Chromatin remodelling: the industrial revolution of DNA around histones

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Abstract | Chromatin remodellers are specialized multi-protein machines that enable access to nucleosomal DNA by altering the structure, composition and positioning of nucleosomes. All remodellers have a catalytic ATPase subunit that is similar to known DNA-translocating motor proteins, suggesting DNA translocation as a unifying aspect of their mechanism. Here, we explore the diversity and specialization of chromatin remodellers, discuss how nucleosome modifications regulate remodeller activity and consider a model for the exposure of nucleosomal DNA that involves the use of directional DNA translocation to pump 'DNA waves' around the nucleosome.

Kinetochore
A large multi-protein complex that assembles onto the centromere of the mitotic chromosome. It links the chromosome to the microtubules of the mitotic spindle to segregate sister chromatids towards the spindle poles.

Centromere
The region of a mitotic chromosome on which the kinetochore assembles.

Telomere
The end of a normal chromosome, which consists of a repeating sequence that is extended by a telomerase to prevent the shortening of DNA that accompanies replication.

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The past decade of research has revolutionized our understanding of chromatin. Early research focused on the packaging and compaction of DNA by nucleosomes, the primary repeating unit of chromatin, which led to the notion of chromatin as a relatively static packaging material. Although DNA packaging and occlusion are indeed attributes of nucleosome function, nucleosomes are now recognized as dynamic and instructive participants in virtually all chromosomal processes, including transcription, replication, DNA repair, kinetochore and centromere construction, and telomere maintenance[1].

However, nucleosomes themselves are stable and show limited mobility, and their dynamic properties are due to the action of nucleosome-modifying and -remodelling complexes. Modifying complexes add or remove covalent modifications at particular residues on the histone proteins, marks that are subsequently recognized by transcriptional regulators and other factors[2,3]. Modifying complexes work in concert with chromatin-remodelling complexes, which restructure, mobilize and eject nucleosomes to regulate access to the DNA[4]. Remodellers have evolved into several families that specialize in particular chromatin tasks. Together, these specialized modifying and remodelling complexes guide the ordered recruitment of transcriptional regulators to particular loci, and give chromatin its dynamic character[5].

In keeping with their specialization *in vivo*, each remodeller affects the structure of nucleosomes and nucleosome arrays in a distinct manner. These differences might be interpreted as evidence that different remodellers use unrelated mechanisms to restructure the nucleosome[6]. However, all remodellers require ATP hydrolysis for their remodelling functions, and all remodellers contain an ATPase domain that is highly similar to those that are present in known DNA translocases. Therefore, an alternative view is that DNA translocation might be employed by all remodellers[7]. Supporting this notion, several remodellers possess DNA-translocation activity[7–11].

In this review, we will explore the basis of remodeller specialization by discussing their numerous functions *in vivo*, and their different effects on nucleosome positioning and structure *in vitro*. We then explore how the process of DNA translocation might be used by remodellers in various capacities to execute specific remodelling tasks. We begin with a brief description of the dynamic properties of nucleosomes.

Dynamic properties of nucleosomes

Nucleosomes exhibit at least three dynamic properties *in vivo*: compositional alteration, covalent modification and translational repositioning (that is, altering the position of the histone octamer to a new position along the DNA) (FIG. 1). Nucleosomes are constructed from the four canonical histones[12] (H2A, H2B, H3 and H4) or, alternatively, from histone variants that specialize chromatin at particular regions[13–15]. Whereas canonical nucleosomes are deposited during DNA replication, histone variants are deposited actively in a replication-independent manner[16]. For example, nucleosomes that contain the histone H2A variant H2A.Z (Htz1 in yeast) are highly enriched at gene promoters, and are deposited by the chromatin-remodelling complex SWR1 (REFS 14,17,18) to help promote gene activation[19].

In addition, nucleosomes can be covalently modified (for example, by acetylation or methylation) on lysine residues that reside in their amino-terminal 'tails', which extend from the octamer core. The repertoire of histone

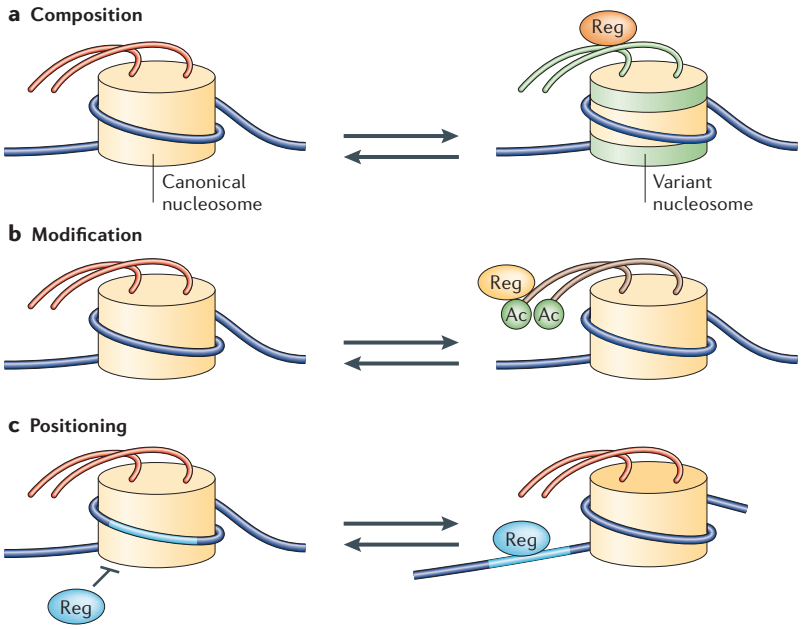

Figure 1 | **Dynamic properties of nucleosomes. a** | Remodelling complexes of the SWR1 family can remove the canonical H2A–H2B dimers and replace them with Htz1–H2B dimers (indicated in green), forming a variant nucleosome with unique tails that might bind unique regulatory proteins (Reg). **b** | Nucleosome modification (only acetylation (Ac) is depicted for simplicity) allows the binding of regulatory factors, which have specialized domains (bromodomains) that recognize acetylated histone tails. **c** | Nucleosome repositioning allows the binding of a regulatory factor to its site on nucleosomal DNA (light-blue segment). Remodellers are necessary to provide rapid access to nucleosomal DNA by sliding of the octamer along the DNA. Alternatively, the site might be accessed on the surface through the generation of a DNA wave or through histone-octamer ejection (not shown; see main text).

modifications and their locations has been reviewed elsewhere[3]. Histone-modifying enzymes are targeted to particular loci through their interaction with site-specific DNA-binding proteins — transcriptional activators will recruit enzymes that provide 'activating' histone modifications, such as acetylation, whereas transcriptional repressors recruit enzymes that catalyse 'repressive' modifications, such as deacetylation. Activating modifications attract remodellers and basal transcription factors to promote transcription, whereas repressive modifications generally deter basal transcription factors and attract proteins that promote chromatin packaging and compaction.

Finally, nucleosomes are mobilized to alternative positions along the DNA, or at times are ejected, by remodellers to provide regulated access to DNA sequences. Nucleosome repositioning and ejection are important for many chromatin functions: to space nucleosomes properly during chromatin assembly, to enable the ordered access of transcription factors to specific genes during transcriptional regulation and to regulate the access of DNA-repair factors to DNA lesions in chromatin[4]. All three of these dynamic processes (composition, modification and repositioning) work in concert to establish or alter the regional properties of chromatin, although the relative importance and order of these processes vary when individual loci are examined.

Bromodomain
A motif that is common in chromatin factors and that binds to acetylated lysine residues in histone tails and other proteins.

SANT domain
An evolutionarily conserved protein domain so named because it is commonly found in Swi3, Ada2, N-CoR and TFIIIB. It is important for DNA and histone-tail binding.

SLIDE domain
A SANT-like ISWI domain that interacts with DNA.

Remodeller diversity and specialization

All eukaryotes contain at least five families of chromatin remodellers: SWI/SNF, ISWI, NURD/Mi-2/CHD, INO80 and SWR1. The remodeller designation might also extend to relatives of the RAD54 protein, which can alter nucleosome structure *in vitro*[8,10] and might reposition nucleosomes during DNA repair. Together, remodellers mediate a remarkable number of biological processes (TABLE 1). To understand their specialized roles, their mechanism of action must be understood. Here, we focus on the two best-studied families of chromatin remodellers, SWI/SNF and ISWI, which have together provided considerable insight into the remodelling process; we then briefly discuss the SWR1 family in light of these studies.

Remodeller specialization. Remodellers of the SWI/SNF and ISWI families execute different tasks *in vivo* and have unique protein compositions (FIG. 2). SWI/SNF remodellers all contain a conserved ATPase subunit and a set of five additional, conserved core members that together define the family[20] (FIG. 2). For example, the yeast SWI/SNF-family remodeller RSC contains the ATPase Sth1 and the core proteins Rsc8, Rsc6, Sfh1, Arp7 and Arp9 (REF. 21). ISWI remodellers share an identical ATPase subunit, ISWI, whereas unique associated proteins specialize each ISWI-containing complex (NURF, CHRAC and ACF)[20]. For example, the ACF complex contains the ISWI ATPase and the protein Acf1 (REF. 22). How unique subunits specialize ISWI complex function or activity is an interesting topic, but is beyond the scope of this review. Instead, we will focus on the function of the ATPase subunits of SWI/SNF and ISWI remodellers, and explore their similarities and differences. Importantly, the ATPase domain that is present in SWI/SNF ATPases is highly similar to the ATPase domain in ISWI and other remodellers[23,24], raising the possibility that these ATPases share a similar fundamental mechanism.

In addition to a conserved ATPase domain, the catalytic subunits of SWI/SNF and ISWI remodellers also contain unique domains that are near their C termini and help target and/or regulate the complex. For example, SWI/SNF-remodeller ATPases contain a bromodomain that is near their C termini, a motif that binds acetylated histone tails[25] (FIG. 2). The bromodomain that is present in the catalytic ATPase (the Snf2/Swi2 subunit) of the yeast SWI/SNF complex is important for the association of yeast SWI/SNF with acetylated chromatin[26], which indicates a role in the targeting or retention of SWI/SNF at certain loci. Certain SWI/SNF-remodeller subunits contain multiple bromodomains with a preference for particular acetylated residues in the histone tails[27], which might help specify the targeting of the remodelling complex to particular nucleosomes. Likewise, the C terminus of the ISWI protein contains two domains, known as SANT and SLIDE (FIG. 2), that might help ISWI in recognizing two nucleosome determinants: the histone tails and the linker DNA that emits from the nucleosome[28], respectively (see below).

ISWI complexes have central roles in chromatin assembly[29], which involves the ordering and spacing (that is, the translational phasing) of nucleosomes

Table 1 | **Biological functions of remodellers**

Remodelling complex	Biological functions	References
SWI/SNF-family remodellers		
Sc SWI/SNF	Pol II activation	84,85
	Elongation	86
	DSB repair	87
	Targeting by activators	88,89
Sc RSC	Pol II regulation	90–92
	Pol III regulation	90
	Cell signalling	91,93
	Spindle-assembly checkpoint	91
	Chromosome/plasmid segregation	94,95
	Cohesion	96
	DSB repair (homologous recombination)	87
	Cell-cycle progression	97
	Targeting by activators	88
	Octamer transfer/ejection	73,74
Dm Brahma	Pol II regulation	98
	Development	99,100
	Elongation	101
Hs SWI/SNF	Tumour suppressor	102–104
	Differentiation	105–107
	Development	108–110
	Elongation	111
	Signalling	112
	Splicing	113
ISWI-family remodellers		
ISWI*	Elongation	34
	Pol II repression	32,114
	Replication	115,116
	X-chromosome regulation	31
	Cohesion	117
	Embryonic development and differentiation	118
Dm ACF and CHRAC	Chromatin assembly	22,36,68
	Nucleosome spacing	36
Dm NURF	Transcriptional activation	119
INO80-family remodellers		
Sc INO80	DNA repair	120–122
	Pol II activation	123
At INO80	Homologous recombination	124
	Gene transcription	124
SWR1-family remodellers		
Sc SWR1	Htz1 deposition	14,17,18
Dm SWR1	DNA repair	125
NURD/Mi-2/CHD-family remodellers		
Hs NURD	Transcriptional repression and silencing	126,127
Ce NURD	Development	128,129

*Based on data from many species. ACF, ATP-utilizing chromatin-assembly and remodelling factor; *At*, *Arabidopsis thaliana*; CHRAC, chromatin-accessibility factor; *Dm*, *Drosophila melanogaster*; DSB, DNA double-strand break; *Hs*, *Homo sapiens*; ISWI, imitation switch; NURD, nucleosome remodelling and deacetylation; NURF, nucleosome-remodelling factor; Pol II, RNA polymerase II; RSC, remodels the structure of chromatin; *Sc*, *Saccharomyces cerevisiae*.

following DNA replication[30]. By contrast, SWI/SNF remodellers lack this function. For their role in transcriptional regulation, ISWI remodellers primarily organize and order nucleosome positioning to promote repression, as shown by the Tsukiyama, Becker, Kadonaga and Tamkun groups[31,32]. By contrast, SWI/SNF remodellers primarily disorder and reorganize nucleosome positioning to promote transcription-factor binding and activation[33]. However, there are reported chromatin loci where ISWI remodellers organize gene chromatin to promote transcriptional elongation[34], and loci where SWI/SNF remodellers promote the binding of transcriptional repressors[35]. So, although these complexes conduct specific tasks, it is the particular chromatin context that determines the precise outcome of their action.

A series of elegant *in vitro* biochemical experiments by the Becker, Owen-Hughes, Wu and Kadonaga laboratories have shown that ISWI remodellers effect nucleosome ordering, whereas SWI/SNF remodellers disorder nucleosomes. ISWI complexes such as ACF promote the ordered and equal spacing between nucleosomes along a DNA template[22,36] (FIG. 3a, right panel). By contrast, SWI/SNF remodellers generally disorder nucleosomes that were initially equally spaced[37,38] (FIG. 3a, left panel), although the SWI/SNF complex from *Drosophila melanogaster* can exhibit limited spacing activity[39]. Another distinction between ISWI and SWI/SNF remodellers involves their action on mononucleosomes, which has provided several insights into their mechanistic differences. SWI/SNF remodellers generate numerous nucleosome products, with the DNA at many different translational positions along the octamer surface[40] (FIG. 3b). However, a prominent nucleosome product is one in which the DNA is recessed by ~50 bp, which results in a nucleosome species that lacks 4–5 histone–DNA contacts[37,41]. By contrast, this product is not observed with ISWI remodellers, which instead generate nucleosomes with a uniform translational position.

Interestingly, the particular translational product that is created depends on the protein factor(s) that is associated with the ISWI ATPase. For example, the ISWI protein in isolation preferentially slides mononucleosomes that are positioned in the centre of the DNA fragment towards the end, whereas the ISWI protein that is within the CHRAC or ACF complexes moves octamers that are positioned at the end towards the centre[42] (FIG. 3b), which implies that the associated proteins influence the reaction. Although the free DNA ends that are present on mononucleosomes are not present in chromatin *in vivo*, these different properties have proved useful for building mechanistic models, as described below.

Taken together, nucleosome sliding is a property that is common to both SWI/SNF and ISWI remodellers, but the different translational products that are generated indicate that each uses a unique mechanism. Alternatively, these remodellers might share a similar underlying mechanism, but apply and regulate this mechanism differently to tailor the remodeller for specific functions *in vivo*. Indeed, over the past few years, several mechanisms have been proposed for increasing access to DNA on the nucleosome surface and for nucleosome sliding (BOX 1). In the following section, we consider ATP-dependent DNA translocation as a possible unifying property of remodellers, and suggest that their mechanistic differences lie in the regulation of this fundamental property.

Translational position
The precise 146-bp region on which the nucleosome resides in a DNA molecule.

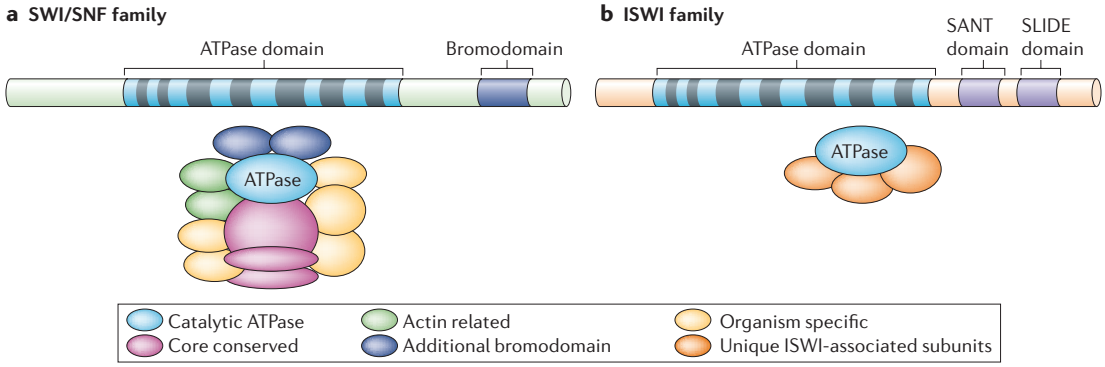

Figure 2 | **Composition of SWI/SNF and ISWI remodelling complexes.** SWI/SNF and ISWI remodellers share a similar ATPase domain, but differ in all other associated subunits. The catalytic subunit of both remodellers contains a conserved ATPase domain that belongs to the DEAD/H-box helicases. **a** | SWI/SNF remodellers typically contain 8–15 subunits, with the core and actin-related subunits conserved among all the members. The ATPase subunit of all SWI/SNF remodellers also contains a bromodomain. **b** | The ATPase subunit of ISWI remodellers contains a C-terminal SANT and a SLIDE domain, which probably bind histone tails and linker DNA. In addition, ISWI remodellers typically contain a further 2–4 subunits that help to specialize the remodeller for particular tasks.

Remodellers as DNA-translocating machines

Remodeller ATPases resemble SF2 DNA translocases. The key to understanding remodeller mechanisms is to understand how the hydrolysis of ATP is converted into a mechanical force that alters histone–DNA contacts. Importantly, all remodelling reactions are ATP dependent and the isolated catalytic ATPase subunit of SWI/SNF or ISWI remodellers can achieve modest levels of remodelling, as shown first by the Kingston and Becker laboratories[43,44]. Importantly, all remodeller ATPases belong to the superfamily II (SF2) of DEAD/H-box helicases and translocases. SF2-family members include both DNA and RNA translocases, some of which have associated helicase activity[45], as well as type I restriction enzymes, which lack helicase activity but exhibit DNA-translocation activity[46]. The SF2-family members RecG and NS3 are structurally and mechanistically similar to the SF1-family translocase PcrA, and together these proteins have been extensively studied[47–49].

SF1 and SF2 helicases contain two domains, a wedge-like DNA-duplex-destabilizing domain that is coupled to a DNA-translocating motor domain; helicase activity is provided by their combined and coupled action to form a moving DNA wedge that separates duplex DNA[45]. However, chromatin remodellers are not helicases, and both sequence alignments and structural studies indicate that the remodeller ATPases contain the translocation domain but lack a wedge domain. Taken together, a consistent property of SF1- and SF2-family enzymes is the ATP-dependent translocation on DNA or RNA, a versatile property that can be used in different capacities in nucleic-acid biology. So, a key question is whether remodellers share this translocation property and use it for remodelling.

Remodellers translocate DNA. Over the past few years, a series of studies with the yeast remodellers SWI/SNF, RSC, ISWI and Rad54 has established that their ATPase subunits are indeed ATP-dependent DNA translocases[7–11]. Initial evidence for DNA translocation included: first, remodeller ATPase activity is proportional to the length of the linear DNA molecule provided, which indicates that ATP is turned over continuously during translocation until the end of the DNA is reached; second, extremely small DNA minicircles elicit maximal ATPase activity, as they mimic DNA of infinite length; and third, the ability of remodellers to remove a physical barrier that is present on the DNA — for example, the displacement of the third strand of a DNA triple helix in an ATP-dependent manner[7,9]. Furthermore, the remodellers SWI/SNF, RSC and ISWI seem to track in a 3′→5′ direction along one strand of the DNA duplex, which indicates that remodellers couple the energy of ATP hydrolysis to directional DNA translocation along the backbone of one strand of the DNA duplex[9,50].

Very recently, single-molecule approaches have provided direct measurements of translocation by the RSC complex along naked DNA. By combining atomic-force microscopy with a magnetic trap, Owen-Hughes and colleagues have observed that the RSC complex forms loops on otherwise-naked DNA. These loops grow in an ATP-dependent manner, which is consistent with RSC using DNA translocation to extend loop size[51]. Interestingly, following their extrusion, a fraction of the loops shortened in an ATP-dependent manner, raising the possibility that translocation might switch direction under certain circumstances.

DNA translocation on nucleosomes. To understand how DNA translocation might be applied to remodel nucleosomes, we must first understand how the remodeller engages the nucleosome substrate, and how it determines the position on the nucleosome from which translocation will occur. For most remodellers, the standard enzyme–substrate unit of remodelling involves a single remodeller that is bound to a single nucleosome[52,53], although certain remodellers can bind

DEAD/H-box ATPase domain
An evolutionarily conserved protein domain that is present in DEAD/H-box proteins with ATP-dependent helicase/translocase activity and that contains seven characteristic motifs.

Helicase
A motor protein that uses the energy of ATP hydrolysis to unwind nucleic-acid duplexes.

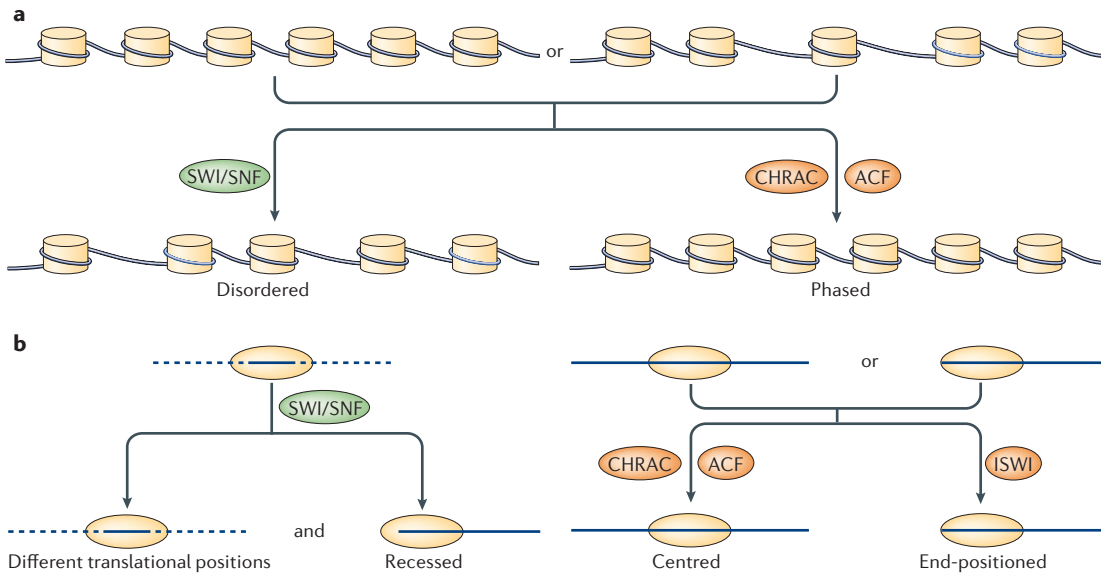

Figure 3 | **Sliding properties of SWI/SNF and ISWI remodelling complexes. a** | The SWI/SNF and ISWI remodellers (such as ACF and CHRAC) have contrasting nucleosome-sliding properties on nucleosome arrays. SWI/SNF remodellers disorder the positions of an initially phased array of nucleosomes, whereas many ISWI remodellers translationally phase an initially random array. **b** | The SWI/SNF and ISWI remodellers have contrasting effects on mononucleosomes. Nucleosomes are depicted in a two-dimensional projection, with the histone-octamer position on the DNA depicted by the beige oval. The solid dark blue lines indicate the translational position of DNA, whereas the dotted lines signify DNA at different translational positions along the octamer. Remodelling by SWI/SNF complexes results in different translational positions, and generates a nucleosome species in which the DNA is recessed by ~50 bp. ISWI remodellers, such as ACF and CHRAC, do not produce recessed nucleosomes, but instead generate nucleosomes that have a uniform translation position that is either centred or end-positioned, depending on the protein partners of the particular ISWI complex.

to the nucleosome as a dimer[54]. ISWI remodellers bind the nucleosome at two separate locations: an internal location ~2 turns from the nucleosomal dyad, and an external site that involves a DNA linker that is near the nucleosome-entry site[55,56] (FIG. 4b). This external interaction with the linker DNA is functionally important, as linker DNA is required to fully activate ISWI ATPase activity[9,56]. The internal binding site is adjacent to the location where the histone H4 tails emit from the nucleosome, and residues 16–19 of the histone H4 tail are crucial for activating ISWI ATPase activity[57,58].

The SWI/SNF-family remodeller RSC and the ISWI remodellers have notable similarities and differences. Similar to ISWI, the ATPase domain of Sth1 seems to engage nucleosomal DNA at a fixed internal site ~2 turns from the nucleosomal dyad[50]. However, definitive proof in the form of structural or crosslinking studies is still needed. In contrast to ISWI, RSC binds to the nucleosome core independent of linker DNA[50], and the ATPase activity of RSC is not significantly affected by linker DNA or the H4 tail. The interaction of the RSC ATPase subunit, Sth1, with the nucleosome (K_d ~100 nM) is much weaker than that observed with the RSC complex (K_d ~7 nM), which indicates that other components of RSC confer high-affinity binding to help anchor the remodeller to the nucleosome[50]. Taken together, the catalytic ATPase of both SWI/SNF and ISWI remodellers seem to engage the nucleosome near the dyad, but these two complexes differ in their interaction with other determinants on the nucleosome.

Two recent papers provide evidence that the ATPase domains of RSC, SWI/SNF and ISWI mobilize nucleosomes through directional DNA translocation that initiates from an internal nucleosomal site[50,59]. With RSC, the ATPase Sth1 binds at a position ~2 turns from the nucleosomal dyad, from which it draws DNA from the proximal linker into the nucleosome and pumps it towards the dyad, around the nucleosome and into the distal linker[50]. To establish this principle, a series of nucleosome substrates were prepared. One set bore gaps in one of the two DNA strands at particular positions along the nucleosomal DNA, which stopped translocation once they were encountered by the translocation domain. Another set of nucleosomes contained DNA linkers of varying lengths that emitted from one side of the nucleosome. Remarkably, the length of intact DNA that is present on one side of the nucleosome determined the length of DNA that is emitted from the opposite side of the nucleosome, and all substrates predicted an origin of DNA translocation initiation and, ultimately, termination that was located ~2 turns from the nucleosomal dyad. Furthermore, gaps that are present ~2 turns from the dyad greatly reduced the binding of Sth1 to the nucleosome. These observations and interpretations are in agreement with an earlier observation with RSC and SWI/SNF by the Owen-Hughes and Bartholomew laboratories, as mentioned above: following chromatin remodelling, DNA is recessed up to ~50 bp within the nucleosome (to a position ~2 turns from the dyad), thereby disrupting 4–5 histone–DNA contacts[37,41].

Nucleosome dyad
The centre of the nucleosome around which there is an overall pseudo two-fold symmetry.

Box 1 | **Strategies for accessing nucleosomal DNA**

A central question in chromatin biology is how factors gain access to nucleosomal DNA. Such strategies for access include: first, unwrapping the DNA from the octamer surface, starting at the nucleosome edge[53]; second, lifting the DNA off the internal surface of the nucleosome, possibly through a conformational change in the octamer[70]; third, ejecting the entire nucleosome[73,74]; or fourth, through the translational movement of the octamer along the DNA[40,42,78]. Widom and colleagues have shown that nucleosomes exist in a dynamic equilibrium between fully-wrapped and partially-unwrapped states, in which DNA unwrapping initiates from the edge of the nucleosome and moves progressively towards the dyad[79,80]. However, DNA accessibility is transient and localized — nucleosomes are fully wrapped for ~250 ms and partially unwrapped near the edge for only ~10–50 ms, whereas the dyad remains essentially wrapped, largely limiting DNA exposure to the edge of the nucleosome[81]. Internal lifting and conformational changes have not been explored in detail, but remain a possible alternative mechanism for remodellers[70]. Studies by the Kornberg and Kingston laboratories have demonstrated that SWI/SNF remodellers catalyse octamer ejection (or transfer) *in vitro*[76,77]. Although this reaction clearly occurs, it is much less efficient than translational repositioning (sliding) under *in vitro* conditions. Sliding involves the breakage and reformation of all histone–DNA contacts, and nucleosomes alone show slow translational movement *in vitro* by thermal diffusion[37,78]. However, certain remodellers enable rapid nucleosome repositioning and access to nucleosomal DNA. Much of this article examines the notion that remodellers catalyse and enhance sliding by providing a DNA-translocation force.

A recent study used a creative approach that involved the placement of a small (2-base) DNA gap in random positions along nucleosomal DNA to determine the locations in the nucleosome where a small (2-base) DNA gap would prevent efficient nucleosome sliding by the yeast SWI/SNF complex and the yeast Isw2 complex[59]. Remarkably, for both remodellers, gaps within a region ~2 turns from the dyad greatly interfered with sliding. With the SWI/SNF complex, interference was DNA-strand specific, indicating a 3′→5′ polarity of DNA translocation on the nucleosome, which is consistent with the polarity of RSC translocation along naked DNA[50]. Together, these studies have established directional DNA translocation from an internal site as a feature of the remodelling mechanism. Next, we explore the mechanics of translocation by SF1- and SF2-family members, and then apply these principles to remodeller action on nucleosomes.

Building a remodeller using an SF1/SF2 blueprint. Crystal structures and biochemical studies of four proteins (PcrA, RecG, NS3 and Rad54) have provided important insights into the mechanism of DNA translocation[11,47–49,60]. Studies of all four translocases indicate that the translocation domain can be divided into two subdomains, a DNA-torsion subdomain and a DNA-tracking subdomain. For PcrA, several co-structures have been determined: in the absence of ATP, both subdomains interact with the DNA, with the intervening DNA residing in a small cleft between the two subdomains. On ATP binding, the torsion subdomain pulls and twists the DNA duplex, which places an extra base pair of DNA in the cleft between the two subdomains. The tracking subdomain includes two tandemly arranged RecA-like motifs, between which lies a pocket for ATP binding as well as a platform for DNA interaction. ATP hydrolysis induces a conformational change between the two RecA-like motifs, which results in the net movement of the DNA-tracking subdomain by one base pair in the 3′→5′ direction along one of the two strands, termed the tracking strand. Put simply, the torsion subdomain feeds the tracking subdomain one base pair of DNA, which then ratchets forward one base following ATP hydrolysis. Once the torsion subdomain resets one base pair forward, the cycle of movement is completed, and results in an 'inchworm-like' movement along the DNA with an efficiency of 1 bp/ATP hydrolysed[48,61] (this is known as the step size).

Recent single-molecule approaches with the SF2-family RNA helicase NS3 support a related inchworm-like mechanism[62], with a slightly more complex mechanism. Analogous to PcrA, NS3 can be considered to have two tethered RNA-binding domains: a forward domain followed by a tracking domain. NS3 tracks in a 3′→5′ direction along RNA by using an inchworm-like mechanism that involves increments of ~11 bp. Remarkably, this movement can be divided into three ATP-dependent sub-steps, which involve the tracking domain ratcheting along the tracking strand (using step sizes of ~3.6 bp/ATP), moving ever closer to the forward domain. Once the tracking domain encounters the forward domain, the forward domain then steps forward ~11 bp to complete the cycle. So, SF1 and SF2 translocases seem to share an inchworm-like mechanism, but might differ in the number of base pairs that are tracked per ATP hydrolysed, and/or the number of tracking sub-steps that occur in each translocation cycle. Next, we apply these principles to DNA translocation on nucleosomes.

The wave–ratchet–wave model

Here, we apply the data and principles that are discussed above to generate models for the SWI/SNF and ISWI remodellers. These are not the only modes by which histone–DNA contacts can be broken (BOX 1), and we note that DNA translocation has not been tested for all remodellers, or all members of the SWI/SNF and ISWI families. These models are based on data that have been obtained so far, and provide a framework for further testing and discussion.

SWI/SNF and ISWI remodellers are proposed to share four features (FIG. 4): first, their binding to the nucleosome at a defined position; second, an ATP-dependent conformational change in the remodeller that is initiated by the torsion/forward subdomain that breaks proximal histone–DNA contacts and creates a DNA wave on the octamer surface; third, the movement of the DNA wave through the tracking subdomain that is located near the dyad, which enforces directional DNA movement in a manner that is analogous to a directional ratchet; and fourth, the propagation of the DNA wave around the nucleosome by one-dimensional diffusion. However, SWI/SNF and ISWI remodellers are proposed to differ in their regulation of these steps, which can result in unique remodelling products.

Applying the model to SWI/SNF. We first apply the model to SWI/SNF (FIG. 4a), which binds the nucleosome core and uses its translocation domain (which is

RecA-like domain
A structurally conserved domain that is found in helicases, which probably evolved from the *Escherichia coli* RecA protein that couples cycles of nucleotide binding and hydrolysis to nucleic-acid translocation.

One-dimensional diffusion
A random walk with one degree of freedom. In this context, it refers to movement of the torsional strain that is imposed on histone–DNA contacts along the length of DNA in the nucleosome.

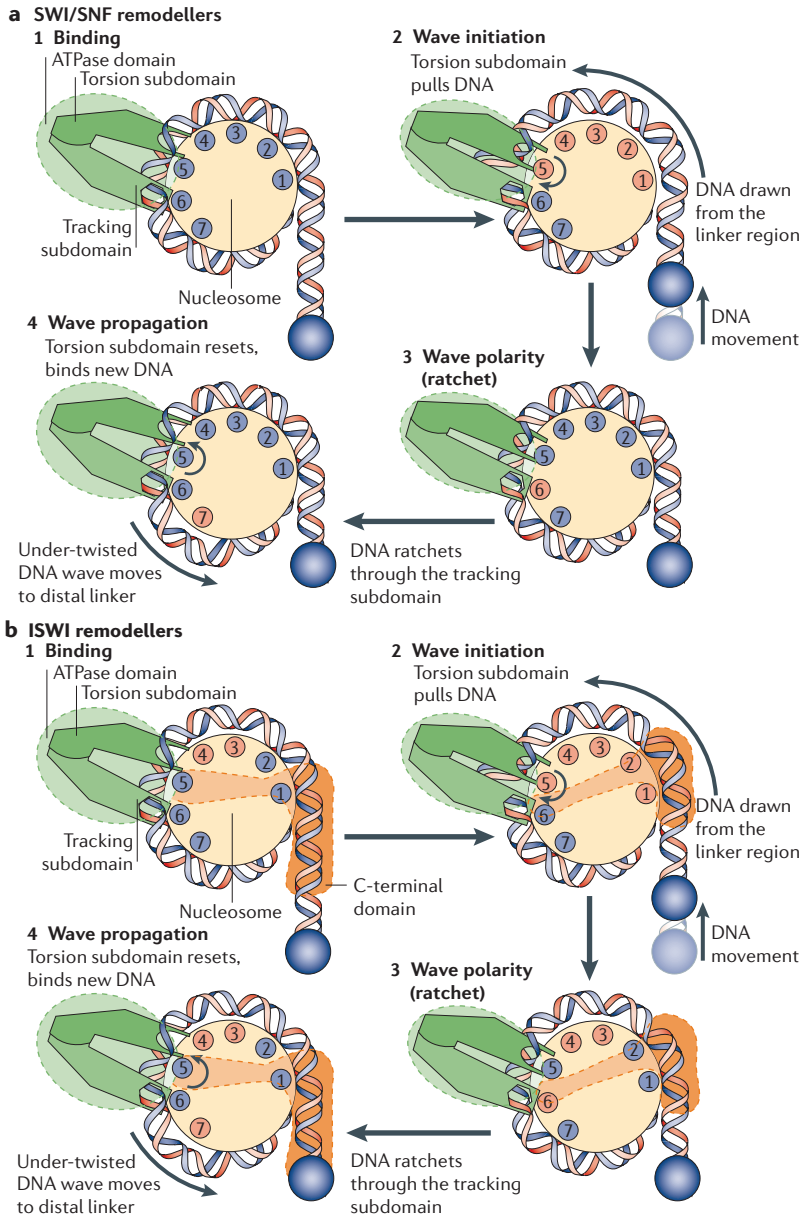

Figure 4 | **The wave–ratchet–wave model for DNA translocation.** The remodeller ATPase subunit is divided into torsion and tracking subdomains that go through a series of movements (inchworm-like) to break histone–DNA contacts (blue numbered circles, intact; red numbered circles, broken) and enable directional sliding (see main text for details). Four steps are proposed. First, the remodeller binds the nucleosome core with its ATPase domain engaging the DNA ~2 turns from the dyad (step 1). In addition, the C terminus of ISWI (but not SWI/SNF) remodellers contacts the DNA linker at the nucleosome entry site (see part **b**). Next, an ATP-dependent conformational change within the translocation domain causes the torsion subdomain to pull DNA from the linker region into the nucleosome. This pulling places more DNA into the cleft between the torsion and tracking subdomains, which creates a DNA wave (step 2). Subsequently, the tracking subdomain uses one of the two strands of the DNA as the tracking strand and allows the DNA wave to pass through it in a 3′→5′ direction (step 3). Finally, the DNA wave propagates around the nucleosome by one-dimensional diffusion, breaking histone–DNA contacts at the leading edge and reforming at the lagging edge (step 4). Following these steps, the torsion domain then resets for another round of translocation. **a** | Adaptation of the model to SWI/SNF remodellers. **b** | Adaptation of the model to ISWI remodellers. We note that the binding of the ISWI remodeller ACF to the nucleosome, without ATP hydrolysis, perturbs histone–DNA contacts that are located just inside the nucleosome, but does not cause sliding[54]. Part **a** is modified with permission from REF. 50 © (2006) Macmillan Publishers Ltd.

composed of the torsion and tracking subdomains) to engage the DNA ~2 turns from the nucleosomal dyad. We emphasize that the tracking subdomain remains fixed at this position on the histone octamer, with the DNA moving through it during translocation — that is, inchworming from a fixed position. Next, the torsion subdomain undergoes a conformational change that pulls and twists the DNA. Evidence for torsional stress during remodelling was first obtained by the Owen-Hughes and Peterson laboratories[63,64]. We note that torsional stress is an integral component of the proposed DNA-translocation mechanism, as translocation of a helical substrate creates torsion. This pulling and twisting component causes the histone–DNA contacts between this site and the proximal nucleosomal entry site to be transiently broken, which draws in DNA from the linker (see BOX 2 for a more detailed discussion of histone–DNA contacts). This disruption is followed by the rapid reformation of histone–DNA contacts at a new translational position.

This motion by the torsion domain provides the tracking domain with a DNA wave — a segment of DNA that is longer than is normally accommodated between two histone–DNA contacts, and that is undertwisted relative to standard B-form DNA. In principle, the minimum length of the DNA wave is the length of DNA that is translocated in one round of ATP hydrolysis (the step size). This length is not known for remodellers; however, a length of 1–2 base pairs is consistent with the step size for PcrA, is near the length of the sub-steps that are used by NS3 and is consistent with the tracking requirement that is observed for RSC[50,61]. This action creates a DNA wave on the surface of the nucleosome in the cleft between the torsion and tracking subdomains. As the tracking subdomain is committed to movement along the tracking strand, this segment of DNA passes through it unidirectionally, in the 3′→5′ direction.

This action places the strained DNA wave on the opposite side of the translocase domain, which forms a DNA wave that is both undertwisted and longer than is typically accommodated within a standard histone–DNA contact. In principle, a 1-bp wave could contain sufficient energy to strain and break the proximal histone–DNA contact. However, further rounds of ATP hydrolysis might be used to create waves of larger size and successively higher energy to ensure wave propagation. As histone–DNA contacts are of similar potential energy, the wave might then propagate by one-dimensional diffusion, with histone–DNA contacts broken at the leading edge of the wave and replaced at the lagging edge. Although these waves can, in principle, move in either direction, the tracking domain (that functions as a molecular ratchet) prevents backward movement. The placement of the ratchet at this position might help to improve the efficiency of wave movement through the dyad region, where histone–DNA contacts are strongest. Following its passage through the dyad, the wave can then propagate around the nucleosome by one-dimensional diffusion to the linker to provide resolution. At the end of the cycle, the torsion domain resets to its initial extended conformation, resulting in the net

Box 2 | **The economics of nucleosome movement**

To move the nucleosome, remodellers must disrupt the 14 histone–DNA contacts on the nucleosome. These contacts involve mainly the sugar–phosphate backbone of the DNA, allowing broad sequence accommodation[12,82]. So, the nucleosome might be considered a cylindrical protein disk that is wrapped by 146 bp of DNA in ~1.7 superhelical turns, and functions as a large, loaded spring that is held in place by 14 contacts with the histone octamer. Each histone–DNA contact stores ~1 kcal/mole of energy, and remodellers use ATP hydrolysis (~7.3 kcal/mole of free energy) to break these contacts. For translational movement of the octamer to occur, all histone–DNA contacts must be broken, and if breakage occurs all at once, it would require ~12–14 kcal/mole[83]. However, the 'wave–ratchet–wave' model (see main text) indicates that remodellers disrupt a subset of histone–DNA contacts by pulling a DNA 'wave' — a segment of DNA that is too long to be accommodated within a standard histone–DNA contact — onto the nucleosome surface. This DNA wave is proposed to strain and break proximal histone–DNA contacts and to propagate around the nucleosome by one-dimensional diffusion. This mechanism enables histone–DNA contacts to sequentially break and reform along the length of the nucleosome, while maintaining most of the contacts at any given time, thereby lowering the total energy that is required for translational repositioning.

translational movement of the octamer. We term this speculative model 'wave–ratchet–wave': a DNA wave is generated by pulling DNA into the nucleosome, is then passed through a directional ratchet near the dyad and is propagated to the distal linker by diffusion.

Applying the model to ISWI. In principle, a similar mechanistic framework might be used by ISWI to slide nucleosomes, but with distinct regulatory modes to explain their unique functions *in vitro* and *in vivo*[65] (FIG. 4b). ISWI has a unique SLIDE domain near its C terminus that interacts with the DNA linker at the nucleosome entry site[28,56]. The binding of the ISWI remodeller ACF to the nucleosome (in the absence of ATP) is known to perturb histone–DNA contacts near the nucleosome entry site (FIG. 4b, top left); this binding does not result in sliding, but the binding energy might be used, in part, to perturb histone–DNA contacts in this region[54]. Interestingly, on ATP binding, ISWI undergoes a significant conformational change[66], and we speculate that this might involve the movement of the C-terminal region in a type of motion that is similar to a lever arm, which results in the full disruption of histone–DNA contacts at the nucleosomal entry site to provide an initial DNA wave.

Important work from many laboratories on ISWI and SWI/SNF remodellers has contributed to this notion of a DNA wave within the nucleosome[7,50,52–55,59,67]. This conformational change might be caused by and coupled to the pulling of DNA by the torsion domain at the internal site near the dyad, which provides a concerted mechanism for drawing DNA into the nucleosome (FIG. 4b). We note that SWI/SNF enzymes might not require an extended lever arm to break the proximal histone–DNA contacts, as the SWI/SNF complex generates higher levels of torsional force than does the ISWI complex[64]. Unlike SWI/SNF, ISWI remodellers require linker DNA for full ATPase activity[9], which indicates that the C-terminal lever arm might activate the ATPase when it binds linker DNA. This can explain why ISWI does not generate a nucleosome product with 50 bp of DNA recessed into the nucleosome: linker DNA regulates ISWI ATPase/translocase activity but not SWI/SNF, which prevents ISWI from translocating free DNA ends beyond the nucleosomal entry site. By contrast, as SWI/SNF enzymes are not regulated by the presence of linker DNA, they can continue to translocate DNA until the free end reaches the translocase domain that is located ~50 bp inside the nucleosome.

The ability of the linker DNA to regulate ISWI translocation activity provides a mechanism for the ordered and processive spacing of nucleosomes during chromatin assembly[68]. As a nucleosome undergoes sliding, it moves closer to the neighbouring nucleosome. As proposed by Bartholomew and colleagues, the linker will shorten until the neighbouring nucleosome interferes with the ability of ISWI or its associated subunits to bind linker DNA, which would halt translocation and place the neighbouring nucleosome at the same fixed distance each time[56]. This might help create the consistent, tight nucleosome spacing that is seen in compacted regions of silent chromatin.

Remarkably, ISWI remodellers have another mode of regulation; ISWI ATPase activity requires the presence of the histone H4 tail (residues 16–19) and the lack of acetylation at histone H4 at residue K16 (H4K16)[57,58]. As the acetylation of H4K16 is correlated with active transcription, this might negatively regulate ISWI association and/or activity at transcriptionally active regions, and therefore largely restrict the nucleosome-spacing/chromatin-compaction activity of ISWI to non-acetylated chromatin. Studies on dosage compensation in flies provides an interesting biological application of these principles. Only the male X chromosome is hyperacetylated at H4K16, whereas the two female X chromosomes contain normal acetylation levels. This modification excludes ISWI from the male X chromosome, which compromises chromatin compaction and might promote the average two-fold increase in gene expression from this chromosome that defines dosage compensation[57,58,69]. So, ISWI complexes might also conform to a DNA-translocation model that uses the 'wave–ratchet–wave' principle, with the binding and/or activity of ISWI also regulated by linker DNA and the lack of acetylation at histone H4K16.

Nucleosome remodelling — catch the wave? One important unresolved issue is whether remodellers render nucleosomal DNA accessible to regulatory factors by sliding the DNA into the linker[50], by transient access to the DNA on the surface of the octamer[53,70] or through a combination of the two (BOX 1). Although these modes are not mutually exclusive, certain physical parameters must be satisfied for DNA access on the octamer, including a DNA wave of sufficient size to expose the entire DNA-binding site. Currently, wave sizes during remodelling are not known and remain to be tested, although waves of 1 bp have been detected on the nucleosome surface by structural studies[71,72]. Furthermore, if large waves can be accommodated on the nucleosome surface, these waves must persist on the nucleosome surface for a sufficient length of time to enable factor binding.

B-form of DNA
The native form of the right-handed DNA helix with 10.6 base pairs per helical turn.

Dosage compensation
The process of equalizing the gene dosage of the X chromosome in males with the two X chromosomes in females.

In principle, wave propagation should be exceptionally fast, on the order of one-dimensional diffusion. However, remodellers might, in principle, have the ability to constrain waves on the surface of the nucleosome, which would enable transcription factors sufficient time to access their binding site.

This principle of constraining a DNA wave on the nucleosome surface could also be used by nucleosome-restructuring factors. SWR1 has the remarkable ability to remove H2A–H2B dimers from a nucleosome and replace them with Htz1–H2B dimers, creating a variant nucleosome that contains the histone H2A variant Htz1 (REFS 14,17,18) (FIG. 1, bottom row). The wave–ratchet–wave model involves both a conformational change in the remodeller and an initial DNA-translocation event that disrupts the outer four histone–DNA contacts, which involve H2A–H2B. In principle, the disruption of histone–DNA contacts could be constrained to this area and assist in the replacement of H2A–H2B dimers with Htz1–H2B variant dimers.

Furthermore, the ability of a remodeller to create and constrain waves might enable the remodeller to break a sufficient number of histone–DNA contacts to eject the octamer from the DNA[73,74]. Many promoters are slightly histone deficient, and become more deficient following activation, which raises the possibility that the ejection of histones helps to regulate transcription by enabling promoter access[75]. Consistent with this principle, SWI/SNF remodellers can transfer a nucleosome from one piece of DNA to another, which resembles a type of ejection[76,77]. Considering its important role in transcriptional regulation, a better understanding of the nucleosome ejection/transfer mechanism will be an active area of future research.

Conclusions and future directions

Here, we have explored the dynamic properties of nucleosomes and summarized evidence from many laboratories that chromatin-remodelling ATPases function as DNA translocases. On the basis of these studies, we presented a basic model for nucleosome remodelling, termed wave–ratchet–wave: a DNA wave is generated on the nucleosome surface by pulling DNA from the linker into the nucleosome, passing the DNA wave through a directional ratchet located near the nucleosomal dyad and then propagating the DNA wave to the distal linker by diffusion. As different chromatin remodellers affect nucleosome structure in different ways, we considered how this basic model might be adapted to accommodate the different products that are generated by SWI/SNF and ISWI remodellers by imposing unique regulatory factors on each complex. This basic model includes features that are not prominent in previous models, including the principle that the catalytic ATPase binds at a site near the nucleosomal dyad and initiates directional translocation from that location. Furthermore, the model can accommodate, at least in principle, a wide range of observed remodelling activities that include sliding, transcription-factor access, nucleosome ejection and nucleosome restructuring. Undoubtedly, more information will be gained with regard to the mechanism of individual remodellers, and it will be of interest to determine whether these new insights support this basic model or whether entirely new models need to be constructed to better explain the observations.

This concept of remodellers as octamer-bound directional DNA translocases is currently being tested through various approaches in many laboratories. For example, proteins that are associated with the ATPase subunit, as well as determinants on the nucleosome, are being examined for their effects on DNA-translocation properties. In addition, single-molecule approaches will be important for examining parameters such as translocation force, speed and processivity on nucleosomes. Furthermore, structural studies of remodellers will be invaluable for understanding the translocation mechanism and its regulation. In the coming years, biophysical, biochemical and molecular approaches will all contribute to our understanding of these remarkable machines.

1. Kornberg, R. D. & Lorch, Y. Twenty-five years of the nucleosome, fundamental particle of the eukaryote chromosome. *Cell* **98**, 285–294 (1999).
2. Jenuwein, T. & Allis, C. D. Translating the histone code. *Science* **293**, 1074–1080 (2001).
3. Strahl, B. D. & Allis, C. D. The language of covalent histone modifications. *Nature* **403**, 41–45 (2000).
4. Owen-Hughes, T. Colworth memorial lecture. Pathways for remodelling chromatin. *Biochem. Soc. Trans.* **31**, 893–905 (2003).
5. Cosma, M. P., Tanaka, T. & Nasmyth, K. Ordered recruitment of transcription and chromatin remodeling factors to a cell cycle- and developmentally regulated promoter. *Cell* **97**, 299–311 (1999).
6. Fan, H. Y., He, X., Kingston, R. E. & Narlikar, G. J. Distinct strategies to make nucleosomal DNA accessible. *Mol. Cell* **11**, 1311–1322 (2003).
7. Saha, A., Wittmeyer, J. & Cairns, B. R. Chromatin remodeling by RSC involves ATP-dependent DNA translocation. *Genes Dev.* **16**, 2120–2134 (2002).
8. Jaskelioff, M., Van Komen, S., Krebs, J. E., Sung, P. & Peterson, C. L. Rad54p is a chromatin remodeling enzyme required for heteroduplex DNA joint formation with chromatin. *J. Biol. Chem.* **278**, 9212–9218 (2003).
9. Whitehouse, I., Stockdale, C., Flaus, A., Szczelkun, M. D. & Owen-Hughes, T. Evidence for DNA translocation by the ISWI chromatin-remodeling enzyme. *Mol. Cell. Biol.* **23**, 1935–1945 (2003).
References 7–9 provide biochemical evidence for DNA translocation by the SWI/SNF and the ISWI family of remodellers.
10. Alexeev, A., Mazin, A. & Kowalczykowski, S. C. Rad54 protein possesses chromatin-remodeling activity stimulated by the Rad51–ssDNA nucleoprotein filament. *Nature Struct. Biol.* **10**, 182–186 (2003).
11. Durr, H., Korner, C., Muller, M., Hickmann, V. & Hopfner, K. P. X-ray structures of the *Sulfolobus solfataricus* SWI2/SNF2 ATPase core and its complex with DNA. *Cell* **121**, 363–373 (2005).
This study, along with reference 60, provides structural evidence for Rad54 as a DNA-translocating enzyme.
12. Luger, K., Mader, A. W., Richmond, R. K., Sargent, D. F. & Richmond, T. J. Crystal structure of the nucleosome core particle at 2.8 Å resolution. *Nature* **389**, 251–260 (1997).
13. Henikoff, S., Furuyama, T. & Ahmad, K. Histone variants, nucleosome assembly and epigenetic inheritance. *Trends Genet.* **20**, 320–326 (2004).
14. Mizuguchi, G. *et al.* ATP-driven exchange of histone H2AZ variant catalyzed by SWR1 chromatin remodeling complex. *Science* **303**, 343–348 (2004).
15. Smith, M. M. Centromeres and variant histones: what, where, when and why? *Curr. Opin. Cell Biol.* **14**, 279–285 (2002).
16. Ahmad, K. & Henikoff, S. Histone H3 variants specify modes of chromatin assembly. *Proc. Natl Acad. Sci. USA* **99** (Suppl. 4), 16477–16484 (2002).
17. Krogan, N. J. *et al.* A Snf2 family ATPase complex required for recruitment of the histone H2A variant Htz1. *Mol. Cell* **12**, 1565–1576 (2003).
18. Kobor, M. S. *et al.* A protein complex containing the conserved Swi2/Snf2-related ATPase Swr1p deposits histone variant H2A. Z into euchromatin. *PLoS Biol.* **2**, E131 (2004).
References 14, 17 and 18 report the identification of SWR1 as the remodeller ATPase that places the histone H2A variant Htz1 into chromatin.
19. Zhang, H., Roberts, D. N. & Cairns, B. R. Genome-wide dynamics of Htz1, a histone H2A variant that poises repressed/basal promoters for activation through histone loss. *Cell* **123**, 219–231 (2005).
20. Vignali, M., Hassan, A. H., Neely, K. E. & Workman, J. L. ATP-dependent chromatin-remodeling complexes. *Mol. Cell. Biol.* **20**, 1899–1910 (2000).
21. Cairns, B. R. *et al.* RSC, an essential, abundant chromatin-remodeling complex. *Cell* **87**, 1249–1260 (1996).

22. Ito, T., Bulger, M., Pazin, M. J., Kobayashi, R. & Kadonaga, J. T. ACF, an ISWI-containing and ATP-utilizing chromatin assembly and remodeling factor. *Cell* **90**, 145–155 (1997).
23. Laurent, B. C., Yang, X. & Carlson, M. An essential *Saccharomyces cerevisiae* gene homologous to SNF2 encodes a helicase-related protein in a new family. *Mol. Cell. Biol.* **12**, 1893–1902 (1992).
24. Eisen, J. A., Sweder, K. S. & Hanawalt, P. C. Evolution of the SNF2 family of proteins: subfamilies with distinct sequences and functions. *Nucleic Acids Res.* **23**, 2715–2723 (1995).
25. Winston, F. & Allis, C. D. The bromodomain: a chromatin-targeting module? *Nature Struct. Biol.* **6**, 601–604 (1999).
26. Hassan, A. H. *et al.* Function and selectivity of bromodomains in anchoring chromatin-modifying complexes to promoter nucleosomes. *Cell* **111**, 369–379 (2002).
27. Kasten, M. *et al.* Tandem bromodomains in the chromatin remodeler RSC recognize acetylated histone H3 Lys14. *EMBO J.* **23**, 1348–1359 (2004).
28. Grune, T. *et al.* Crystal structure and functional analysis of a nucleosome recognition module of the remodeling factor ISWI. *Mol. Cell* **12**, 449–460 (2003).
29. Haushalter, K. A. & Kadonaga, J. T. Chromatin assembly by DNA-translocating motors. *Nature Rev. Mol. Cell Biol.* **4**, 613–620 (2003).
30. Corona, D. F. & Tamkun, J. W. Multiple roles for ISWI in transcription, chromosome organization and DNA replication. *Biochim. Biophys. Acta* **1677**, 113–119 (2004).
31. Deuring, R. *et al.* The ISWI chromatin-remodeling protein is required for gene expression and the maintenance of higher order chromatin structure *in vivo*. *Mol. Cell* **5**, 355–365 (2000).
32. Goldmark, J. P., Fazzio, T. G., Estep, P. W., Church, G. M. & Tsukiyama, T. The Isw2 chromatin remodeling complex represses early meiotic genes upon recruitment by Ume6p. *Cell* **103**, 423–433 (2000).
33. Martens, J. A. & Winston, F. Recent advances in understanding chromatin remodeling by Swi/Snf complexes. *Curr. Opin. Genet. Dev.* **13**, 136–142 (2003).
34. Morillon, A. *et al.* Isw1 chromatin remodeling ATPase coordinates transcription elongation and termination by RNA polymerase II. *Cell* **115**, 425–435 (2003).
35. Martens, J. A. & Winston, F. Evidence that Swi/Snf directly represses transcription in *S. cerevisiae*. *Genes Dev.* **16**, 2231–2236 (2002).
36. Varga-Weisz, P. D. *et al.* Chromatin-remodelling factor CHRAC contains the ATPases ISWI and topoisomerase II. *Nature* **388**, 598–602 (1997).
37. Flaus, A. & Owen-Hughes, T. Dynamic properties of nucleosomes during thermal and ATP-driven mobilization. *Mol. Cell. Biol.* **23**, 7767–7779 (2003).
38. Owen-Hughes, T., Utley, R. T., Cote, J., Peterson, C. L. & Workman, J. L. Persistent site-specific remodeling of a nucleosome array by transient action of the SWI/SNF complex. *Science* **273**, 513–516 (1996).
39. Kal, A. J., Mahmoudi, T., Zak, N. B. & Verrijzer, C. P. The *Drosophila* Brahma complex is an essential coactivator for the *trithorax* group protein Zeste. *Genes Dev.* **14**, 1058–1071 (2000).
40. Whitehouse, I. *et al.* Nucleosome mobilization catalysed by the yeast SWI/SNF complex. *Nature* **400**, 784–787 (1999).
41. Kassabov, S. R., Zhang, B., Persinger, J. & Bartholomew, B. SWI/SNF unwraps, slides, and rewraps the nucleosome. *Mol. Cell* **11**, 391–403 (2003).
References 37 and 41 show that nucleosome repositioning by SWI/SNF remodellers enables DNA unwrapping from the edge of the nucleosome, disrupting up to 4–5 histone–DNA contacts.
42. Langst, G., Bonte, E. J., Corona, D. F. & Becker, P. B. Nucleosome movement by CHRAC and ISWI without disruption or *trans*-displacement of the histone octamer. *Cell* **97**, 843–852 (1999).
References 40 and 42 provide biochemical evidence for nucleosome sliding along the DNA without complete dissociation/reassociation of the histone octamer.
43. Phelan, M. L., Sif, S., Narlikar, G. J. & Kingston, R. E. Reconstitution of a core chromatin remodeling complex from SWI/SNF subunits. *Mol. Cell* **3**, 247–253 (1999).
44. Corona, D. F. *et al.* ISWI is an ATP-dependent nucleosome remodeling factor. *Mol. Cell* **3**, 239–245 (1999).
References 43 and 44 demonstrate that the ATPase subunit in isolation can achieve limited remodelling *in vitro*.
45. Singleton, M. R. & Wigley, D. B. Modularity and specialization in superfamily 1 and 2 helicases. *J. Bacteriol.* **184**, 1819–1826 (2002).
46. Murray, N. E. Type I restriction systems: sophisticated molecular machines. *Microbiol. Mol. Biol. Rev.* **64**, 412–434 (2000).
47. Kim, J. L. *et al.* Hepatitis C virus NS3 RNA helicase domain with a bound oligonucleotide: the crystal structure provides insights into the mode of unwinding. *Structure* **6**, 89–100 (1998).
48. Velankar, S. S., Soultanas, P., Dillingham, M. S., Subramanya, H. S. & Wigley, D. B. Crystal structures of complexes of PcrA DNA helicase with a DNA substrate indicate an inchworm mechanism. *Cell* **97**, 75–84. (1999).
This study presents two different structures of PcrA, providing snapshots of different steps of ATP-dependent DNA translocation.
49. Singleton, M. R., Scaife, S. & Wigley, D. B. Structural analysis of DNA replication fork reversal by RecG. *Cell* **107**, 79–89 (2001).
50. Saha, A., Wittmeyer, J. & Cairns, B. R. Chromatin remodeling through directional DNA translocation from an internal nucleosomal site. *Nature Struct. Mol. Biol.* **12**, 747–755 (2005).
This report, along with reference 59, demonstrates that remodellers translocate nucleosomal DNA from a fixed internal site on the nucleosome.
51. Lia, G. *et al.* Direct observation of DNA distortion by the RSC complex. *Mol. Cell* **21**, 417–425 (2006).
Reference 51 provides the first evidence for translocation by a remodeller in a single-molecule format.
52. Lorch, Y., Cairns, B. R., Zhang, M. & Kornberg, R. D. Activated RSC–nucleosome complex and persistently altered form of the nucleosome. *Cell* **94**, 29–34 (1998).
53. Langst, G. & Becker, P. B. ISWI induces nucleosome sliding on nicked DNA. *Mol. Cell* **8**, 1085–1092 (2001).
54. Strohner, R. *et al.* A 'loop recapture' mechanism for ACF-dependent nucleosome remodeling. *Nature Struct. Mol. Biol.* **12**, 683–690 (2005).
55. Schwanbeck, R., Xiao, H. & Wu, C. Spatial contacts and nucleosome step movements induced by the NURF chromatin remodeling complex. *J. Biol. Chem.* **279**, 39933–39941 (2004).
56. Kagalwala, M. N., Glaus, B. J., Dang, W., Zofall, M. & Bartholomew, B. Topography of the ISW2–nucleosome complex: insights into nucleosome spacing and chromatin remodeling. *EMBO J.* **23**, 2092–2104 (2004).
References 55 and 56 describe how ISWI remodellers engage nucleosome substrates, showing interaction near the dyad and also with proximal linker DNA.
57. Clapier, C. R., Langst, G., Corona, D. F., Becker, P. B. & Nightingale, K. P. Critical role for the histone H4 N terminus in nucleosome remodeling by ISWI. *Mol. Cell. Biol.* **21**, 875–883 (2001).
58. Corona, D. F., Clapier, C. R., Becker, P. B. & Tamkun, J. W. Modulation of ISWI function by site-specific histone acetylation. *EMBO Rep.* **3**, 242–247 (2002).
References 57 and 58 provide evidence for the role of the N-terminal tail of histone H4 in regulating the activity of ISWI remodellers.
59. Zofall, M., Persinger, J., Kassabov, S. R. & Bartholomew, B. Chromatin remodeling by ISW2 and SWI/SNF requires DNA translocation inside the nucleosome. *Nature Struct. Mol. Biol.* **13**, 339–346 (2006).
60. Thoma, N. H. *et al.* Structure of the SWI2/SNF2 chromatin-remodeling domain of eukaryotic Rad54. *Nature Struct. Mol. Biol.* **12**, 350–356 (2005).
61. Dillingham, M. S., Wigley, D. B. & Webb, M. R. Demonstration of unidirectional single-stranded DNA translocation by PcrA helicase: measurement of step size and translocation speed. *Biochemistry* **39**, 205–212 (2000).
62. Dumont, S. *et al.* RNA translocation and unwinding mechanism of HCV NS3 helicase and its coordination by ATP. *Nature* **439**, 105–108 (2006).
Provides single-molecule evidence for the inchworming mechanism of DNA translocation by SF2 family translocases and the concept of sub-steps by the tracking domain.
63. Gavin, I., Horn, P. J. & Peterson, C. L. SWI/SNF chromatin remodeling requires changes in DNA topology. *Mol. Cell* **7**, 97–104 (2001).
64. Havas, K. *et al.* Generation of superhelical torsion by ATP-dependent chromatin remodeling activities. *Cell* **103**, 1133–1142 (2000).
References 63 and 64 demonstrate that remodellers generate torsional stress during remodelling.
65. Fan, H. Y., Trotter, K. W., Archer, T. K. & Kingston, R. E. Swapping function of two chromatin remodeling complexes. *Mol. Cell* **17**, 805–815 (2005).
66. Fitzgerald, D. J. *et al.* Reaction cycle of the yeast Isw2 chromatin remodeling complex. *EMBO J.* **23**, 3836–3843 (2004).
67. Lorch, Y., Davis, B. & Kornberg, R. D. Chromatin remodeling by DNA bending, not twisting. *Proc. Natl Acad. Sci. USA* **102**, 1329–1332 (2005).
68. Fyodorov, D. V. & Kadonaga, J. T. Dynamics of ATP-dependent chromatin assembly by ACF. *Nature* **418**, 897–900 (2002).
69. Rastelli, L. & Kuroda, M. I. An analysis of maleless and histone H4 acetylation in *Drosophila melanogaster* spermatogenesis. *Mech. Dev.* **71**, 107–117 (1998).
70. Narlikar, G. J., Phelan, M. L. & Kingston, R. E. Generation and interconversion of multiple distinct nucleosomal states as a mechanism for catalyzing chromatin fluidity. *Mol. Cell* **8**, 1219–1230 (2001).
71. Suto, R. K. *et al.* Crystal structures of nucleosome core particles in complex with minor groove DNA-binding ligands. *J. Mol. Biol.* **326**, 371–380 (2003).
72. Richmond, T. J. & Davey, C. A. The structure of DNA in the nucleosome core. *Nature* **423**, 145–150 (2003).
73. Reinke, H. & Horz, W. Histones are first hyperacetylated and then lose contact with the activated PHO5 promoter. *Mol. Cell* **11**, 1599–1607 (2003).
74. Boeger, H., Griesenbeck, J., Strattan, J. S. & Kornberg, R. D. Removal of promoter nucleosomes by disassembly rather than sliding *in vivo*. *Mol. Cell* **14**, 667–673 (2004).
75. Lee, C. K., Shibata, Y., Rao, B., Strahl, B. D. & Lieb, J. D. Evidence for nucleosome depletion at active regulatory regions genome-wide. *Nature Genet.* **36**, 900–905 (2004).
76. Lorch, Y., Zhang, M. & Kornberg, R. D. Histone octamer transfer by a chromatin-remodeling complex. *Cell* **96**, 389–392 (1999).
References 73–76 provide evidence for nucleosome loss *in vivo* and *in vitro*.
77. Phelan, M. L., Schnitzler, G. R. & Kingston, R. E. Octamer transfer and creation of stably remodeled nucleosomes by human SWI–SNF and its isolated ATPases. *Mol. Cell. Biol.* **20**, 6380–6389 (2000).
78. Hamiche, A., Sandaltzopoulos, R., Gdula, D. A. & Wu, C. ATP-dependent histone octamer sliding mediated by the chromatin remodeling complex NURF. *Cell* **97**, 833–842 (1999).
79. Widom, J. Structure, dynamics, and function of chromatin *in vitro*. *Annu. Rev. Biophys. Biomol. Struct.* **27**, 285–327 (1998).
80. Li, G. & Widom, J. Nucleosomes facilitate their own invasion. *Nature Struct. Mol. Biol.* **11**, 763–769 (2004).
81. Li, G., Levitus, M., Bustamante, C. & Widom, J. Rapid spontaneous accessibility of nucleosomal DNA. *Nature Struct. Mol. Biol.* **12**, 46–53 (2005).
82. Widom, J. Role of DNA sequence in nucleosome stability and dynamics. *Q. Rev. Biophys.* **34**, 269–324 (2001).
83. Gottesfeld, J. M. & Luger, K. Energetics and affinity of the histone octamer for defined DNA sequences. *Biochemistry* **40**, 10927–10933 (2001).
84. Hirschhorn, J. N., Brown, S. A., Clark, C. D. & Winston, F. Evidence that SNF2/SWI2 and SNF5 activate transcription in yeast by altering chromatin structure. *Genes Dev.* **6**, 2288–2298 (1992).
85. Sudarsanam, P., Iyer, V. R., Brown, P. O. & Winston, F. Whole-genome expression analysis of *snf/swi* mutants of *Saccharomyces cerevisiae*. *Proc. Natl Acad. Sci. USA* **97**, 3364–3369 (2000).
86. Davie, J. K. & Kane, C. M. Genetic interactions between TFIIS and the Swi-Snf chromatin-remodeling complex. *Mol. Cell. Biol.* **20**, 5960–5973 (2000).
87. Chai, B., Huang, J., Cairns, B. R. & Laurent, B. C. Distinct roles for the RSC and Swi/Snf ATP-dependent chromatin remodelers in DNA double-strand break repair. *Genes Dev.* **19**, 1656–1661 (2005).
88. Neely, K. E., Hassan, A. H., Brown, C. E., Howe, L. & Workman, J. L. Transcription activator interactions with multiple SWI/SNF subunits. *Mol. Cell. Biol.* **22**, 1615–1625 (2002).

89. Yudkovsky, N., Logie, C., Hahn, S. & Peterson, C. L. Recruitment of the SWI/SNF chromatin remodeling complex by transcriptional activators. *Genes Dev.* **13**, 2369–2374 (1999).
90. Ng, H. H., Robert, F., Young, R. A. & Struhl, K. Genome-wide location and regulated recruitment of the RSC nucleosome-remodeling complex. *Genes Dev.* **16**, 806–819 (2002).
91. Angus-Hill, M. L. *et al.* A Rsc3/Rsc30 zinc cluster dimer reveals novel roles for the chromatin remodeler RSC in gene expression and cell cycle control. *Mol. Cell* **7**, 741–751 (2001).
92. Moreira, J. M. & Holmberg, S. Transcriptional repression of the yeast *CHA1* gene requires the chromatin-remodeling complex RSC. *EMBO J.* **18**, 2836–2844 (1999).
93. Damelin, M. *et al.* The genome-wide localization of Rsc9, a component of the RSC chromatin-remodeling complex, changes in response to stress. *Mol. Cell* **9**, 563–573 (2002).
94. Huang, J. & Laurent, B. C. A Role for the RSC chromatin remodeler in regulating cohesion of sister chromatid arms. *Cell Cycle* **3**, 973–975 (2004).
95. Wong, M. C., Scott-Drew, S. R., Hayes, M. J., Howard, P. J. & Murray, J. A. *RSC2*, encoding a component of the RSC nucleosome remodeling complex, is essential for 2μm plasmid maintenance in *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* **22**, 4218–4229 (2002).
96. Huang, J., Hsu, J. M. & Laurent, B. C. The RSC nucleosome-remodeling complex is required for cohesin's association with chromosome arms. *Mol. Cell* **13**, 739–750 (2004).
97. Cao, Y., Cairns, B. R., Kornberg, R. D. & Laurent, B. C. Sfh1p, a component of a novel chromatin-remodeling complex, is required for cell cycle progression. *Mol. Cell. Biol.* **17**, 3323–3334 (1997).
98. Armstrong, J. A. *et al.* The *Drosophila* BRM complex facilitates global transcription by RNA polymerase II. *EMBO J.* **21**, 5245–5254 (2002).
99. Zraly, C. B., Marenda, D. R. & Dingwall, A. K. SNR1 (INI1/SNF5) mediates important cell growth functions of the *Drosophila* Brahma (SWI/SNF) chromatin remodeling complex. *Genetics* **168**, 199–214 (2004).
100. Marenda, D. R., Zraly, C. B., Feng, Y., Egan, S. & Dingwall, A. K. The *Drosophila* SNR1 (SNF5/INI1) subunit directs essential developmental functions of the Brahma chromatin remodeling complex. *Mol. Cell. Biol.* **23**, 289–305 (2003).
101. Srinivasan, S. *et al.* The *Drosophila* trithorax group protein Kismet facilitates an early step in transcriptional elongation by RNA polymerase II. *Development* **132**, 1623–1635 (2005).
102. Roberts, C. W., Galusha, S. A., McMenamin, M. E., Fletcher, C. D. & Orkin, S. H. Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. *Proc. Natl Acad. Sci. USA* **97**, 13796–13800 (2000).
103. Wong, A. K. *et al.* BRG1, a component of the SWI-SNF complex, is mutated in multiple human tumor cell lines. *Cancer Res.* **60**, 6171–6177 (2000).
104. Hendricks, K. B., Shanahan, F. & Lees, E. Role for BRG1 in cell cycle control and tumor suppression. *Mol. Cell. Biol.* **24**, 362–376 (2004).
105. Gresh, L. *et al.* The SWI/SNF chromatin-remodeling complex subunit SNF5 is essential for hepatocyte differentiation. *EMBO J.* **24**, 3313–3324 (2005).
106. Vradii, D. *et al.* Brg1, the ATPase subunit of the SWI/SNF chromatin remodeling complex, is required for myeloid differentiation to granulocytes. *J. Cell Physiol.* **206**, 112–118 (2006).
107. de la Serna, I. L., Carlson, K. A. & Imbalzano, A. N. Mammalian SWI/SNF complexes promote MyoD-mediated muscle differentiation. *Nature Genet.* **27**, 187–190 (2001).
108. Bultman, S. *et al.* A *Brg1* null mutation in the mouse reveals functional differences among mammalian SWI/SNF complexes. *Mol. Cell* **6**, 1287–1295 (2000).
109. Wang, Z. *et al.* Polybromo protein BAF180 functions in mammalian cardiac chamber maturation. *Genes Dev.* **18**, 3106–3116 (2004).
110. Lickert, H. *et al.* Baf60c is essential for function of BAF chromatin remodelling complexes in heart development. *Nature* **432**, 107–112 (2004).
111. Corey, L. L., Weirich, C. S., Benjamin, I. J. & Kingston, R. E. Localized recruitment of a chromatin-remodeling activity by an activator *in vivo* drives transcriptional elongation. *Genes Dev.* **17**, 1392–1401 (2003).
112. Zhao, K. *et al.* Rapid and phosphoinositol-dependent binding of the SWI/SNF-like BAF complex to chromatin after T lymphocyte receptor signaling. *Cell* **95**, 625–636 (1998).
113. Batsche, E., Yaniv, M. & Muchardt, C. The human SWI/SNF subunit Brm is a regulator of alternative splicing. *Nature Struct. Mol. Biol.* **13**, 22–29 (2006).
114. Vary, J. C., Jr. *et al.* Yeast Isw1p forms two separable complexes *in vivo*. *Mol. Cell. Biol.* **23**, 80–91 (2003).
115. Bozhenok, L., Wade, P. A. & Varga-Weisz, P. WSTF–ISWI chromatin remodeling complex targets heterochromatic replication foci. *EMBO J.* **21**, 2231–2241 (2002).
116. Collins, N. *et al.* An ACF1–ISWI chromatin-remodeling complex is required for DNA replication through heterochromatin. *Nature Genet.* **32**, 627–632 (2002).
117. Hakimi, M. A. *et al.* A chromatin remodelling complex that loads cohesin onto human chromosomes. *Nature* **418**, 994–998 (2002).
118. Stopka, T. & Skoultchi, A. I. The ISWI ATPase Snf2h is required for early mouse development. *Proc. Natl Acad. Sci. USA* **100**, 14097–14102 (2003).
119. Badenhorst, P., Voas, M., Rebay, I. & Wu, C. Biological functions of the ISWI chromatin remodeling complex NURF. *Genes Dev.* **16**, 3186–3198 (2002).
120. Shen, X., Mizuguchi, G., Hamiche, A. & Wu, C. A chromatin remodelling complex involved in transcription and DNA processing. *Nature* **406**, 541–544 (2000).
121. van Attikum, H., Fritsch, O., Hohn, B. & Gasser, S. M. Recruitment of the INO80 complex by H2A phosphorylation links ATP-dependent chromatin remodeling with DNA double-strand break repair. *Cell* **119**, 777–788 (2004).
122. Morrison, A. J. *et al.* INO80 and γ-H2AX interaction links ATP-dependent chromatin remodeling to DNA damage repair. *Cell* **119**, 767–775 (2004).
123. Jonsson, Z. O., Jha, S., Wohlschlegel, J. A. & Dutta, A. Rvb1p/Rvb2p recruit Arp5p and assemble a functional Ino80 chromatin remodeling complex. *Mol. Cell* **16**, 465–477 (2004).
124. Fritsch, O., Benvenuto, G., Bowler, C., Molinier, J. & Hohn, B. The INO80 protein controls homologous recombination in *Arabidopsis thaliana*. *Mol. Cell* **16**, 479–485 (2004).
125. Kusch, T. *et al.* Acetylation by Tip60 Is required for selective histone variant exchange at DNA lesions. *Science* **306**, 2084–2087 (2004).
126. Wade, P. A. *et al.* Mi-2 complex couples DNA methylation to chromatin remodelling and histone deacetylation. *Nature Genet.* **23**, 62–66 (1999).
127. Jones, P. L. *et al.* Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. *Nature Genet.* **19**, 187–191 (1998).
128. Unhavaithaya, Y. *et al.* MEP-1 and a homolog of the NURD complex component Mi-2 act together to maintain germline–soma distinctions in *C. elegans*. *Cell* **111**, 991–1002 (2002).
129. von Zelewsky, T. *et al.* The *C. elegans* Mi-2 chromatin-remodelling proteins function in vulval cell fate determination. *Development* **127**, 5277–5284 (2000).

Competing interests statement
The authors declare no competing financial interests.

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