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ATP-dependent chromatin remodeling enzymes: two heads are not better, just different

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ATP-dependent chromatin remodeling complexes enable rapid rearrangements in chromatin structure in response to developmental cues. The ATPase subunits of remodeling complexes share homology with the helicase motifs of DExx box helicases. Recent single-molecule experiments indicate that, like helicases, many of these complexes use ATP to translocate on DNA. Despite sharing this fundamental property, two key classes of remodeling complexes, the ISWI class and the SWI/SNF class, generate distinct remodeled products. SWI/SNF complexes generate nucleosomes with altered positions, nucleosomes with DNA loops and nucleosomes that are capable of exchanging histone dimers or octamers. In contrast, ISWI complexes generate nucleosomes with altered positions but in standard structures. Here, we draw analogies to monomeric and dimeric helicases and propose that ISWI and SWI/SNF complexes catalyze different outcomes in part because some ISWI complexes function as dimers while SWI/SNF complexes function as monomers.

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Introduction

The packaging of DNA into chromatin serves to regulate and coordinate all the manipulations of DNA: replication, segregation, transcription, recombination, and repair. Packaging into even the smallest unit of chromatin, a nucleosome, greatly decreases the accessibility of the DNA to transcription factors and can have large effects on gene expression [1,2]. Over the past two decades, several ATP utilizing chromatin remodeling complexes have been identified that rearrange chromatin in a manner that changes the accessibility of the underlying DNA [3–6]. Some of these complexes alter chromatin structure to make the DNA more accessible for transcription, whereas others help generate chromatin structures that lead to long-term silencing of genes. In many cases, the distinct biological functions appear to be correlated with the different biochemical outcomes catalyzed by each class of chromatin remodeling enzymes [6,7]. Given that these enzymes have homologous ATPase domains and share several basic biochemical properties, a key unanswered question is how different classes of chromatin remodeling enzymes generate different products. Here we address this question by comparing remodeling complexes from two of the best-studied classes, the SWI/SNF class and the ISWI class. The two classes are defined based on the identity of the catalytic ATPase subunit. The catalytic ATPase subunits of SWI/SNF family complexes are homologs of the yeast SWI2/SNF2 ATPase while the catalytic ATPase subunits of ISWI complexes are homologs of the Drosophila ISWI ATPase. SWI/SNF complexes are generally large and contain 8–15 subunits [5]. In contrast, ISWI complexes are smaller and typically contain two to four subunits. We compare data for three well-studied SWI/SNF complexes; human SWI/SNF, yeast SWI/SNF and yeast RSC with data for three well-studied homologs of one type of ISWI complex, ACF; human ACF, Drosophila ACF, and yeast ISW2. While SWI/SNF family complexes play roles in activation and repression of genes, ACF complexes appear to be mainly involved in repression [4,6].

Basic features of SWI/SNF and ACF complexes

The enzymatic activity of each complex resides within a catalytic ATPase subunit, which can remodel nucleosomes in the absence of the remaining subunits [3,4,7]. These ATPase subunits are part of the SF2 superfamily of helicases [8•,9•]. They all contain two RecA-like domains: 1A, which contains the DExx motif, and 2A. ATP binds in the cleft formed by these two domains. Changes in the ATP state during the ATPase cycle are thought to drive movement of 1A relative to 2A. Analogous to SF1 and SF2 helicases, these small movements are thought to be amplified by accessory domains that extend out from 1A and 2A. These accessory domains often differ structurally between different classes of helicases, and are generically termed 1B and 2B [8•,9•]. For simplicity, we refer to the region containing the 1A, 2A, 1B and 2B domains as the helicase-like region (H). Analogous to helicases, the ATPase activity of remodeling complexes is stimulated upon binding substrate, namely nucleosomes or free DNA [3]. Although neither class of remodeling enzyme has detectable DNA helicase

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activity, both classes do display another hallmark of helicases, the ability to translocate on DNA. Early studies using a triplex displacement technique had suggested that the ATPase subunits of RSC and ACF complexes can translocate on DNA [10,11]. Recent elegant studies using single-molecule approaches now directly demonstrate processive movement of yeast SWI/SNF and yeast RSC along DNA [12••,13••]. Both classes of complexes thus share fundamental mechano-chemical properties. However, they appear to use the energy of ATP hydrolysis to achieve very different outcomes.

SWI/SNF and ACF complexes generate different products

Both SWI/SNF and ACF can move nucleosomes from one location on DNA to another. SWI/SNF complexes have the following additional outcomes that are not observed with ACF [3]: SWI/SNF complexes can introduce changes in superhelicity in closed circular nucleosomal arrays; SWI/SNF complexes can generate nucleosomes containing stable loops of DNA, and dinucleosome-like species; SWI/SNF complexes can also transfer the histone octamer to acceptor DNA and exchange H2A/H2B dimers between nucleosomes. In contrast, ACF complexes can regularly space multiple nucleosomes, while SWI/SNF complexes cannot [3].

The ability of SWI/SNF complexes to generate diverse products is consistent with their biological role of locally disrupting histone–DNA interactions at promoters [7]. Generating stable DNA loops within a nucleosome would allow SWI/SNF complexes to expose nucleosomal DNA in crowded chromatin environments where there is insufficient room to slide the nucleosomes. Removing dimers or octamers could be coupled with the action of a histone chaperone to generate nucleosome-free regions or regions that can exchange regular dimers with variant dimers at promoters. By contrast, the ability of ACF complexes to generate regularly spaced nucleosomes over large stretches of DNA is consistent with their biological role of promoting the chromatin compaction required for gene silencing [4,6]. Regular spacing of nucleosomes is thought to promote cooperative folding of nucleosomes into higher order chromatin fibers.

Recent work suggests that the ability of SWI/SNF and ACF complexes to generate different products resides in a smaller piece of each catalytic ATPase subunit that includes the helicase-like region [14••]. These experiments swapped the helicase-like region of BRG1, the human homolog of yeast SWI2/SNF2, with that of SNF2h, the human homolog of Drosophila ISWI. The swapped regions also included some flanking sequence (Figure 2). The chimeric ATPase that contained the SNF2h helicase-like region flanked by BRG1 domains generated products similar to those generated by an intact SNF2h. By contrast, the chimeric ATPase containing the helicase-like region from BRG1 flanked by SNF2h domains generated the diverse set of nucleosomal products seen with BRG1 and the human SWI/SNF complex. These results were unexpected as the helicase-like regions of both SNF2h and BRG1 are very homologous.

In helicases, one mechanistic difference between structurally similar enzymes is their ability to form dimeric complexes. There are several examples of dimeric and monomeric helicases in both the SF1 and SF2 superfamilies of helicases [15–19]. We therefore hypothesize that one difference between SWI/SNF and ACF remodeling complexes may be their oligomeric state, which in turn would influence the outcome of remodeling. Dimerization in SF1 helicases is proposed to be mediated by the 2B domain [20]. However, the 2B domain is homologous between SNF2h and BRG1. The chimeric enzyme experiments described above which swapped the helicase-like regions of SNF2h and BRG1 also exchanged small nonconserved regions surrounding the helicase-like region. In the case of SNF2h this included the HAND domain, which is specific to the ISWI class (Figure 2a). We therefore propose that domains like the HAND domain that flank the helicase-like region and are specific to a particular class of remodeling enzyme may regulate the oligomeric state of the enzyme.

DNA helicases can act as monomers or oligomers

The SF1 and SF2 superfamily of helicases contain some of the best-studied helicases, both mechanistically and structurally [21]. In these helicases, the 1B and 2B domains are thought to directly interact with DNA. Several of these helicases can translocate on DNA or RNA as monomers. However, while some SF1 helicases can also unpair DNA as monomers, there are others which need to dimerize to unpair DNA [21,22]. It has been proposed that the ability of DExx box helicases to translocate as monomers can help promote the displacement of proteins bound to nucleic acids while an additional ability to dimerize can allow these proteins to function as processive helicases [23]. In addition, helicases outside of the SF1 and SF2 superfamilies also function as hexamers, but a discussion of hexameric helicases is outside the scope of this analysis [21].

Monomeric helicases are thought to function by an 'inchworm' mechanism (Figure 1a). ATP binds in the cleft created by 1A and 2A. As a result, ATP binding causes translocation of the 1A domain along DNA toward the 1B domain. ATP binding promotes DNA distortion by the 1B and 2B domains [21,24]. ATP hydrolysis allows translocation of the 2A domains though the destabilized duplex. In several cases, dimerization or oligomerization of the helicase dramatically increases the processivity of RNA or DNA unpairing [16,20]. One of the best-studied dimeric helicases is the bacterial Rep helicase. Dimeriza-

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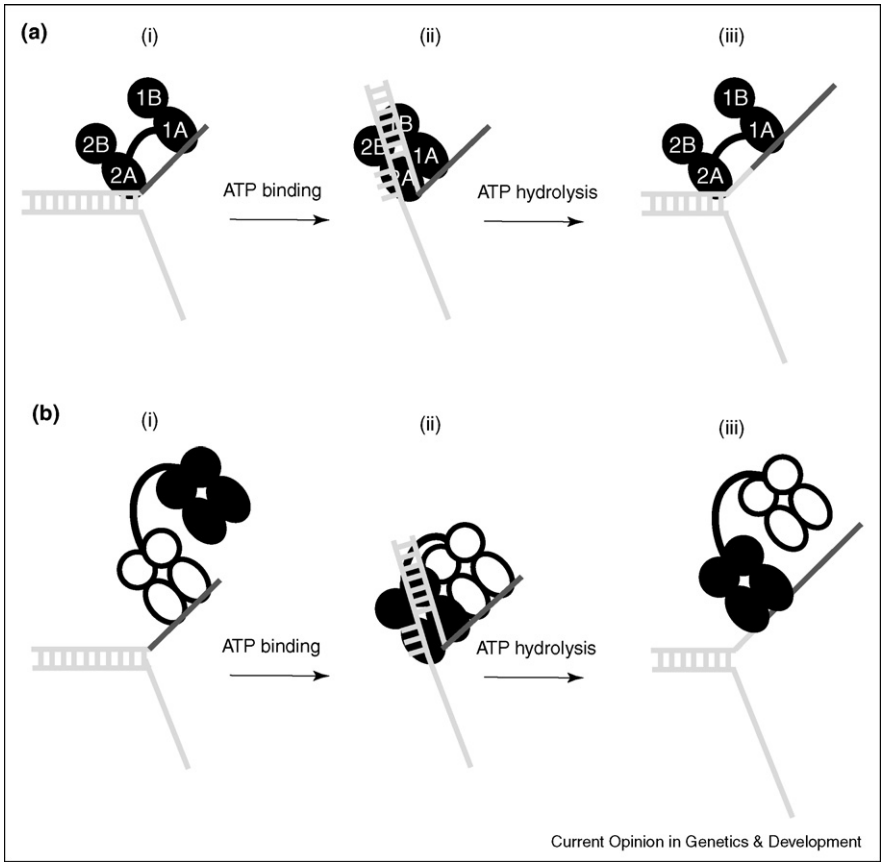
Figure 1



(a) Inchworm mechanism proposed for monomeric SF1 helicases. Translocation occurs in two steps: (i) the helicase binds at the junction between single-stranded and double-stranded DNA. (ii) Domain 1A translocates toward 2A upon ATP binding because the binding site is formed by the cleft between 1A and 2A. In this state, domains 1B and 2B tightly bind and destabilize duplex DNA. (iii) Phosphate release allows translocation of 2A through the destabilized duplex. The absence of unhydrolyzed ATP reduces the interactions between 1A and 2A, allowing for this translocation. **(b)** Rolling mechanism proposed for dimeric SF1 helicases: (i) In the absence of ATP only one monomer binds at the junction between single stranded and double stranded DNA. (ii) ATP binding promotes tight binding of the leading helicase (black) to the ssDNA–dsDNA fork while the lagging helicase (white) remains bound to ssDNA. (iii) ATP hydrolysis results in dsDNA unpairing and subsequent phosphate release allows dissociation of the lagging helicase (white), which can then become the leading helicase in the next ATP cycle. In both (a) and (b), for ease of visualization three base pairs are shown to be disrupted in each ATPase cycle. In reality most helicases appear to unpair one base pair per ATPase cycle.

tion of another SF1 member, UvrD, has also been shown to be required for helicase activity [19,25]. Dimerization of Rep is thought to make helicase action more processive because one subunit actively engages the double-stranded DNA while the other holds on to the single-stranded DNA [18] (Figure 1B). The ATP state is thought to regulate which subunit binds single-stranded DNA versus double-stranded DNA. According to the current model, in the absence of ATP, only one subunit binds single-stranded DNA. ATP binding promotes binding of one subunit to double-stranded DNA and the other to single-stranded DNA. ATP hydrolysis promotes DNA unpairing and/or translocation. The presence of ADP promotes the binding of both monomers to single-stranded DNA (step not shown in figure). Two mechanisms have been proposed for the roles of each subunit in a dimeric helicase [18]. In the rolling mechanism (Figure 1B), the subunits alternate in engaging with double-stranded DNA. In the dimeric inchworm mechanism (not shown in figure), the same subunit always engages with the double-stranded DNA and unpairs DNA via a mechanism similar to monomeric helicases, while the other subunit holds on to the newly generated single-stranded region.

Different chromatin remodeling enzymes may act as monomers or dimers

By analogy to nucleic acid helicases, we hypothesize that the ATPase subunits of SWI/SNF complexes may act as monomers while the ATPase subunits of ACF complexes may act as dimers. We describe below some suggestive evidence. Yeast SWI/SNF and yeast RSC each contain one copy of the ATPase per complex, as shown through double affinity tagging methods for both enzymes and

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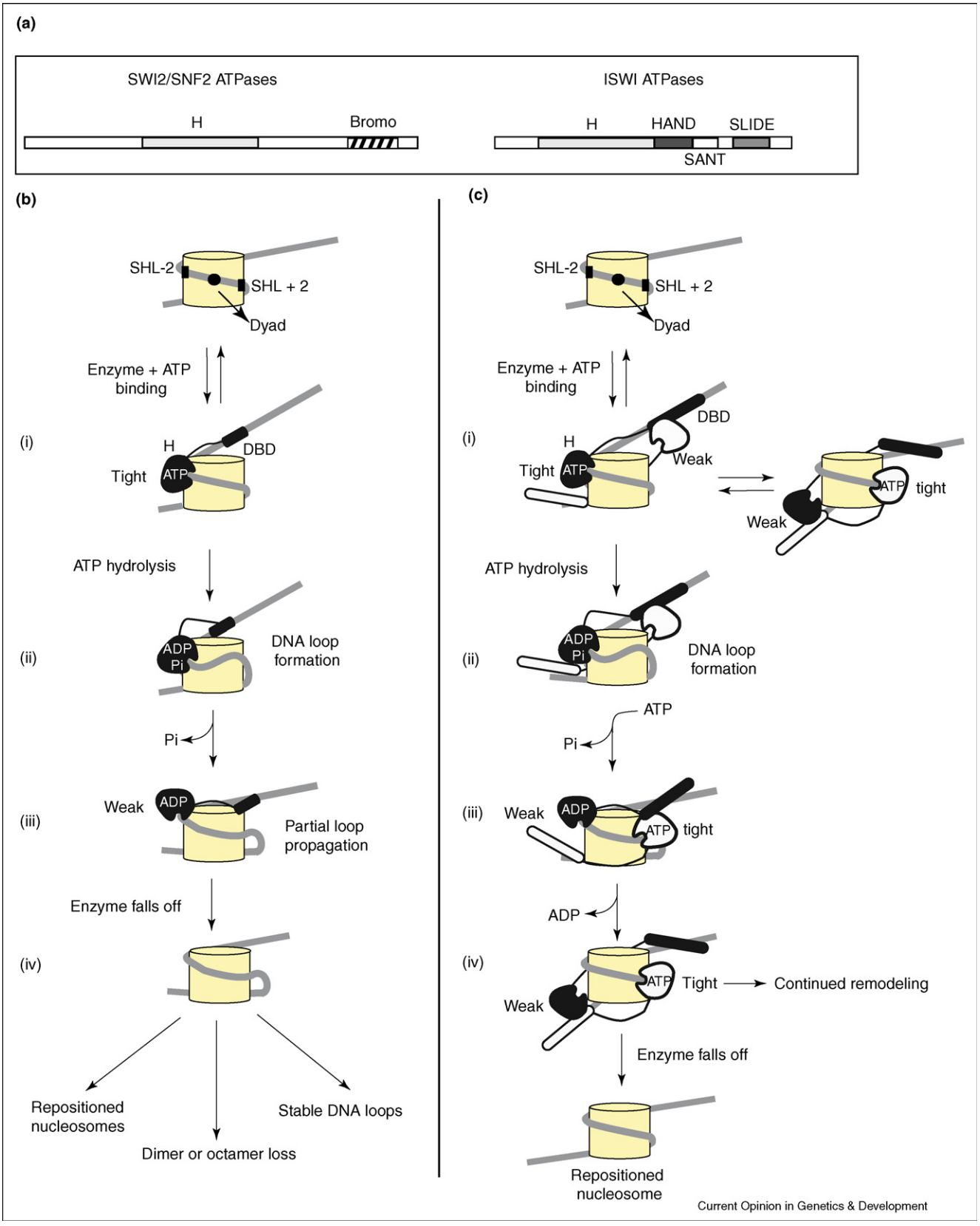
Figure 2



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additionally by scanning transmission electron microscopy and subunit radio-iodination for ySWI/SNF [11,26]. The steric constraints from the electron microscopy (EM)-based structures of SWI/SNF family members further suggest that one nucleosome can interact with only one molecule of the complex [26–30]. This is most obvious in the EM-based structure of the RSC complex, which reveals a deep cavity that has the dimensions to surround a single nucleosome [27,29]. By contrast, Drosophila ACF, which contains two subunits: the ATPase ISWI and dACF1, appears to contain two ISWI molecules and two dACF1 molecules per complex, as suggested by gel filtration and glycerol gradient sedimentation [31••]. In addition, fluorescent correlation spectroscopy experiments suggest that ACF binds DNA using two ISWI subunits and two ACF1 subunits [31••]. Finally, gel mobility shift studies with different ACF homologs often show more than one complex binding to a single nucleosome [32•,33].

Model for alteration of nucleosome structure by monomeric chromatin remodeling enzymes

Substantial work in the helicase field has helped elucidate how different steps in the ATP hydrolysis cycle are coupled to specific steps in the unpairing of DNA. Significantly less is known about how ATP is used by chromatin remodeling enzymes. The high conservation of the 1A and 2A domains across SF1 and SF2 families suggests that, at a minimum, the coordinated movements of these domains relative to one another as a function of ATP state may be conserved [8•,9•,21]. For helicases, it is clear that the site of translocation is at the junction of the single-stranded and double-stranded DNA. For a nucleosome substrate, it is not immediately obvious where the site of translocation might be. Pioneering work with RSC and ISW2 suggested somewhat unexpectedly that remodeling enzymes translocate from an internal site that is about two helical turns from the dyad (SHL−2 and SHL+2, Figure 2). This is based on experimental data showing that the helicase-like domain (H) interacts with the nucleosome at these internal sites and that nicks and gaps in this region impair remodeling [34•,35•,36•,37]. Below we attempt to adapt the experimentally known steps in helicase function to putative steps in chromatin remodeling. We note that many of the details in the models proposed below are not based on experimental data but are solely meant to illustrate how different ATP states can regulate the affinity of chromatin remodeling enzymes for different nucleosomal states. The hypothetical steps associated with ATP binding and hydrolysis are described below for the H domain binding at SHL−2 (Figure 2a).

ATP binding

We propose that, analogous to SF1 helicases, binding of ATP by the 1A and 2A domains of remodeling enzymes causes local DNA distortion at SHL−2 by the 1B and 2B domains. The observation that nicks and gaps in this region of the DNA impair remodeling has led to the previous proposal that a local distortion in this region may destabilize histone-DNA contacts [34•,35•,36•]. It has previously been proposed that an additional DNA-binding domain (DBD) captures transiently unpeeled DNA near the entry and exit site [31••,34•,35•]. This proposal helps resolve the apparent paradox of translocation from an internal DNA site and is based on the following evidence: (a) DNA can spontaneously unpeel from the entry and exit site on a millisecond time scale [38]. (b) DNAse footprinting and cross-linking studies with ACF and its Drosophila homologue ISW2 suggest that these complexes also contact DNA near the entry-exit site of the nucleosome [32•,36•,37] via the HAND-SANT-SLIDE region [37]. We propose that this stabilization of unpeeled DNA occurs upon ATP binding. The captured, unpeeled DNA can then be translocated through the enzyme, avoiding the need to simultaneously break several DNA–histone contacts during translocation from an internal site such as SHL−2 (Figure 2). We propose that the SWI2/SNF2 ATPase also has a DBD, which serves a similar function, but that it binds DNA closer to the SHL−2/+2 locations. This is based on the observation that RSC and SWI/SNF do not rely on flanking DNA to alter histone–DNA contacts, and can move the histone octamer off the end of the DNA [34•].

ATP hydrolysis

In helicases, ATP hydrolysis results in translocation through the destabilized duplex DNA. By analogy, ATP hydrolysis results in translocation of the H domain

(a) Schematic representation of known domains in SWI2/SNF2 and ISWI ATPases. The helicase-like region (H) is highly conserved between the two types of ATPases whereas the flanking sequences are not conserved. **(b)** Model for monomeric chromatin remodeling ATPases: (i) ATP binding by the helicase domain (H) causes DNA distortion at SHL−2 and stabilization of unpeeled DNA 'slack' by the DNA-binding domain (DBD). The H domain binds tightly in this state. (ii) ATP hydrolysis causes translocation of the H domain on the disrupted DNA at SHL−2, generating a DNA loop. (iii) Phosphate release weakens affinity of H domain increasing the probability of falling off. (iv) Dissociation of enzyme allows stochastic collapse of disrupted nucleosome into multiple distinct products. **(c)** Model for dimeric chromatin remodeling ATPases: (i) Only one monomer can bind ATP via its H domain at a given time. ATP can rapidly switch between the two monomers. The monomer that contacts the longer flanking DNA hydrolyzes ATP faster. Here this is the black monomer. (ii) ATP hydrolysis causes translocation of the H domain on the DNA at SHL−2, generating a DNA loop. (iii) Phosphate release from the black H domain weakens the affinity of the black H domain but at the same time allows ATP binding to the white H domain switching it to a tight binding state at SHL+2. This allows propagation of the DNA loop without enzyme dissociation. In this state the white DBD does not properly engage the flanking DNA preventing ATP hydrolysis by the white H domain. (iv) Loss of ADP from the black H domain allows the white DBD to engage the flanking DNA. At this stage ATP can rapidly switch between the two monomers and further DNA movement can occur or the enzyme can dissociate resulting in a repositioned nucleosome.

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through the destabilized DNA–histone interface created at SHL−2. Because the H domain is anchored to the nucleosome via interactions with the histones, translocation of the H-domain results in the generation of DNA loops as previously proposed [11,31••,35•]. The size of these loops is determined by how far on the DNA the enzyme can translocate per ATPase cycle. Translocation step sizes range from a few bp for some helicases up to 20 bp for others [21]. The translocation step size for chromatin remodeling enzymes is not fully characterized [31••,35•,36•,39].

Phosphate release

Binding studies with yeast ISW2 suggest that the presence of ADP reduces the affinity of the enzyme for DNA [40]. We therefore propose that in the presence of ADP, the remodeling enzyme is in a weakly bound state and dissociates with a high probability before the DNA loop has completely propagated across the nucleosome. As a result the disrupted nucleosomes can stochastically collapse to one of many fates: First, the loop may completely propagate across the nucleosome and result in a translationally repositioned histone octamer. Second, disruption of the histone–DNA contacts caused by loop formation may promote dimer and octamer loss. In some cases dimer loss may be promoted by specific subunits within the SWI/SNF, as has been shown recently for the yeast SWI/SNF complex [41]. Third, the loop may become kinetically trapped. Fourth, the dissociated DNA from one nucleosome may bind to histones exposed in another nucleosome to form a di-nucleosome like species.

Model for alteration of nucleosome structure by dimeric chromatin remodeling enzymes

The above model explains the different outcomes catalyzed by SWI/SNF complexes. While monomers of ACF are likely to have the same biochemical properties as SWI/SNF, we hypothesize that the dimeric nature of ACF complexes allows for the generation of a single class of remodeled product, namely translationally repositioned nucleosomes. By analogy to dimeric helicases, the coordinated action of the two monomers in a dimeric chromatin remodeling enzyme would ensure that one monomer is always bound to the nucleosome. Helicases are thought to exploit dimerization to increase the number of base pairs that are unpaired before the enzyme dissociates. For remodeling enzymes, we propose that dimerization increases the proportion of translationally repositioned nucleosomes by allowing completion of loop propagation before the enzyme dissociates. Dimerization may also explain the processive action of ACF on nucleosomal arrays [42]. A key feature of dimeric helicases is that the two ATPase subunits alternate between tight and loose binding in an ATP-dependent manner (Figure 1b). Below we describe a hypothetical model where this concept of alternating tight binding versus loose binding is applied to explain the mechanism of a dimeric ATP-dependent chromatin remodeling complex.

In this model, the second subunit, shown in white, interacts with the HAND domain of the first subunit. This feature of the model incorporates the observation that the HAND domain cross-links to the flanking DNA near the entry and exit site [37]. We further hypothesize that only one ATPase subunit can bind ATP at a time because of allosteric communication between the two subunits. Moreover, only the subunit that binds ATP can interact functionally with the flanking DNA. This is based on recent work suggesting that flanking DNA allosterically regulates the rate of ATP hydrolysis and nucleosome movement by ACF [43]. These data suggest that ACF can rapidly sample flanking DNA on either side of the nucleosome but reels in the longer flanking DNA faster than the shorter DNA. We therefore speculate that ACF can sample the DNA on either side because ATP may be able to rapidly exchange between the two subunits. However, the ISWI ATPase subunit that contacts the longer piece of flanking DNA will hydrolyze ATP faster, thereby setting the direction of DNA propagation across the nucleosome. In the ADP state, the black subunit becomes weakly bound but the presence of ADP promotes ATP binding to the white subunit, causing it to bind tightly at SHL+2 and preventing premature release of the disrupted nucleosome. Hydrolysis of ATP by the white subunit is inhibited because the DBD of the white subunit does not properly engage the flanking DNA until the black subunit dissociates. Release of ADP from the black subunit resets the cycle and again allows either subunit to bind and hydrolyze ATP.

Conclusions

ATP-dependent chromatin remodeling enzymes orchestrate changes in chromatin structure to help regulate transcription. The different classes of complexes appear to have evolved to perform specialized biochemical reactions to meet the demands of different gene regulatory processes. By analogy to DNA helicases, it is possible that some remodeling complexes function as dimers and others as monomers. However, while helicases appear to exploit dimerization to gain processivity, remodeling enzymes might further exploit the increased processivity gained from dimerization to tailor their activities for specific types of remodeled products. A test of this hypothesis will require additional mechanistic and structural studies on chromatin remodeling complexes.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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