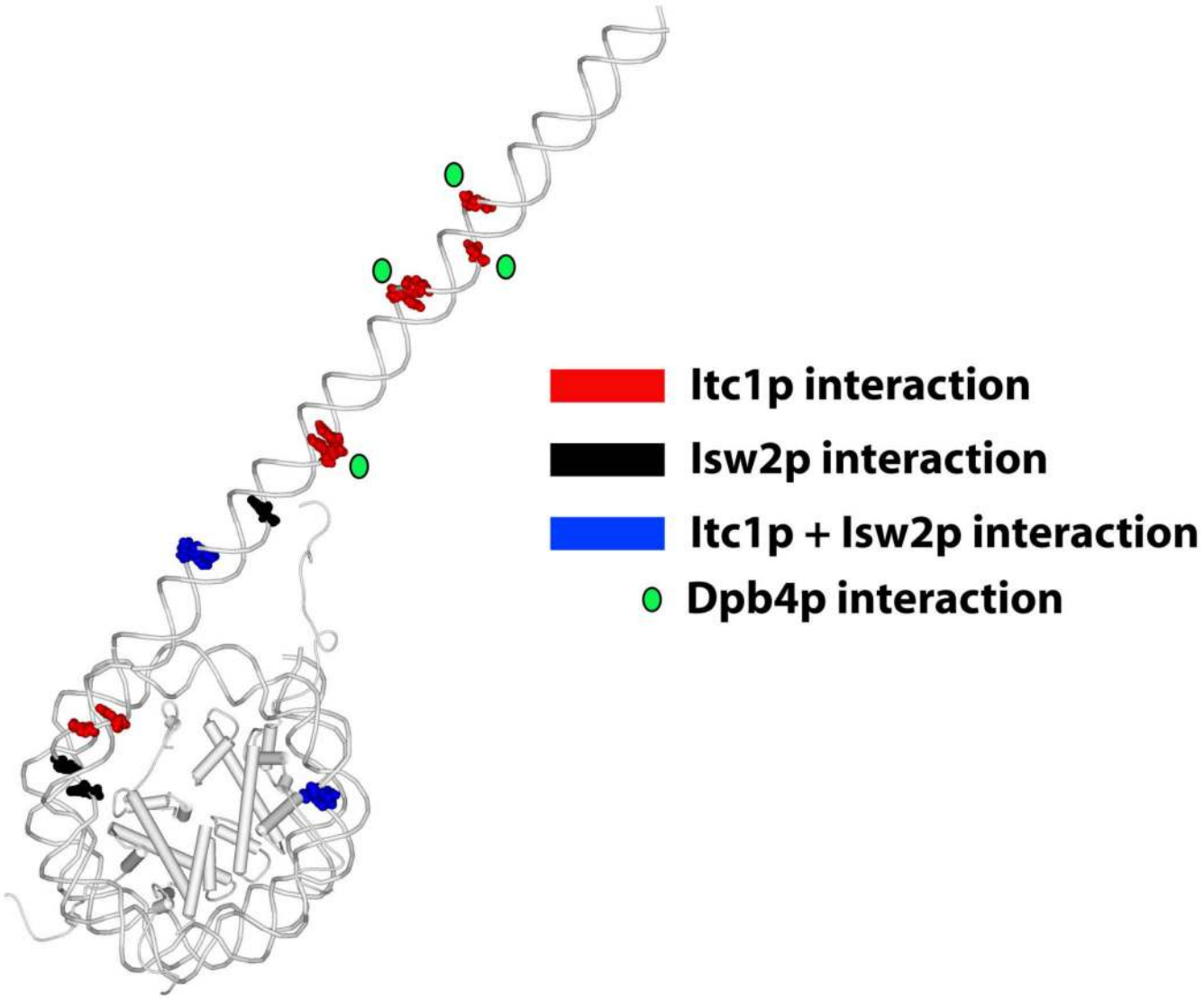

Figure 4.

Nucleosome interactions by ISW2. ISW2 interacts at three distinct sites on the nucleosome – linker DNA, 10bp into entry/exit site and two helical turns away from the dyad axis (SHL-2) [130]. Itc1p interacts predominantly with the linker DNA and is represented in red. Isw2p interacts with linker DNA close to the entry/exit site and near SHL2 and is represented in black. Regions where both Isw2p and Itc1p are present are represented in blue. Dpb4p interaction is restricted to the linker DNA and is represented by green circles.

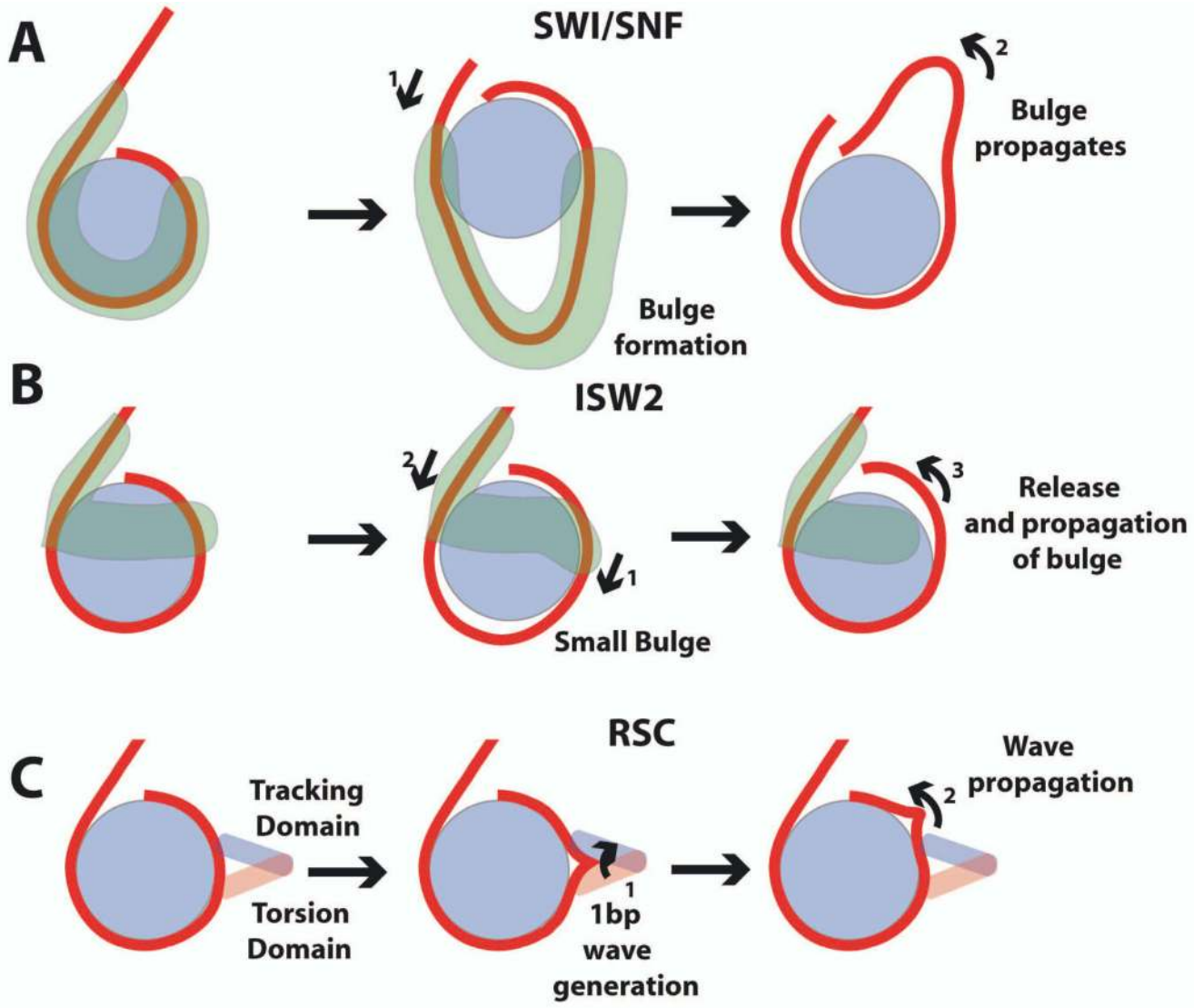

Figure 5.

Two models for nucleosome remodeling.

(A) SWI/SNF interacts with a large section of nucleosomal DNA and this interaction may facilitate in peeling DNA off the surface of the histone octamer. The generation of a large DNA loop on the surface of the histone octamer would next propagate along the nucleosome surface [129].

(B) Unlike SWI/SNF, ISW2 generates smaller bulges of ~10bp by a concerted action of two contact points along the nucleosomal DNA – one at SHL2 and the other at the entry/exit site and extranucleosomal DNA (1 and 2) [129]. After formation of the bulge, the bulge is allowed to move in the correct position by release of the contact at SHL2 (3).

(C) The RSC model with generation of a 1bp wave by a concerted action between the torsion and tracking domains within the ATPase motif of Sth1p. The 1bp wave propagates along the nucleosomal DNA as depicted [132]