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Biophysics of Chromatin Remodeling

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Abstract

As primary carriers of epigenetic information and gatekeepers of genomic DNA, nucleosomes are essential for proper growth and development of all eukaryotic cells. Although intrinsically dynamic, nucleosomes are actively reorganized and replaced by ATP-dependent chromatin remodelers. Chromatin remodelers contain helicase-like ATPase motor domains that can translocate along DNA, and a long-standing question in the field is how this activity is used to reposition or slide nucleosomes. In addition to ratcheting along DNA like their helicase ancestors, remodeler ATPases appear to dictate specific alternating geometries of the DNA duplex, providing an unexpected means for moving DNA past the histone core. Together with intrinsic dynamics of nucleosomal DNA, emerging evidence supports twist-based mechanisms for ATP-driven repositioning of nucleosomes along DNA. In this review, we discuss core experimental findings and ideas that have shaped the view of how nucleosome sliding may be achieved.

Keywords

Nucleosome; histone; SF2 superfamily; Snf2-type ATPase motor; twist defect; bulge/loop propagation

INTRODUCTION

Nucleosomes are the fundamental packaging units of eukaryotic chromosomes. They consist of a ~146 base pair (bp) segment of DNA intimately associated with a central histone core (Figure 1). With these tight interactions, nucleosomes are inherently repressive, as they antagonize most other DNA-binding factors by both blocking access and altering geometry of the DNA duplex (64). Additionally, through post-translational modifications, the histone core is extensively used for storing epigenetic information, critical for providing both short- and long-term memory that allows cells to differentiate and respond to environmental cues (3). To dynamically alter their positions and composition, nucleosomes rely on chromatin remodelers. Chromatin remodelers are ATP-driven enzymes that are essential gatekeepers needed to maintain and drive changes in the epigenetic landscape. As demonstrated by their established roles in many developmental disorders and dozens of cancers, chromatin remodelers are critical for normal cell physiology and determination of cellular identity (2, 43, 52, 60, 72, 84, 110).

Chromatin remodelers are defined by the presence of a Snf2-type ATPase motor, named for the ATPase-containing subunit of the founding SWI/SNF remodeler (34, 40). The ATPase motor can be flanked by a variety of different domains and sequence motifs that allow remodelers to be classified into distinct families. Whereas some Snf2-type ATPases, such

as Rad54 and CSB/Rad26, can also include non-nucleosomal targets, chromatin remodelers typically refer to those that primarily act on nucleosomal substrates. The most extensively studied remodeler families include SWI/SNF (SWI/SNF, RSC, BAF, PBAF), ISWI (ISWI, ACF, CHRAC, NURF), CHD (CHD1–9, Mi-2, NURD), and INO80 (INO80, SWR1, SRCAP, p400/Tip60, DOMINO). In addition to family-specific signatures surrounding the ATPase motor, most remodelers also possess unique non-ATPase subunits that further distinguish remodeling complexes from one another (8, 12, 25, 45, 52). Consistent with their diverse compositions, remodelers can catalyze a range of remodeling outcomes such as nucleosome disassembly, nucleosome assembly, histone exchange, and nucleosome sliding (8, 26, 87).

In this review, we focus on nucleosome sliding, an extensively studied aspect of chromatin remodeling that can now be explained through changes in DNA twist. We first review early ideas and results demonstrating dynamic and spontaneous changes in DNA twists on the nucleosome. We then describe supportive and challenging findings for the bulge/loop propagation model, proposed to describe how remodelers shift nucleosomes along DNA. Finally, we explore more recent findings showing how the ATPase motors of remodelers stimulate unique changes in DNA twist, which provide viable alternatives for a nucleosome sliding mechanism.

MOBILITY OF REMODELERS AND NUCLEOSOMES ALONG DNA

Architecture and DNA translocation of remodeler ATPase motors

Chromatin remodelers constitute a defined class of Snf2-type ATPase motors that are themselves part of a larger family of helicase-like enzymes known as superfamily 2 (SF2) (34, 40, 46, 107). As initially suggested from sequence conservation and now apparent from multiple structures, remodelers share a number of characteristic features in common with both SF2 and the related SF1 ATPases that underlie basic principles of how these enzymes work. Many SF1 and SF2 proteins are true helicases, and either disrupt duplexes by clamping onto and distorting one nucleic acid strand, as seen by RNA DEAD Box helicases (74), or by translocating along one strand while displacing the other, as seen by RecBCD and NS3 helicases (48, 106, 107). Whereas chromatin remodelers can move along naked duplex DNA and therefore have more similarity to translocating helicases (55, 73, 100, 101, 109), all SF1 and SF2 proteins share common architectural features (107). At their core, all SF1 and SF2 proteins consist of two RecA-type domains: lobe 1 binds to ATP through the classical Walker A (P-loop) and Walker B (DExx box) motifs, whereas lobe 2 presents arginine finger residues needed for catalysis. Together, both ATPase lobes present a conserved binding surface for cradling one strand of DNA or RNA, which lays over the motor with its 5’ end on lobe 2 and 3’ end on lobe 1 (102). To hydrolyze ATP, the ATPase motor must achieve a specific, tightly packed organization, where the phosphate tail of the bound ATP is buried and coordinated by conserved residues at the lobe 1/lobe 2 interface. ATP hydrolysis is typically stimulated by binding to nucleic acid substrates, which therefore help to properly organize the ATPase motor for catalysis.

Relative to the ATP-bound state, which is tightly closed, the ATPase motor in ADP-bound and nucleotide-free states favors a more open conformation. For translocating SF1 and SF2

enzymes, the ATPase motor alternates between open and closed states that ratchet it along DNA or RNA through what has been termed an inchworm mechanism (48, 69, 126). For translocation to occur, the two halves of the ATPase motor must alternate their grip on the nucleic acid upon switching between open and closed states. For translocating helicases that move in a 3'→5' direction, lobe 2 is on the front edge and lobe 1 trails behind. ATPase opening is stimulated by ATP hydrolysis, and closure by ATP binding. In transitioning from a closed to an open state, lobe 2 shifts forward on the nucleic acid by 1 nt. After ATP binding, lobe 2 keeps its position on the nucleic acid, and instead lobe 1 shifts upon closure of the ATPase motor.

Although some SF2 proteins, like chromatin remodelers, travel along duplex rather than single-stranded nucleic acids, these motors make similar nucleotide-dependent motions and interactions as single-stranded translocases, with the strand corresponding to single-stranded templates called the tracking strand, and its complement called the guide strand. For chromatin remodelers that shift nucleosomes, the ATPase motor not only has to travel along a duplex but has the added challenge of moving double-stranded DNA around the histone core.

DNA movement on the nucleosome via twist defects

Early studies showed that nucleosomes can spontaneously slide along DNA over long distances (10, 111) and that nucleosomal DNA displays similar twist dynamics as free DNA (129). Subsequent work demonstrated that shorter-range nucleosome repositioning (over several turns of the DNA duplex) can be driven by thermal motion (41, 42, 83, 94). An early idea to explain such spontaneous repositioning, put forth more than a decade before the first high resolution nucleosome crystal structure, was the twist diffusion model proposed by van Holde (123, 124). In this model, van Holde postulated that a helical turn of nucleosomal DNA may transiently support the gain or loss of a bp – a so-called twist defect. Creation of a twist defect would result from a local, right-handed corkscrew shift of DNA (Figure 2a). Such a shift of DNA toward the nucleosome would add a bp (decreasing local twist), whereas a shift away would remove a bp (increasing local twist). Once made, a twist defect can likewise be passed on to neighboring DNA segments in the helix with a subsequent corkscrew shift, which would locally restore the canonical twist of the duplex while conveying the bp gain or loss to a new location. A central aspect of this model is that, although some histone-DNA contacts must transiently shift due to repositioning of backbone DNA contacts, the resulting twist defect allows canonical histone-DNA interactions to be maintained.

Support for the twist defect idea was obtained with the first nucleosome crystal structure and reinforced through many subsequent structures (23, 29, 53, 80, 81, 90, 98, 117, 118, 125). Although palindromic in sequence, the 146 bp DNA in the first nucleosome structure was unequally distributed on the two halves of the histone octamer, with 1 bp at the dyad, 72 bp on one side, and 73 bp on the other (80). Both halves of the nucleosome showed essentially the same interactions at each histone-DNA contact, with the 1 bp difference between the two sides localized to a region called superhelix location 2 (SHL2; see Figure 1c). Comparison of the two SHL2 sites shows that the +/− 1 bp was staggered on the two strands by ~5

nt, such that the insertion/removal of phosphates occurred where each strand was farthest from histone contacts (Figure 2b). The SHL2 site with one fewer bp (10 bp versus 11 bp) is stretched with increased twist, which gives rise to both bp buckling as well as bp tilting in the major groove to accommodate the different placements of nucleotides (Figure 2c).

Analysis of a number of nucleosome crystal structures has shown that such heterogeneity in DNA twist commonly occurs at SHL2 and SHL5, suggesting that it is relatively easy for the histone core to accommodate 10 or 11 bp at these sites (23, 29, 53, 80, 81, 90, 98, 117, 118, 125). Interestingly, one nucleosome crystal structure showing DNA stretching at SHL5 used the same 146 bp DNA sequence as the original structure (117). The SHL5-stretched structure differed by having a pyrrole-imidazole polyamide bound in the minor groove at SHL4, yet since the sequence was the same, it showed an ability for the twist defect at SHL2 to be transmitted to SHL5 (Figure 2d). Through the use of polyamides that favor particular phases of DNA on the nucleosome, twist defects were shown to be in dynamic equilibrium (33, 47). Although the extent to which other SHLs might accommodate changes in twist is not currently known, molecular modeling suggests that transmission around the nucleosome may not require a twist defect to occupy each successive SHL. Instead, a twist defect could transfer to a non-neighboring site through a coordinated corkscrew shift of the intervening DNA (19). The dynamic oscillations suggest that only modest energies are required to transfer twist defects between different sites on the nucleosome, making it a natural mechanism to relieve strain caused by DNA translocating motors (33, 117, 123).

BULGE/LOOP PROPAGATION MECHANISMS OF NUCLEOSOME SLIDING BY CHROMATIN REMODELERS

In concert with the discovery in the 1990's that SWI/SNF is a nucleosome-disrupting complex involved in gene regulation (27, 57, 66, 91, 95), the chromatin remodeling field rapidly expanded with discoveries of additional remodelers and detailed biochemical analyses (20, 58, 76, 86, 93, 120–122, 136). Two elegant studies in this early period provided a link between DNA twist and remodeling: one showed that SWI/SNF generates negative superhelical torsion on naked DNA (55), and the other showed that torsionally constrained DNA blocks nucleosome sliding (44). However, the idea that DNA twisting was mechanistically important for nucleosome mobility was overshadowed by the idea that DNA was shifted around the histone core in large (≥10 bp) loops or bulges.

Early support for the bulge/loop propagation model

The bulge/loop propagation model differs from twist diffusion in that DNA loops are proposed to lift off the surface of the histone octamer, locally breaking one or more minor groove contacts (Figure 3a) (11, 25, 68, 112). Being a high-energy conformation of DNA, such a bulge or loop is expected to rapidly travel around the nucleosome, maintaining the same number of histone-DNA contacts during loop propagation since contacts on the trailing edge of the loop reform as new contacts are disrupted at the leading edge. Passage of a loop from one side of the nucleosome to the other, which was shown to be theoretically feasible (103), would shift the histone core by the size of the loop.

An attractive aspect of the bulge/loop propagation model was that it paralleled the explanation for nucleosome repositioning by RNA polymerases (65, 115). When bacteriophage RNA polymerase or eukaryotic RNA polymerase III were artificially loaded to transcribe through nucleosomes *in vitro*, the histone cores shifted toward the side of the invading polymerase motor (113, 114). This phenomenon can be understood by initial DNA unwrapping as the polymerase enters, and then DNA rewrapping to a shifted site as polymerase travels further into the nucleosome (Figure 3b). In agreement with this idea, chromatin remodelers were observed to translocate along DNA (55, 73, 100, 101, 109, 131, 141), and an initial interpretation was that, like RNA polymerases, remodelers unwrapped DNA from the histone core by translocating at the nucleosome edge (68, 76, 131).

The bulge/loop propagation model was also consistent with several other experimental findings. SWI/SNF was shown to create large DNA loops with naked DNA and also with long DNA segments containing 1–2 nucleosomes (9, 73, 141). Large loops on the nucleosome surface were proposed to explain otherwise perplexing restriction cutting experiments, where SWI/SNF and RSC made more central DNA sites accessible even for nucleosomes flanked by little or no linker DNA (1, 37, 76, 86) (Figure 3c). Further support for DNA loops rather than twist defects came from experiments suggesting that DNA rotation was unnecessary for nucleosome sliding (4, 5, 112). Without rotation, DNA should maintain its phasing and therefore loops would be expected to form in ~10 bp increments. Consistent with this idea, ISWI and SWI/SNF remodelers were first estimated to shift nucleosomes in steps of ~10 bp and ~50 bp, respectively (61, 104).

Another observation that appeared to favor DNA loops over twists was that DNA nicks did not block nucleosome sliding by remodelers (4, 68, 77). Since DNA nicks relieve torsional strain in naked DNA, these results were interpreted to mean that a DNA translocase, especially one located just outside the nucleosome, could not impart twist into nucleosomal DNA as a primary means of shifting DNA onto the histone core.

Diversification and challenges of the bulge/loop propagation model

Although not counter to the bulge/loop propagation model, several subsequent experimental findings turned out to be inconsistent with initial interpretations and assumptions supporting the original model. For one, SWI/SNF was shown to slide nucleosomes ~50 bp farther than the DNA ends, such that one DNA end was pulled to an internal position, ~20bp from the dyad (41, 61, 100, 142). This off-the-end sliding, not observed for ISWI or Chd1 remodelers, can explain the peculiar restriction site accessibility without invoking large internal DNA loops (41, 59, 100).

Another difference from initial assumptions/interpretations, which also explained the off-the-end sliding, was the finding that the ATPase motors of SWI/SNF, RSC, ISWI, and Chd1 ATPase motors act at the internal SHL2 site rather than the edge of the nucleosome (82, 100, 104, 142). Two variants of the bulge/loop propagation model were put forth to address the ATPase motor being in a more internal location. In one, the DNA loop is proposed to still form at the entry side, but additionally requires a DNA-binding domain that holds entry DNA tightly in place, either to help generate tension (in collaboration with the ATPase motor) or to provide a barrier that prevents the loop from escaping on

the side it just entered (Figure 3d) (25, 26, 142). Both Chd1 and ISWI remodelers have a DNA-binding domain that binds to entry DNA, but we and others showed that insertion of flexible segments between the ATPase motor and DNA-binding domain did not disrupt sliding, arguing against mechanical coupling to the ATPase motor (79, 89). Further, the structures of these DNA-binding domains with DNA only show limited interactions via the sugar-phosphate backbone (105, 137), which is suggestive of easy diffusion and inconsistent with an ability to tightly grip and release DNA in a coordinated way to regulate buildup of torsional strain. In addition, the native DNA-binding domain of Chd1 is dispensable for robust sliding when substituted by foreign binding domains that target either entry DNA or histone tails, suggesting that the native DNA-binding domain has a regulatory rather than mechanical role (82, 89, 92).

Although not clearly utilized for nucleosome sliding, this idea of two separated domains cooperating to create a constrained loop of entry DNA agrees with structures of the large multisubunit INO80 and SWR1 complexes bound to the nucleosome (7, 36, 132). In each of these complexes, two ATPases bound nucleosomal DNA on either side of the entry H2A/H2B dimer. One ATPase was the remodeler motor and the other, ~30–50 bp away, was an actin-related protein (Arp): Arp6 with Swc6 for SWR1 and Arp5 with Ies2 for INO80. Creating torsional strain through this dual grip suggests an attractive mechanism for stimulating H2A/H2B dimer exchange (7, 36, 132).

Regarding the site of ATPase motor action on the nucleosome, it is important to point out that INO80 differs from remodelers in SWI/SNF, ISWI, and CHD families, as well as SWR1 in the INO80 family. Instead of SHL2, the INO80 ATPase motor binds close to the nucleosome edge and appears to translocate on DNA near SHL5 (7, 18, 36). This result implies that remodelers target the two sites on the nucleosome shown to accommodate twist defects (SHL2 and SHL5), while also indicating that sliding can be accomplished by translocases engaging DNA at more than one site on the nucleosome.

Based on the ATPase motor acting at SHL2, another variant of the bulge/loop propagation model proposed that the DNA loop is directly created by the ATPase motor at the dyad (Figure 3e) (25, 141). This model is consistent with interpretations of single molecule data yet departs from the original idea of nucleosome invasion by RNA polymerases, stimulating unwrapping/rewrapping at the entry site. A potential complication for this variation is the negative supercoiling that would be created with a dyad-placed loop. On naked DNA, the RSC remodeler was shown to translocate in ~2 bp steps (109), close to the 1 bp stepsize expected for an inchworm-based mechanism of translocation (48, 69, 107, 126). With this small stepsize, a loop at the nucleosome dyad would be increasingly negatively supercoiled due to the corkscrew motions of DNA being fed into it. Although not precluding loop propagation, a supercoiled loop should be highly sensitive to breaks in the DNA backbone. Yet nicks and single-stranded DNA gaps outside the ATPase site, which would allow relaxation and thus alter energetics of an extruded loop, have little effect on nucleosome sliding (4, 68, 77, 82, 100, 104, 142). Although the nick/gap findings have been used to argue against twist diffusion, twist defects have the important difference that DNA does not detach from the histone surface, and therefore nucleosomal DNA is not free to rotate, but is constrained to a defined helical path (123).

Adding further challenges to interpreting nucleosome sliding by loop propagation, remodelers have been found to shift DNA off the nucleosome in ~1 bp steps (31, 51). Such movement is most consistent with a corkscrew shift of duplex out the exit side. Thus, DNA most likely rotates as it is shifted by remodelers, despite previous experimental designs to block rotation with DNA hairpins and streptavidin, which appeared to allow nucleosome sliding (4, 5, 112, 123).

TWIST DIFFUSION MECHANISMS OF NUCLEOSOME SLIDING BY CHROMATIN REMODELERS

Uncovering timing of DNA movements on the nucleosome

Recent three-color single molecule FRET (Förster resonance energy transfer) experiments have revealed real-time, asynchronous movement of entry and exit DNA during sliding by remodelers (99). These results have impacted our understanding of chromatin remodeling in several ways. First, by simultaneously monitoring movements of entry and exit DNA, the three-color FRET experiments showed unequivocally that entry DNA is first pulled onto the nucleosome before exit DNA is pushed off (Figure 4a). This order of DNA movement corrects a mistaken interpretation from previous two-color FRET experiments, where DNA was proposed to first shift off the nucleosome before new DNA was pulled on (31). The previous interpretation arose from comparing time delays for nucleosomes with two different orientations of the Widom 601 positioning sequence. The Widom 601 sequence (78) is asymmetric in terms of the strength of histone-DNA contacts (49) and unwrapping propensity (88), with one side possessing a higher number of TA dinucleotide steps at minor groove contacts that correlate with stronger histone-DNA interactions. Although not known at the time, Chd1 and ISWI remodelers shift 601 nucleosomes faster or slower when the TA-rich side is on the exit or entry half of the nucleosome, respectively (70, 133). The previous two-color model for DNA timing arose from comparing nucleosomes having the TA-rich sequence on the same side as the DNA fluorophore – on the front half with the entry-side probe (slower) and on the back half with the exit-side probe (faster) (31). In subsequent two-color single molecule FRET experiments, where the 601 was maintained in the same orientation when separately observing entry and exit probes, the time delays were similar for entry and exit DNA movement (63).

Another important finding from the three-color FRET experiments was that nucleosomes transiently absorb DNA during the sliding reaction (Figure 4a). The time delay between movement of entry- and exit-side DNA was ATP dependent, which means that after the remodeler pulled entry DNA onto the nucleosome, the nucleosome absorbed at least one extra bp before a subsequent ATP-binding event stimulated movement of DNA out the exit side (99). As suggested by cross-linking experiments using gapped substrates, as little as 3–4 bp of DNA could be shifted around the nucleosome, indicating that large loops are not necessary for ATP-driven repositioning (99). Although not direct proof of twist diffusion, the small increments and delays between entry and exit DNA movements are consistent with twist defect intermediates.

Initiating DNA movement around the nucleosome through twist defects

Strong support for remodeler-induced twist defects on the nucleosome came from cross-linking studies with the Chd1 remodeler (134). Simply through binding and without ATP hydrolysis, the remodeler altered DNA twist on the nucleosome in a nucleotide-dependent manner. In nucleotide-free and ADP-bound conditions, the ATPase motor reduced DNA twist at SHL2, corresponding with a shift of entry DNA toward the remodeler. This result was unanticipated, as a pure inchworm mode of translocation would predict DNA movement toward the remodeler upon ATPase closure, achieved by ATP binding. By alternating between different conformations of DNA, the remodeler was proposed to behave as a Brownian ratchet, using changes in DNA twist as the core mechanism of DNA translocation (Figure 4a) (16, 17, 134).

Structural insights into chromatin remodeling have been gained from an explosion of nucleosome-bound complexes solved by cryo-EM (6, 7, 21, 36, 38, 39, 50, 71, 75, 116, 128, 132, 139, 140). With regard to the nucleosome sliding mechanism, several cryo-EM structures have beautifully revealed how initial DNA movements prior to ATP binding are achieved (21, 71, 139), bringing us to an exciting new level of understanding. Strikingly, the open state of the ATPase creates a DNA bulge at SHL2 that only shifts the register of the tracking but not guide strand of entry DNA. In the open state, ATPase lobe 2 presents its DNA-binding surface ~6 Å from the surface of unbound nucleosomal DNA at SHL2, effectively forcing the tracking strand to shift by one phosphate to take this detour (Figure 5a). The DNA backbone occupies the same path outside the ATPase binding site, yet this shift appears to change the register of histone-DNA contacts for just the tracking strand by 1 nt over the entire ~50 bp segment of entry DNA. Although the path of the guide strand is also perturbed at the ATPase binding site, it maintains its original register. This unexpected shift of only one strand recapitulates earlier single molecule unzipping studies (49). By using a unique single molecule setup to progressively break each bp of the double helix, that study showed that each strand of DNA binds independently to the histone core, even after half of a minor groove contact had been disrupted (49).

To maintain base pairing, the shift of the tracking strand causes tilting of stacked base pairs (Figure 5b). Interestingly, the bp tilt appears analogous to the tilt accompanying the 1 bp difference at SHL2 in isolated nucleosome structures (Figure 2c). In fact, the bp tilting caused by the tracking strand shift is what one would expect for +1 bp twist defect at each SHL, since a staggered bp insertion would place the tracking strand locally “ahead” of the guide strand, favoring bp tilting in the same direction. Aside from bp tilting, however, DNA geometry for a +1 bp insertion would require greater untwisting of the duplex and therefore would differ from effects of tracking-strand-only movement seen here. Nonetheless, the propagation of bp tilting throughout the entry DNA shows a new and unexpected geometry possible on the nucleosome. Since it has not been seen in any previous nucleosome structures, such bp tilting has an energetic cost that is paid for by binding of the ATPase motor. The strain from bp tilting may therefore assist in subsequent movement of the guide strand (16, 17, 138).

The origin of the bp tilting is intrinsic to the ATPase conformation itself. Both DNA strands at SHL2 are contacted by both lobes of the ATPase motor. Importantly, however, the

tracking strand segment bound by lobe 2 base pairs with the guide strand segment bound by lobe 1. As it transitions between closed and open states, the ATPase motor appears to constrain the duplex to two different geometries. When these two states are aligned on ATPase lobe 2, both ATPase lobes appear to keep a similar grip on the DNA duplex, yet the register of the phosphate backbone for one strand differs between these two states, demonstrating bp tilting within the ATPase binding site (Figure 5c). Thus, the ATPase motor likely behaves as a nucleotide-dependent clamp, enforcing two distinct geometries of duplex DNA at its binding site as it alternates between open and closed states.

Whereas the tracking strand shifts by 1 nt upon binding of the ATPase motor in the open state, the guide strand likely shifts upon closure of the ATPase motor, stabilized by ATP binding. Guide strand movement would be favored by both the two-lobed grip of the ATPase motor, which locally restricts the DNA duplex to a more canonical bp tilt, as well as the strain from bp tilting due to the tracking and guide strands being out of register in the open state. Thus, conformational changes in DNA induced by the ATPase motor can explain a 1 bp shift of entry DNA up to the remodeler binding site.

Inchworming DNA past the histone core

How are movements of entry DNA propagated past the remodeler binding site? A key question is whether the DNA geometry and energetics permit a twist defect at SHL2 in the presence of a translocating ATPase motor. In the simplest scenario, where a +1 bp twist defect is disfavored, closure of the ATPase would simultaneously shift the tracking and guide strand toward the dyad as the entry guide strand is pulled in (71, 138, 139) (Figure 4, step 1→3). This shift would push a bp toward the dyad in a corkscrew motion, creating a twist defect in another location. This simultaneous shift would be driven by the geometrical constraints placed on DNA by the ATPase motor, as it transitions from an open to closed (ATP-bound) state, as well as by histone-DNA contacts and DNA duplex geometry outside the ATPase binding site.

In this case, the remodeler ATPase would shift DNA toward the dyad in concert with inchworm motions expected for a 3’→5’ single-stranded translocase, with closure of the ATPase motor ratcheting DNA past lobe 1. Since sliding requires DNA to shift relative to the histone core, lobe 1 must remain in a similar location on the nucleosome during this process. When bound at SHL2, ATPase lobe 1 contacts DNA at SHL6 on the opposite gyre (21, 38, 39, 71, 75, 116, 139) and it has been suggested that this may help anchor lobe 1 in place during translocation (75, 138). Consistent with a functional importance of the SHL6 contact, basic residues on lobe 1 facing the opposite gyre are conserved across different remodeler families and were shown to be necessary for full nucleosome sliding activity of an isolated SWI/SNF ATPase subunit (75). Yet these secondary DNA contacts are much less extensive than those in the primary DNA-binding cleft, making it unclear whether these residues have an anchoring role. However, movement of nucleosomal DNA relative to the histone core could be ensured by contacts that lobe 2 makes with the histone core (71). In the open state, where the tracking strand has already shifted by 1 nt, lobe 2 contacts the histone core in a manner that would block a backsliding of DNA toward the entry side (21, 71, 139). In particular, lobe 2 contains several helical elements uniquely inserted in remodeler-type

ATPases, called HD2 or the B2 domain (32, 119). The loop immediately preceding one helix of this Snf2-insertion, called the gating helix (71), packs against histone H3 residues at the L1/L2 loops that coordinate SHL2.5 (Figure 5d). In addition to the open state, similar contacts have also been observed for several remodeler ATPases in the closed state (6, 38, 39, 71, 116, 139). Thus, as the DNA duplex is pressed back into a more canonical geometry with closure of the ATPase motor, lobe 2 would ensure that the 1 nt bulge of the tracking strand and compensatory movement of the guide strand are directed from SHL2.5 toward the dyad.

Pumping DNA with twist defects

Instead of entry DNA moving in concert with DNA shifting toward the dyad, another possibility is that DNA movement is discontinuous, with a shift of only the entry DNA creating a twist defect (Figure 4, step 1→2). In this scenario, DNA could be pumped toward the dyad with repeated formation and relaxation of twist defects, with a 1 bp corkscrew shift toward the dyad eliminating each twist defect (Figure 4, step 2→3). Here, the ATPase motor, which binds duplex DNA tightly in the closed ATP-bound form, would remain clamped on DNA during relaxation back to canonical twist. Importantly, a canonical twist of DNA at SHL2 was shown to be reinforced by the Chd1 remodeler in the presence of ADP·BeF_3^- and transition state analogs, suggesting that the relaxation back to canonical twist could potentially be a trigger for ATP hydrolysis (17, 134). In this fashion, the ATPase motor would behave as a Brownian ratchet, with the open and closed states of the ATPase stabilizing otherwise high energy states of DNA that relax to new positions through thermal motion. ATP binding and hydrolysis drive the cycle forward by switching the ATPase between open and closed states, resetting the position of the motor for another round as the neighboring segment corkscrew shifts toward the dyad. This twist defect mechanism notably differs from other translocation models by not requiring an anchoring domain to shift DNA.

The gating helix is a remodeler-specific element poised to create twist defects on the nucleosome

An example of a remodeler-induced twist defect on the nucleosome was revealed with the structure of the SWR1-nucleosome complex (Figure 6a), which provided unique insight into how a more extreme DNA distortion can be created by a remodeler ATPase and accommodated by the nucleosome (132). SWR1 is a large, multisubunit complex dedicated to histone replacement (H2A/H2B with H2A.Z/H2B) and is incapable of repositioning nucleosomes (85, 97). Nonetheless, this complex reveals intriguing structural features that might apply to other remodeler-type ATPases, including those that slide nucleosomes.

The twist defect observed in the SWR1-nucleosome structure corresponds to a 1 bp shift of entry DNA onto SHL2, with the ATPase-bound DNA bulging away from its canonical path on the nucleosome. The ATPase appears to induce a structural distortion of the duplex at the edge of its binding site that manifests as a widening and flattening of the minor groove, which sets DNA on a unique trajectory compared to other remodeler-nucleosome complexes (Figure 6b). Trapped in an ADP·BeF_3^-–bound state, the SWR1 ATPase has a nearly identical closed conformation as other remodelers bound to nucleosomes with ADP·BeF_3^- (132). With this matching domain arrangement, the ATPase motor locally coordinates the

majority of the bound duplex DNA along a similar path as other remodelers. A striking difference in local DNA trajectory, however, occurs where the gating helix of SWR1 packs into the widened minor groove (Figure 6c). In the SWR1 structure, the N-terminal end of the gating helix is sterically incompatible with the canonical path of the guide strand, and this steric conflict is relieved by a sharp bend of the guide strand, which redirects the trajectory of the DNA duplex. A hallmark of remodeler-type ATPases (32, 40, 119), the gating helix and accompanying helical segments occupy a similar location in all structures solved to date. However, the N-terminal end of the gating helix is reorganized in all other structures bound to nucleosomal DNA compared with the same remodeler types solved in isolation (Figure 6d). This structural incompatibility between canonical placement of the guide strand and the gating helix N-terminus suggests a possible conformational switch, where helical extension of the gating helix N-terminus is coupled to kinking of the guide strand and local distortion of the duplex, as observed in the SWR1-nucleosome structure. Although the underlying mechanism remains to be clarified, point mutations of the gating helix in SWI/SNF and a deletion of the loop preceding the gating helix in Chd1 dramatically slowed or stopped nucleosome sliding (71, 116).

In addition to the gating helix, two other aspects contribute to the localized DNA distortion in the SWR1 structure: the tight grip of the closed ATPase on the duplex and the 1 bp insertion. The 1 bp insertion at SHL2 reduced the twist of DNA. However, since the closed ATPase enforces canonical twist of the duplex for ~6–7 bp, reduced twist was not distributed over the full helical turn, but localized to a short segment between the ATPase motor and histone contacts at SHL2.5. Due to the distorted conformation of the DNA duplex, one of the DNA strands was pulled away from the histone core at SHL2.5 (Figure 6e). Compared to other remodelers bound to the nucleosome, the SWR1 ATPase sits one bp closer to the dyad. Therefore, for remodeler ATPases that bind closer to SHL2.5, a similar distortion of the double helix could have a more significant impact on SHL2.5 histone-DNA contacts. Interestingly, when a disulfide bond was introduced at this L1/L2 loop of H3 and H4, immediately beneath the contact made by the gating helix, nucleosome sliding by ISWI was blocked and RSC was altered, suggesting that conformation and/or dynamics of this region may be coupled to sliding activity (108).

If the gating helix of other remodeler ATPases were used to kink the guide strand on the nucleosome, such localized DNA distortion could assist DNA translocation in several ways. For one, this +1 bp twist defect could constitute the basic step of DNA translocation through twist diffusion (Figure 4b, step 1→2→3). Since DNA untwisting is focused into a short segment, the +1 bp insertion would be more energetically costly than if it were allowed to be distributed, making transfer to another location on the nucleosome energetically downhill. Another possibility is that the sharp kink in the DNA duplex may enable the ATPase motor to enter a rapid translocation phase. In this scenario, the sharp kink would be maintained as the motor cycles through the ATP hydrolysis cycle and pumps DNA around the nucleosome (Figure 4b, step 2).

Although it remains to be shown for a remodeler translocating on the nucleosome, an extended gating helix has been observed for CSB/Rad26 bound to the double-stranded/single-stranded DNA junction behind RNA polymerase II (Pol II) (135). CSB/Rad26 helps

Pol II transcribe through pauses on undamaged DNA, and consistent with this role, it was oriented to translocate toward Pol II, which could assist a stalled polymerase by pushing it in the direction of transcription (135). In the structure, the extended gating helix, which would be incompatible with duplex DNA, appears like a rudder just ahead of where the two DNA strands reanneal. In addition to assisting Pol II, CSB/Rad26 can reposition nucleosomes (22, 24, 130), raising the possibility that translocation on DNA with an extended gating helix may also occur on the nucleosome.

More generally, the gating helix and Snf2-insertions are positioned analogously to the duplex-melting “pin” elements of true helicases, immediately in front of the translocating ATPase motor (54). Unlike helicases, however, the motor binds and appears to define a structural template for duplex DNA, as would be expected for an annealing helicase. Thus, the gating helix could be used to distort the duplex and thus antagonize DNA-bound factors immediately in the path of the motor, without melting DNA. Most DNA-binding factors are extremely sensitive to DNA groove width (62), and therefore a groove-widening/duplex-kinking element like the Snf2-insertions would be an ideal tool to stimulate dissociation. Such a mechanism would explain action of remodeler-type ATPases like Rad54 (28) and Mot1 (127) that disrupt non-nucleosomal DNA binding proteins. Given the large footprint of nucleosomal targets, however, dissociation due to ATPase action a single site seems impractical. Instead, local distortions of the duplex allow remodelers to reposition nucleosomes along DNA, which can lead to disruption if neighboring nucleosomes are shifted into one another (30, 35). By stimulating movement of DNA around the histone core from action at a single site, the remodeler ATPase appears to act as a jiu-jitsu master, exploiting the intrinsic geometrical constraints of duplex DNA.

OUTLOOK

Ever since the discovery of ATP-dependent enzymes that alter chromatin structure, understanding the mechanistic basis of nucleosome sliding has remained a major focus of the remodeling field. Equipped with new insights into initiation of the nucleosome remodeling process, we are now entering an exciting new phase. Further advancing our understanding will require exploring unresolved questions on both the nucleosome and remodeler side of the reaction. On the nucleosome side, what capacity exists for twist defects beyond what has been observed in crystal structures? How do DNA sequence and histone variants affect the location and dynamics of twist defects? The histone core has been captured with alternative structures beneath the DNA wrapping (13, 14), and yet how such dynamic changes affect DNA are presently unknown. On the remodeler side, do the ATPases that translocate DNA at SHL2 create twist defects analogous to that seen with SWR1? What is the trigger for ATP hydrolysis? Unlike the RSC remodeler, ISWI and Chd1 shift DNA in multi-bp bursts (15, 31, 51, 56, 63, 96). Does this reflect differences in the translocation process at SHL2, or does it arise from unique regulation? Does INO80, acting around SHL5, utilize a similar mechanism as remodelers that slide nucleosomes from SHL2? Addressing these and other emerging questions will no doubt continue to reveal fascinating secrets of these remarkable machines.

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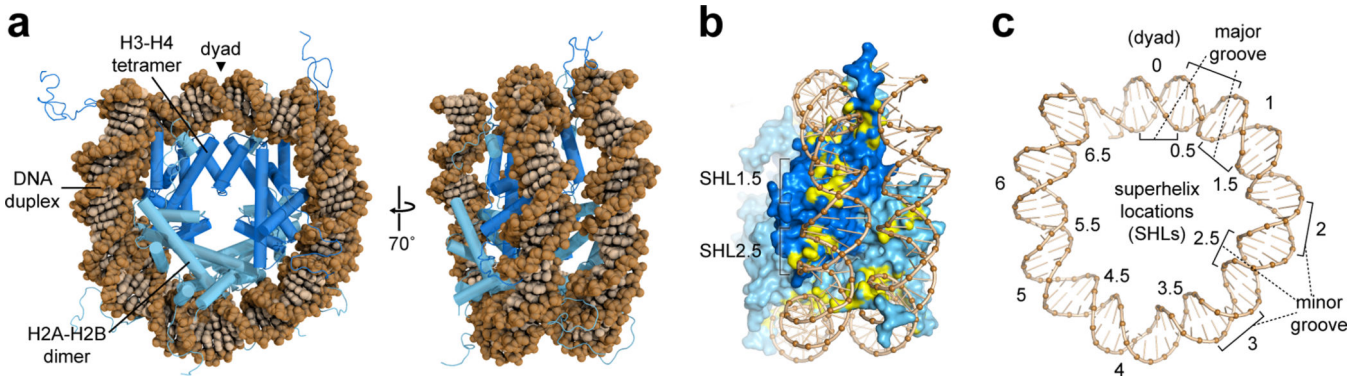

Figure 1. The structure of the nucleosome.

(***a***) Overview of a high-resolution nucleosome crystal structure (PDB code 1KX5; Reference 29). The 147 bp DNA duplex wraps around the histone octamer approximately 1.65 times. The dyad indicates the central two-fold axis of symmetry.

(***b***) With each turn of the DNA duplex, the histone core makes regular interactions with DNA where the phosphate backbone faces the core. Yellow surfaces represent regions of the histone core that make direct hydrogen bonding and van der Waals contacts with the DNA backbone.

(***c***) DNA sites around the nucleosome are referred to by their superhelix location (SHL). SHL0 defines where the inward-facing major groove aligns with the central two-fold or dyad axis of the nucleosome, and each successive inward-facing major or minor groove is given integer (major) or half integer (minor) values (80).

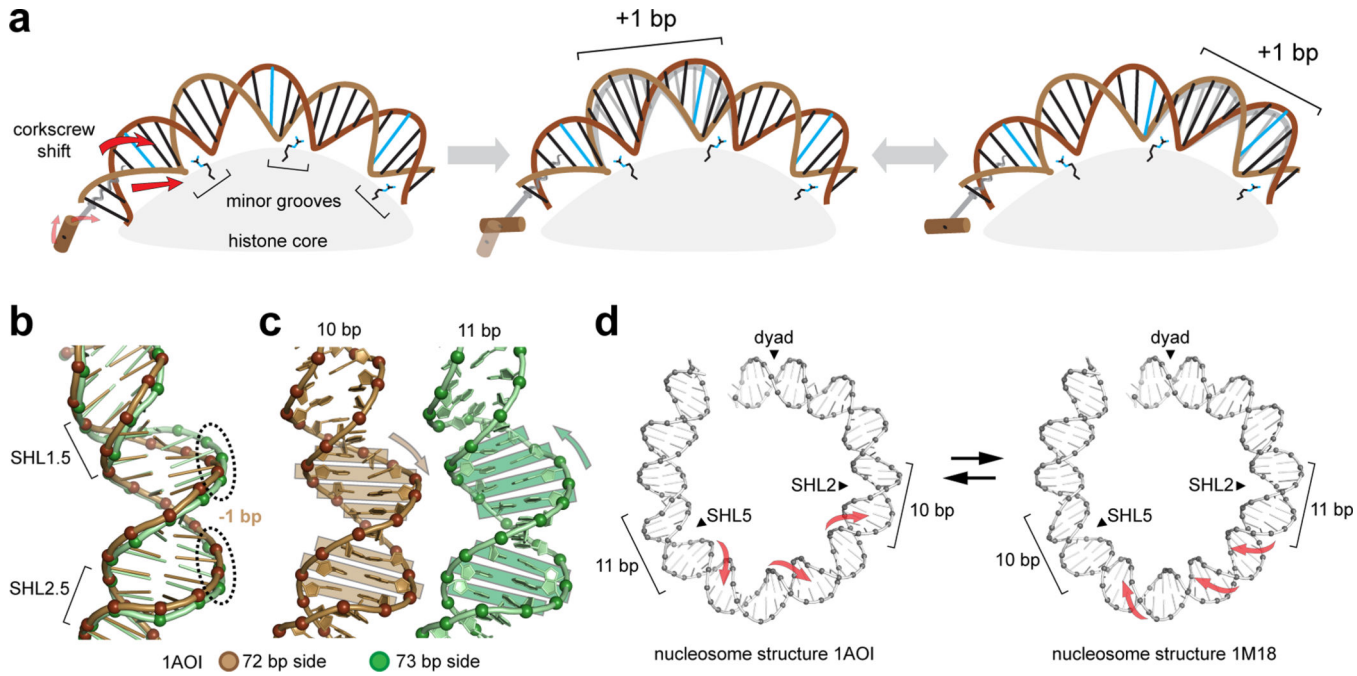

Figure 2. Twist defects on the nucleosome.

(***a***) The twist diffusion model for nucleosome repositioning (123, 124). A corkscrew shift of the duplex causes a DNA segment between two minor groove contacts to absorb an additional bp, which locally changes DNA twist (a twist defect). Once formed, a corkscrew shift on the other side transfers the twist defect further onto the nucleosome, accompanied by a 1 bp translation of DNA.

(***b***) Changes in DNA geometry accompanying twist defects. Comparison of the two sides of the original 146 bp nucleosome structure at SHL2 shows that the one bp difference is distributed ~5 nt away on the two strands, farthest from histone-DNA contacts.

(***c***) As highlighted by rectangular boxes, the shift in the DNA backbone at the farthest point from the histone core correlates with bp tilting.

(***d***) Two nucleosome crystal structures that captured twist defects at two separated locations, SHL2 and SHL5 (80, 117). These nucleosomes had the same DNA sequence and length, only differing by the presence or absence of a pyrrole-imidazole polyamide at SHL4 (1M18 structure). Red arrows represent expected corkscrew rotations of intervening DNA needed for a twist defect to collapse at one location and appear at the other.

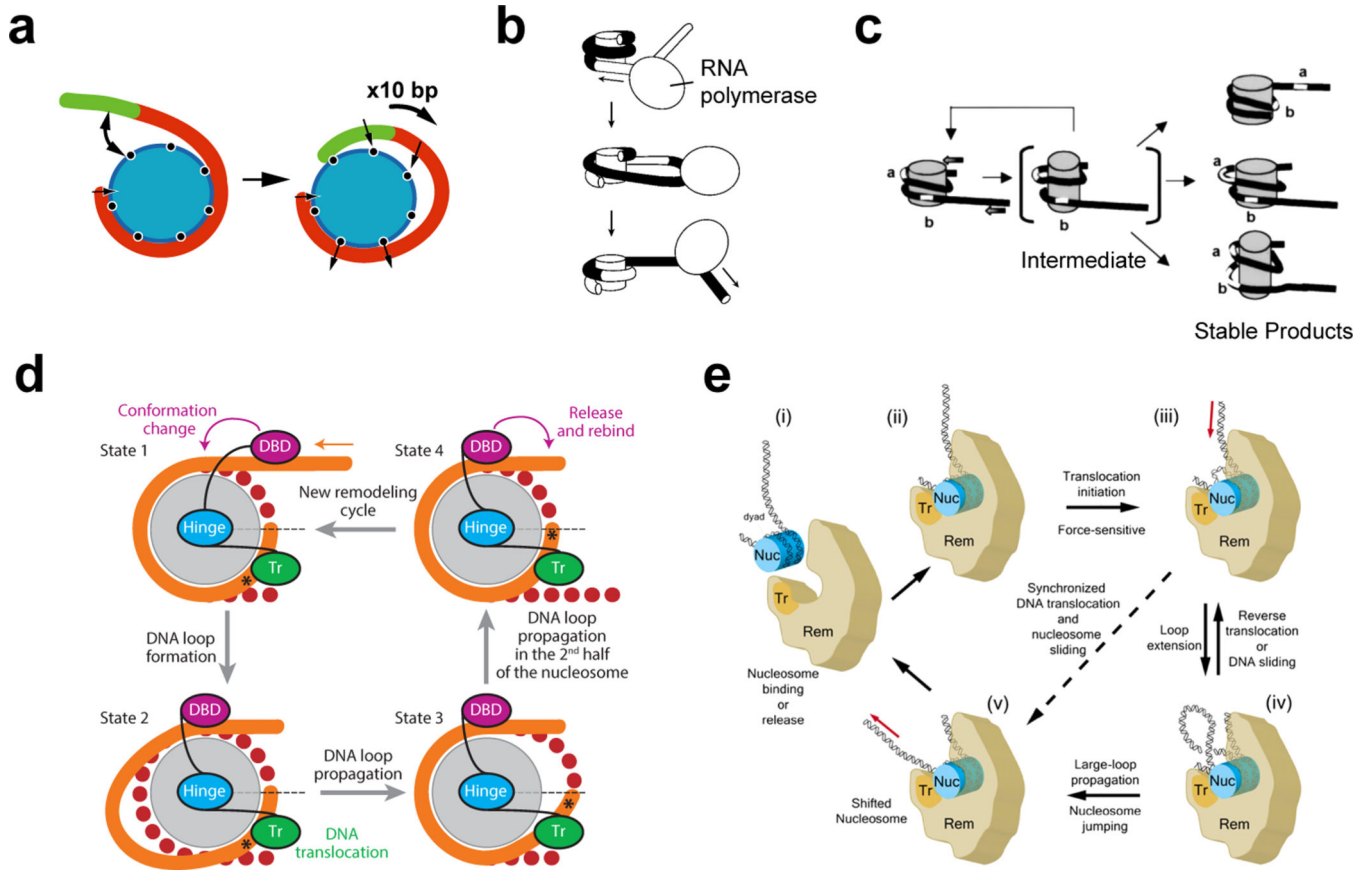

Figure 3. Bulge/loop propagation models of nucleosome sliding.

(***a***) A loop recapture model. In this model, DNA unwraps and then rewraps with a shifted position, trapping a loop of DNA. Adapted from Längst & Becker 2004 (67).

(***b***) Nucleosome repositioning resulting from transcription by an RNA polymerase around the histone core. Adapted with permission from Studitsky et al., 1997 (114).

(***c***) A model for how the SWI/SNF remodeler alters nucleosome structure, creating persistent DNA loops on the histone surface. Adapted from Fan et al., 2003 (37).

(***d***) A loop propagation model where the entry-side loop is created by cooperation between the ATPase motor at SHL2 (Tr) and a DNA-binding domain (DBD) at the nucleosome edge. DNA movement past the ATPase motor occurs between states 2 and 3, highlighted by the shift of an asterisk (*) reference point. Adapted from Clapier & Cairns, 2009 (25).

(***e***) A model where translocation of the RSC ATPase motor (Tr) at the internal SHL2 site directly spools out DNA into a loop at the dyad. Adapted from Zhang et al., 2006 (141).

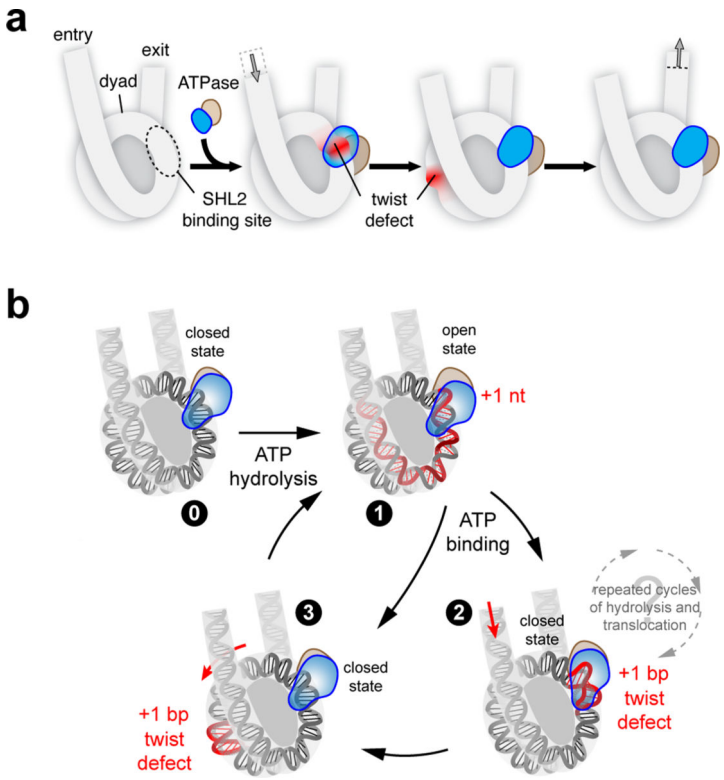

Figure 4. Models of nucleosome sliding via twist defects.

(***a***) Overview of remodeler-catalyzed DNA motions, showing that DNA first shifts onto the nucleosome from the entry side, is transiently absorbed on the nucleosome after being expelled from SHL2, and then shifts off the exit side.

(***b***) Possible pathways for how remodeler ATPases stimulate 1 bp shifts of DNA around the nucleosome.

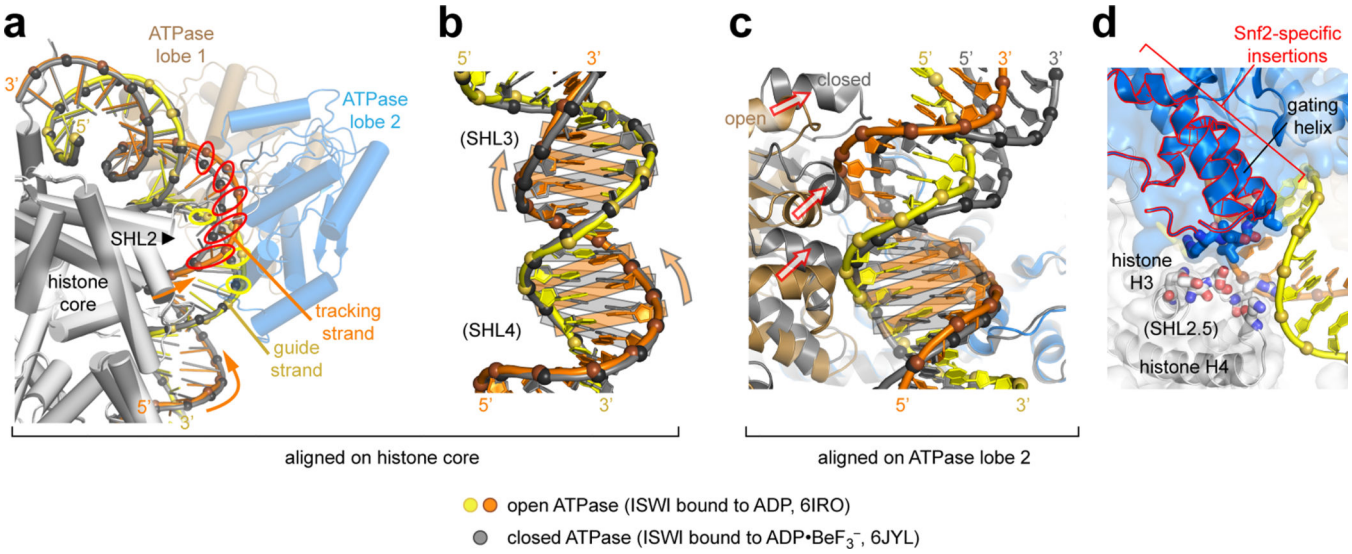

Figure 5. Contacts and structural changes associated with the open state ATPase at SHL2.

(***a***) In the open state, the shifted position of ATPase lobe 2 on the nucleosome alters the path for the tracking strand, which correlates with a change in register (red ovals) of the tracking strand (orange) but not guide (yellow).

(***b***) Due to the shift in register of the tracking strand, DNA base pairs show a marked tilting, which continues outside the SHL2 binding site.

(***c***) Base pair tilting originates in the ATPase motor. Superpositioning lobe 2 from a closed ATPase (gray, 6JYL) onto that of an open ATPase (colored, 6IRO) shows a similar path of the DNA backbone even though the register of the two strands differs by 1 nt, evident as bp tilting. This is consistent with a change in DNA geometry due to contacts made by both ATPase lobes.

(***d***) Snf2-specific insertions on lobe 2 contact the histone core. In most nucleosome-bound structures, the polypeptide segment immediately preceding the gating helix contacts residues on the L1 loop of histone H3 (sticks). The loop prior to this segment is often disordered, however in nucleosome-bound complexes of Chd1 (116), CHD4 (38), and SNF2h (6), this loop was ordered and appeared to make more extensive contacts with histone H3.

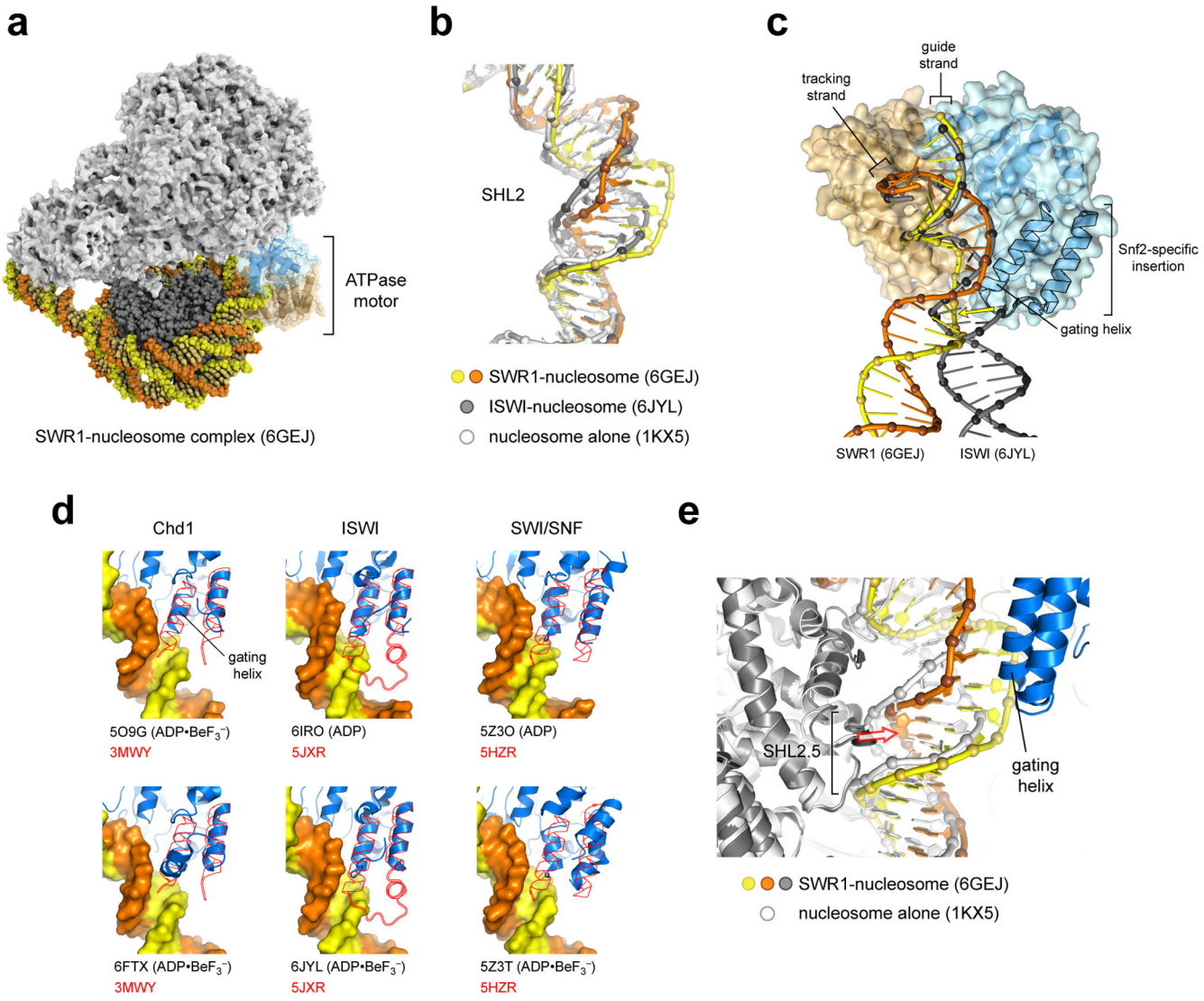

Figure 6. SWR1 distorts DNA on the nucleosome.

(***a***) Overview of the SWR1-nucleosome complex, bound with ADP·BeF_3^- (132).

(***b***) Comparison of DNA conformations at SHL2. Histone and remodeler proteins are omitted for clarity.

(***c***) A kink in the guide strand alters the path of the DNA duplex in the SWR1 complex. Shown is a surface/backbone representation of the SWR1 ATPase motor (tan, blue; 6GEJ) bound to a segment of DNA surrounding SHL2. The position of the gray DNA results from superimposing the ATPase motor of an ISWI remodeler (6JYL), also bound to ADP·BeF_3^-, with the SWR1 ATPase motor (ISWI ATPase motor omitted for clarity).

(***d***) Comparison of the gating helices of Snf2-insertions for remodelers bound to nucleosomes (solid) to the same regions of the nucleosome-free structures (red outlines). For each structure, superpositioning ATPase lobe 2 from unbound structures onto the nucleosome complex produces a steric clash with the guide strand.

(***e***) The SWR1 ATPase lifts the DNA backbone away from SHL2.5, partially disrupting histone contacts. This shifts the minor groove away from H3 arginine 83, which appears to

no longer be inserted (not shown). The nucleosome alone structure (white, 1KX5) is shown for comparison.