Mechanisms of action and regulation of ATP-dependent chromatin-remodelling complexes

Cedric R. Clapier[1], Janet Iwasa[2], Bradley R. Cairns[1] and Craig L. Peterson[3]

Abstract | Cells utilize diverse ATP-dependent nucleosome-remodelling complexes to carry out histone sliding, ejection or the incorporation of histone variants, suggesting that different mechanisms of action are used by the various chromatin-remodelling complex subfamilies. However, all chromatin-remodelling complex subfamilies contain an ATPase–translocase 'motor' that translocates DNA from a common location within the nucleosome. In this Review, we discuss (and illustrate with animations) an alternative, unifying mechanism of chromatin remodelling, which is based on the regulation of DNA translocation. We propose the 'hourglass' model of remodeller function, in which each remodeller subfamily utilizes diverse specialized proteins and protein domains to assist in nucleosome targeting or to differentially detect nucleosome epitopes. These modules converge to regulate a common DNA translocation mechanism, to inform the conserved ATPase 'motor' on whether and how to apply DNA translocation, which together achieve the various outcomes of chromatin remodelling: nucleosome assembly, chromatin access and nucleosome editing.

[1]*Howard Hughes Medical Institute and Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, Utah 84112, USA.*
[2]*Department of Biochemistry, University of Utah School of Medicine, Salt Lake City, Utah 84112, USA.*
[3]*Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA.*

Correspondence to B.R.C. and C.L.P.
brad.cairns@hci.utah.edu; Craig.Peterson@umassmed.edu

doi:10.1038/nrm.2017.26
Published online 17 May 2017

Chromatin-structure dynamics are important for the regulation of gene expression and chromosome function. The basic components of chromatin are nucleosomes, which comprise octamers of histone proteins around which DNA is wrapped. The majority of nucleosome assembly occurs during DNA replication, directly in the wake of the replisome, and involves the delivery of histones to nascent DNA by histone chaperones. Chromatin dynamics involve the action of specialized ATP-dependent chromatin-remodelling complexes (herein termed remodellers). Remodellers include enzymes that ensure the proper density and spacing of nucleosomes and that can also contribute to gene repression. Another set of remodellers cooperates with site-specific transcription factors and histone-modification enzymes to move or to eject histones to enable the binding of transcription factors to DNA. Yet another set of remodellers is involved in creating specialized chromosomal regions where canonical histones are replaced by histone variants. Thus, genome-wide nucleosome occupancy and composition are tailored by specialized remodellers[1,2]. Genetic experiments have revealed that ATP-dependent chromatin-remodelling enzymes are essential regulators of nearly every chromosomal process, and their deregulation leads to a variety of diseases, including cancer[1,3,4].

Phylogenetic and functional analyses have classified all remodeller ATPases within the RNA/DNA helicase superfamily 2, which can be divided into four subfamilies of chromatin-remodelling enzymes: imitation switch (ISWI), chromodomain helicase DNA-binding (CHD), switch/sucrose non-fermentable (SWI/SNF) and INO80 (REFS 5–9) (BOX 1; see Supplementary information S1 (figure)). As the most extensive structure and mechanism studies have been conducted on the yeast enzymes, we focus on the yeast members of each subfamily, but we also discuss studies on the related mammalian complexes. Given their differential effect on nucleosomes, early models suggested that each subfamily used unrelated enzymatic mechanisms to achieve nucleosome organization, disorganization, ejection or changes in nucleosome composition. This Review instead proposes a unifying central mechanism for all types of remodellers: ATP-dependent DNA translocation; that is, the ATP-dependent movement of DNA by an enzyme, which, for remodellers, involves moving the DNA along the histone surface. Evidence for this mechanism begins with the observation that the catalytic subunits of all remodellers have an ATPase domain and activities that are consistent with DNA translocation. This ATPase domain may thus be considered to be a common 'motor' that uses DNA translocation to

Replisome
A large protein complex that carries out the DNA replication process, from the unwinding of double-stranded DNA to strand duplication by DNA synthesis.

Histone chaperones
Proteins that bind to free histones, prevent histone aggregation and that can promote either nucleosome assembly or nucleosome disassembly.

break histone–DNA contacts and to propel DNA along the histone surface. As different remodellers prefer different nucleosomes as substrates and generate distinct remodelling outcomes, we discuss how DNA translocation can be regulated to achieve these outcomes through remodeller-specific domains and proteins, and their interactions with histone modifications and histone variants. In this Review, we synthesize the available data and propose an 'hourglass' model for chromatin remodeller function — targeting specificity requires diverse remodeller-specific proteins, the functions of which converge on a common DNA translocation mechanism, which is regulated by diverse remodeller-specific proteins to achieve different remodelling outcomes.

Functional taxonomy of remodellers

Chromatin remodellers can be classified by their phylogenetic relationships[10] and/or by their different functionalities[1,5]. We first describe their functionalities and then integrate this with phylogenetic and subfamily designations. Most remodellers are specialized to preferentially conduct one of the following three functions: nucleosome assembly and organization, chromatin access and nucleosome editing (installing or removing histone variants) (FIG. 1a).

Nucleosome assembly and organization. Following replication, histone chaperones deliver histone complexes (H3–H4 tetramers and H2A–H2B dimers) to nascent DNA behind the replisome[11], where assembly remodellers, such as the ISWI and CHD subfamily remodellers, have two functions (FIG. 1a): they first help the initial histone–DNA complexes (pre-nucleosomes) to mature into canonical octameric nucleosomes[12,13], and they next form nucleosome arrays by spacing nucleosomes at relatively fixed distances apart[14–17]. This assembly and spacing process also takes place during transcription at locations where nucleosomes have been dynamically ejected.

Box 1 | **Remodeller classification and specialization**

Chromatin remodellers can be classified into four subfamilies: imitation swtich (ISWI), chromodomain helicase DNA-binding (CHD), switch/sucrose non-fermentable (SWI/SNF) and INO80, on the basis of the similarities and differences in their catalytic ATPases[10] (FIG. 1b) and associated subunits (Supplementary information S1 (figure)). In addition, most higher eukaryotes have multiple remodeller subtypes within each subfamily, to provide cell type-specific or developmentally specific remodellers[1,157,158]. Furthermore, orphan remodellers, which do not belong to a subfamily (for example, α-thalassaemia/mental retardation syndrome X-linked (ATRX)[21,156,159] and Cockayne syndrome group B (CSB)[160,161]) also exist, but are less well-characterized mechanistically, and are therefore not discussed here. See Supplementary information S1 (figure) for the composition of remodeller complexes and Supplementary information S2 (figure) for remodeller structures.

ISWI subfamily

The ATPase domain of the ISWI subfamily remodellers contains two RecA-like lobes, which are separated by a small insertion sequence[162,163] (FIG. 1b), and a carboxy-terminal HAND–SANT–SLIDE (HSS) domain[164] that binds the unmodified histone H3 tail[165] and the linker DNA flanking the nucleosome[166]. Two domains that flank the ATPase lobes (autoinhibitory N terminal (AutoN) and negative regulator of coupling (NegC)) regulate the activity of the ATPase domain[33]. Budding yeast have two highly similar ISWI ATPases, Isw1 and Isw2, which assemble into three distinct complexes[43,167]. Functionally, most ISWI subfamily complexes assemble and regularly space nucleosomes to limit chromatin accessibility and gene expression; however, a subset, such as the nucleosome remodelling factor (NURF) complex, have accessory subunits that confer access and that promote transcription[168,169].

CHD subfamily

The ATPase domain of CHD subfamily remodellers resembles that of the ISWI remodellers[48], but uniquely bears in its amino terminus two signature, tandemly arranged chromodomains[170,171] (FIG. 1b). Analogous to ISWI, the C terminus of CHD remodellers contains a NegC domain[48] followed by a DNA-binding domain (DBD) comprised of only the SANT and the SLIDE domains[172]. In *Saccharomyces cerevisiae*, Chd1 functions as a monomeric remodeller[170], whereas CHD remodellers have diverse complexes in metazoans[171,173] and conduct all three general remodelling processes: assembly (spacing nucleosomes)[16], access (exposing promoters)[174] and editing (incorporating histone H3.3)[175]. For example, yeast Chd1 mainly conducts chromatin assembly, whereas the metazoan nucleosome remodelling deacetylase (NuRD) complex remodeller helps repressors to bind to chromatin and represses genes through its associated histone deacetylases[173,176].

SWI/SNF subfamily

The ATPase domain of SWI/SNF remodellers contains two RecA-like lobes that flank a small conserved insertion, an N-terminal helicase/SANT-associated (HSA) domain that binds actin and/or actin-related proteins[177–179] (ARPs; see Supplementary information S8 (box)), an adjacent post-HSA domain, AT-hooks and a C-terminal bromodomain (FIG. 1b). Organisms often have two similar SWI/SNF subtypes: in yeast, the Sth1 and Snf2/Swi2 ATPases nucleate the remodels the structure of chromatin (RSC) and SWI/SNF complexes, respectively. SWI/SNF subfamily complexes contain core subunits (for example, yeast Swi3, Swp73, Snf5 and ARPs). In higher eukaryotes, combinatorial construction of SWI/SNF complexes using different core paralogues results in tissue- and developmental-specific SWI/SNF subtypes[2]. SWI/SNF subfamily remodellers typically facilitate chromatin access (FIG. 1a), as they slide and eject nucleosomes, and are used for either gene activation or gene repression.

INO80 subfamily

Two closely related ATPases, known as Ino80 and Swr1 in yeast, define this subfamily[180,181]. These proteins contain a variable, large insertion between the RecA-like lobes (FIG. 1b). This insertion is shorter in yeast (~250 amino acids) than in mammals (>1,000 amino acids) and binds a single heterohexameric ring of the helicase-related (AAA+ ATPase) ruvB-like protein 1 (Rvb1) and Rvb2 (REFS 101,182), one ARP and one YL-1 protein family member. The N terminus of INO80 subfamily ATPases contains an HSA domain that nucleates actin and ARPs[102], which has been validated by structural studies of the yeast Swr1 HSA domain–actin–Arp4 module of SWR1C[183]. Thus, INO80 subfamily ATPases scaffold three modules: the N terminus, Rvb1 and Rvb2, and the C terminus[99–101] (Supplementary information S2 (figure)). In higher eukaryotes, certain Swr1 complex subtypes also contain histone acetyltransferase (HAT) subunits (for example, human p400), whereas their yeast counterparts functionally interact with HATs[184].

INO80 subfamily remodellers have unique editing functions, although INO80C also conducts chromatin access and nucleosome spacing functions. The SWR1C, p400 and Snf2-related CBP activator protein (SRCAP) complex subtypes replace canonical H2A–H2B dimers with H2A.Z histone variant-containing H2A.Z–H2B dimers, whereas INO80C can catalyse the reciprocal reaction[19,89]. Of note, the vertebrate p400 subtype may also replace H3.1 with the variant H3.3 (REF. 185). Finally, yeast INO80C removes the variant H2A.X, which probably underlies its DNA repair functions[186,187], as well as its chromatin access and transcription activation functions[188,189].

Chromatin access. Rendering the chromatin more accessible to proteins and RNA involves sliding nucleosomes along the DNA, evicting nucleosome components (such as H2A–H2B dimers) or ejecting full nucleosomes (FIG. 1a). These functions are primarily (but not solely) carried out by SWI/SNF subfamily remodellers. Access remodellers can expose binding sites for transcription activators or transcription repressors at gene promoters or enhancers[18], and can increase accessibility for DNA repair and recombination factors. Whereas assembly remodellers promote gene silencing through the creation of tightly packed nucleosome arrays, access remodellers usually promote gene expression by opening the chromatin for transcription factors.

Nucleosome editing. Remodellers of the INO80 subfamily conduct the replication-independent removal of a particular histone within a nucleosome and its replacement with either a canonical or a variant histone (FIG. 1a). Common examples of editing include the replacement of canonical H2A or H3 histones with related variants, which is assisted by editing remodellers, such as yeast Swr1 complex (SWR1C) and mammalian Snf2-related CBP activator protein (SRCAP) and p400 (REFS 19–21). The inclusion of histone variants at a single nucleosome or at an array of nucleosomes can affect factor recruitment, exclusion and activity.

Together, remodellers help to ensure dense nucleosome packaging (at steady state) in the vast majority of the genome, while also allowing factors rapid access to particular loci and acting to specialize chromosomal regions by inserting histone variants. These diverse and complex tasks involve different specialized remodeller complexes (BOX 1). Despite this diversity, we explore below the shared properties and mechanisms of action of the remodeller complexes and how they might be differentially regulated to achieve these different tasks.

A shared DNA translocation mechanism

Although they affect nucleosomes differently, all remodellers share particular properties, including: a greater affinity for the nucleosome than for naked DNA; a single catalytic subunit, which contains an ATPase domain that is split into two RecA-like lobes (DExx, lobe 1; HELICc, lobe 2) (FIG. 1b,c); domains and/or proteins that regulate the ATPase domain; and domains and/or proteins for interaction with other chromatin proteins, chaperones or site-specific transcription factors (FIG. 1b). Together, the first two shared properties listed above enable the remodellers to act on nucleosomes, whereas the other two attributes enable their selective action on particular nucleosomes at specific locations.

We discuss below the evidence that a particular enzymatic property — DNA translocation — is shared by all types of chromatin remodellers and provides the underlying force that is needed to break histone–DNA contacts, which each remodeller then tailors to achieve nucleosome repositioning and sliding, ejection or editing. This perspective has emerged from the accumulation of more than a decade of evidence from multiple laboratories. The evidence obtained from these studies can be tiered by the extent to which the assays directly test and support translocation: first, direct assays, which provide real-time, single-molecule and/or visual observations of DNA translocation (for example, optical or magnetic tweezers and DNA curtains)[22–26]; second, indirect assays, which specifically test translocation (for example, triple-helix displacement, 'tethered' translocation and nucleosomes with strand-specific gapped DNA)[27–35]; and third, indirect assays, which test the effect of remodellers on DNA or nucleosomes (for example, nucleosome sliding, facilitated access of factors to nucleosomal DNA and changes in DNA topology) and which can be interpreted as being consistent with DNA translocation, or equally with other models, such as imposing DNA twist or histone octamer conformational changes[21,36–46] (see Note added in proof).

Perhaps the most thoroughly studied remodellers are those of the SWI/SNF subfamily ATPases, for which all the assays listed above have been applied, resulting in strong cumulative evidence for DNA translocation. These studies include the assessment of the major biophysical parameters of DNA translocation (velocity, processivity and force) through direct single-molecule studies[23,24]. Although only a subset of the assays above have been applied to other remodellers (or their ATPase subunits), the data are similarly consistent with DNA translocation being a unifying mechanism of chromatin remodelling. Below, we explore how this unifying mechanism, when combined with regulation from associated subunits, can explain the remodelling outcomes of all the remodeller subtypes. We note that a unifying property still allows for other mechanistic contributions (for example, changes in octamer conformation) that might facilitate or inhibit the DNA translocation process or which might affect octamer stability.

The mechanism of DNA translocation. Our current understanding of the mechanism of DNA translocation by remodellers is influenced by prior work on monomeric DNA (and RNA) helicases, which conduct ATP-dependent translocation by directional tracking along the phosphate backbone of one of the two DNA strands[47]. Helicases and remodeller ATPases are related enzymes that belong to a much larger family of ATP-dependent nucleic acid translocases — all of which have the shared property of the using two RecA-like lobes (DExx, lobe 1; HELICc, lobe 2) to conduct DNA translocation (FIG. 1b; see Supplementary information S2 (figure)). During translocation, helicases insert a protein domain between the two DNA strands, which causes DNA strand separation, whereas remodeller ATPases do not.

Multiple structures of monomeric DNA/RNA helicases are available[47], which are similar to the three currently available remodeller ATPase structures: *Saccharomyces cerevisiae* Chd1 (REF. 48) (Supplementary information S2 (figure)), and *Myceliophthora thermophila* Snf2 (REF. 49) and ISWI[50]. As none of these three structures contains DNA, our understanding relies more on structures of monomeric DNA helicases–translocases, which reveal the existence of

Canonical histones
The four core histones (H2A, H2B, H3 and H4) that are most commonly assembled into nucleosomes during replication and that constitute almost all of the nucleosomes across the genome.

Histone variants
Differ by a few amino acids from canonical histones and are expressed at low-to-moderate levels and typically inserted into nucleosomes independently of replication; they create specific chromatin regions and functions.

RecA-like lobes
Protein domains of helicases and remodellers, similar in structure and sequence to the ATPase domain of the *Escherichia coli* DNA-binding protein RecA.

DNA twist
A measure of the extent of helical winding of the DNA strands around each other, along their common axis. Often expressed as the number of base pairs of DNA per helical turn in B-form DNA.

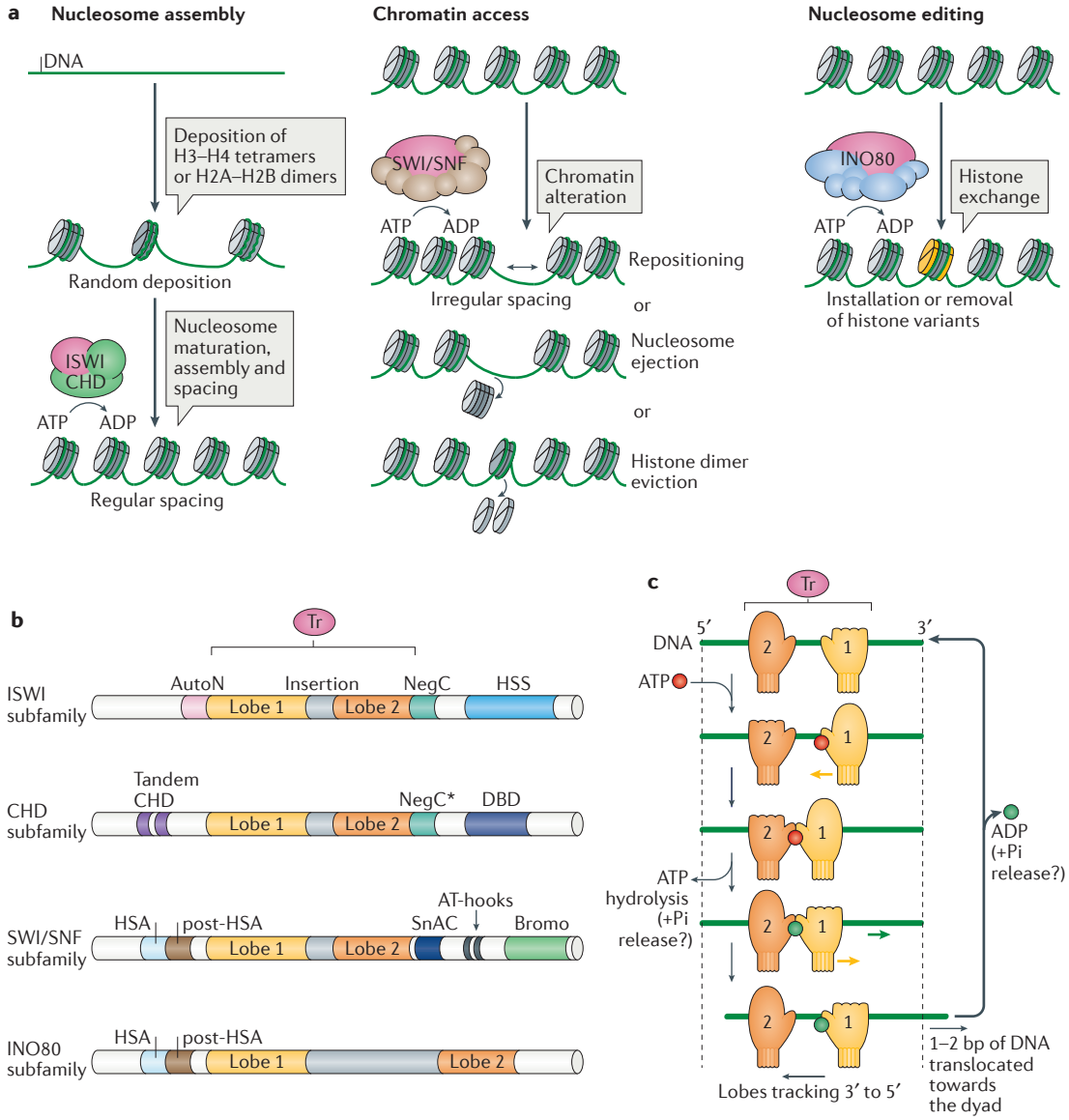

Figure 1 | **Functions and domain organization of chromatin remodellers. a** | Functional classification of remodellers. The ATPase–translocase subunit of all remodellers is depicted in pink; additional subunits are depicted in green (imitation switch (ISWI) and chromodomain helicase DNA-binding (CHD)), brown (switch/sucrose non-fermentable (SWI/SNF)) and blue (INO80). Nucleosome assembly: particular ISWI and CHD subfamily remodellers participate in the random deposition of histones, the maturation of nucleosomes and their spacing. Chromatin access: primarily, SWI/SNF subfamily remodellers alter chromatin by repositioning nucleosomes, ejecting octamers or evicting histone dimers. Nucleosome editing: remodellers of the INO80 subfamily (INO80C or Swr1 complex (SWR1C)) change nucleosome composition by exchanging canonical and variant histones, for example, and installing H2A.Z variants (yellow). We note that this functional classification is a simplification, as INO80C, the ISWI remodeller nucleosome remodelling factor (NURF) and certain CHD remodellers can promote chromatin access. **b** | Domain organization of remodeller subfamilies. The ATPase–translocase domain (Tr) of all the remodellers is sufficient to carry out DNA translocation. It is comprised of two RecA-like lobes (lobe 1 and lobe 2, which are separated by a short or long (such as in the INO80 subfamily) insertion (grey)). Remodellers can be classified into four subfamilies based on the length and function of the insertion and on their domain organization. **c** | 'Inchworming' mechanism of DNA translocation. An ATP binding–hydrolysis-dependent conformational cycle of the RecA-like lobes ('mittens') drives DNA translocation. Mittens are depicted closed when lobes have high affinity for DNA and open when lobes have low affinity for DNA (Supplementary information S3 (movie)). Although the DNA can be double-stranded, only the tracking strand of DNA is depicted, along which the lobes move in the 3′–5′ direction (validated by single-stranded DNA studies[53]). Steps are depicted as sequential, but they may be concerted, and a similar model with mitten/lobe 1 being stationary is equally supported. The yellow arrows represent remodeller movement; the green arrow represents DNA translocation. The precise step in which inorganic phosphate (Pi) is released is not known. NegC* is a region with structural similarity to the ISWI negative regulator of coupling (NegC) domain. AutoN, autoinhibitory N-terminal; Bromo, bromodomain; DBD, DNA-binding domain; HSA, helicase/SANT-associated; HSS, HAND–SANT–SLIDE; SnAC, Snf2 ATP coupling. Part **c** is adapted from REF. 52, Cell Press.

Box 2 | **Nucleosome structure and thermodynamics**

Understanding chromatin-remodelling mechanisms requires an appreciation of the biophysical features and challenges that are presented by their substrate, the nucleosome, which consists of a histone octamer wrapped by 147 bp of DNA. The canonical octamer is composed of two histone H3–H4 dimers that form the central tetramer, which is then capped on each end by an H2A–H2B dimer[190]. Together, they form an interlocked right-handed helical staircase upon which the DNA climbs[191]. Positively charged amino acids facing outwards from the histone staircase contact the negatively charged phosphate backbone of the DNA (Supplementary information S4 (movie)). An important nucleosomal landmark is the dyad, which is the central location where the nucleosome shows two-fold rotational symmetry; the dyad axis that defines this feature is depicted with a grey stippled bar in all the figures and animations.

Although each single histone–DNA contact is fairly weak (~1 kcal mole^{-1}, requiring ~1 pN of force to disrupt), the sum of all the 14 histone–DNA contacts that are normally present on the nucleosome confers considerable positional stability (~12–14 kcal). Together, these histone–DNA contacts define the energetic barrier that chromatin remodellers must overcome. As ATP hydrolysis provides ~7.3 kcal mole^{-1} of free energy, remodellers must either break only a few histone–DNA contacts at a time or must accumulate the energy from more than one ATP hydrolysis event to yield a repositioned, ejected or edited nucleosome. Thus, rather than breaking all histone–DNA contacts simultaneously, the need for a lower input of energy can be envisioned through the sequential disruption of subsets of histone–DNA contacts, thereby creating a DNA 'wave' that propagates around the octamer surface by one-dimensional diffusion. This mechanism enables histone–DNA contacts to sequentially break and re-form 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 repositioning. Although nucleosomes bind more strongly to certain types of DNA sequences (those favouring left-handed curvature), the energy differences between favourable and unfavourable sequences are small relative to the energy provided by ATP hydrolysis; thus, remodellers can impart sufficient force to slide nucleosomes along any DNA sequence.

Within nucleosomes, the energy cost associated with wrapping DNA far beyond its persistence length is compensated for by the energy gained through histone–DNA contacts. Thus, the nucleosome can be considered a loaded spring, with energy stored in DNA bending. Remodellers that conduct nucleosome ejection implement the eventual disruption of all histone–DNA contacts, which releases the bending energy in the DNA, and may therefore take advantage of the bending energy in the disruption process. By contrast, remodellers that only conduct nucleosome sliding may limit the disruption of histone–DNA contacts to avoid the binding energy falling below the stored bending energy, which would favour and cause ejection.

a DNA-binding cleft and a site for ATP binding and hydrolysis between the RecA-like lobes, which together constitute the DNA translocation motor. Both lobes bind to the same strand of DNA, with one lobe slightly ahead of the other. This enables an 'inchworming' mechanism of unidirectional movement that involves the reciprocal action of the two RecA-like lobes that sequentially bind to and release DNA — like two 'mittens' (FIG. 1c; see Supplementary information S3 (movie)) apparently moving 1–2 bp of DNA per cycle of ATP binding–hydrolysis–release[24,25,47,51,52]. Within the SWI/SNF subfamily enzymes, these lobes track along one of the two strands of the DNA, moving in the 3′–5′ direction following the phosphate backbone, as gaps limited even to a single base pair can greatly impair tracking and translocation[28,53]. A change in perspective reveals how this property is applied to the nucleosome: when the translocating enzyme is fixed, the DNA appears to be propelled by the enzyme, causing one helical rotation of DNA for every ~10 bp that is translocated (Supplementary information S3 (movie)).

Implementation of DNA translocation on the nucleosome. We explore below how the enzyme, if it is anchored to a fixed position on the histone octamer, can confer both translocation and twist to the DNA in order to break histone–DNA contacts. We provide a biophysical perspective on nucleosomes and histone–DNA contacts in BOX 2, complemented by an animation of nucleosome structure (Supplementary information S4 (movie)). An important aspect to consider is where the translocating enzyme engages the histone octamer and nucleosomal DNA. At present, we lack a high-resolution structure of a remodeller bound to a nucleosome with the ATPase engaged (see Note added in proof). Early models of remodeller–nucleosome engagement and translocation by remodellers stipulated a processive movement of the remodeller along the DNA, involving the peeling off of DNA while travelling around the octamer, much like an RNA or DNA polymerase[54], as well as the use of translocation from outside the nucleosome to push linker DNA into the nucleosome[28,31]. However, many studies (including hydroxyl-radical footprinting, crosslinking, DNase I hypersensitivity, fluorescence resonance energy transfer (FRET) and comparative analysis of mononucleosomes containing or lacking strand-specific DNA gaps) now support an alternative model, in which the RecA-like lobes (the translocase domain) bind to chromatin within the nucleosome at superhelical location 2 (SHL2), which is two DNA helical turns away from the nucleosome dyad[27,43,44,53,55]. Importantly, the position of the translocase domain remains fixed on the octamer, probably through the use of a histone-binding domain (HBD). For SWI/SNF, a clear HBD is located in the carboxyl terminus[56] (FIG. 1b), known as Snf2 ATP coupling (SnAC), which helps to maintain octamer attachment during forcible DNA translocation, a property that is likely to be necessary for nucleosome ejection. For ISWI and CHD, moderate sliding activity is observed with derivatives that lack the C terminus, suggesting that an HBD resides within the translocase domain or the amino termini of these proteins[33,48]. Although isolated INO80 subfamily ATPases have not yet been tested, combined results from SWI/SNF, ISWI and CHD subfamily enzymes converge on a unifying concept: the implementation of DNA translocation from a fixed location, two helical turns away from the nucleosome dyad.

Once bound to the SHL2 position on the octamer, studies suggest that the translocase domain carries out directional DNA translocation by pulling in DNA from the proximal side of the nucleosome (the DNA entry site, which is ~50 bp from the translocase) and pumping it towards the distal side (the DNA exit site, which is ~97 bp from the translocase)[53,55] (FIGS 2,3). This DNA propelling action involves the reciprocal action of the two RecA-like subdomains, moving 1–2 bp of DNA per cycle of ATP binding–hydrolysis–release[24,51] (Supplementary information S5,S6 (movies)). This translocation creates DNA twist of opposite polarity on each side of the translocase domain: the proximal side is under-twisted and lacks sufficient DNA, whereas the distal side is overtwisted and contains excess DNA. On the proximal side, the translocase action breaks histone–DNA contacts,

Persistence length
A mechanical property of polymer stiffness, which for DNA is approximately 100 bp.

Nucleosome dyad
A pseudo-two-fold symmetry element of the nucleosome core particle.

Gyre
In the context of a nucleosome, refers to one DNA wrap around the surface of the octamer.

drawing DNA from the proximal linker into the nucleosome. Viewed from the location of the translocase domain, this DNA segment can propagate in a wave-like manner towards the distal exit site of the nucleosome by diffusion, with histone–DNA contacts broken at the leading edge of the wave and re-forming at the lagging edge of the wave. On arrival at the distal linker, the DNA twist is resolved, and the linker is extended by 1–2 bp, resulting in the overall sliding of the histone octamer 1–2 bp along the DNA. Through iteration, ATP hydrolysis cycles lead to additional directional displacement. This model has been termed wave–ratchet–wave to denote the movement of DNA both towards and away from the internal translocase domain[53]. These 'waves' can be as small as 1 bp (REFS 24,25) (Supplementary information S5 (movie)), or can instead involve more than 1 bp

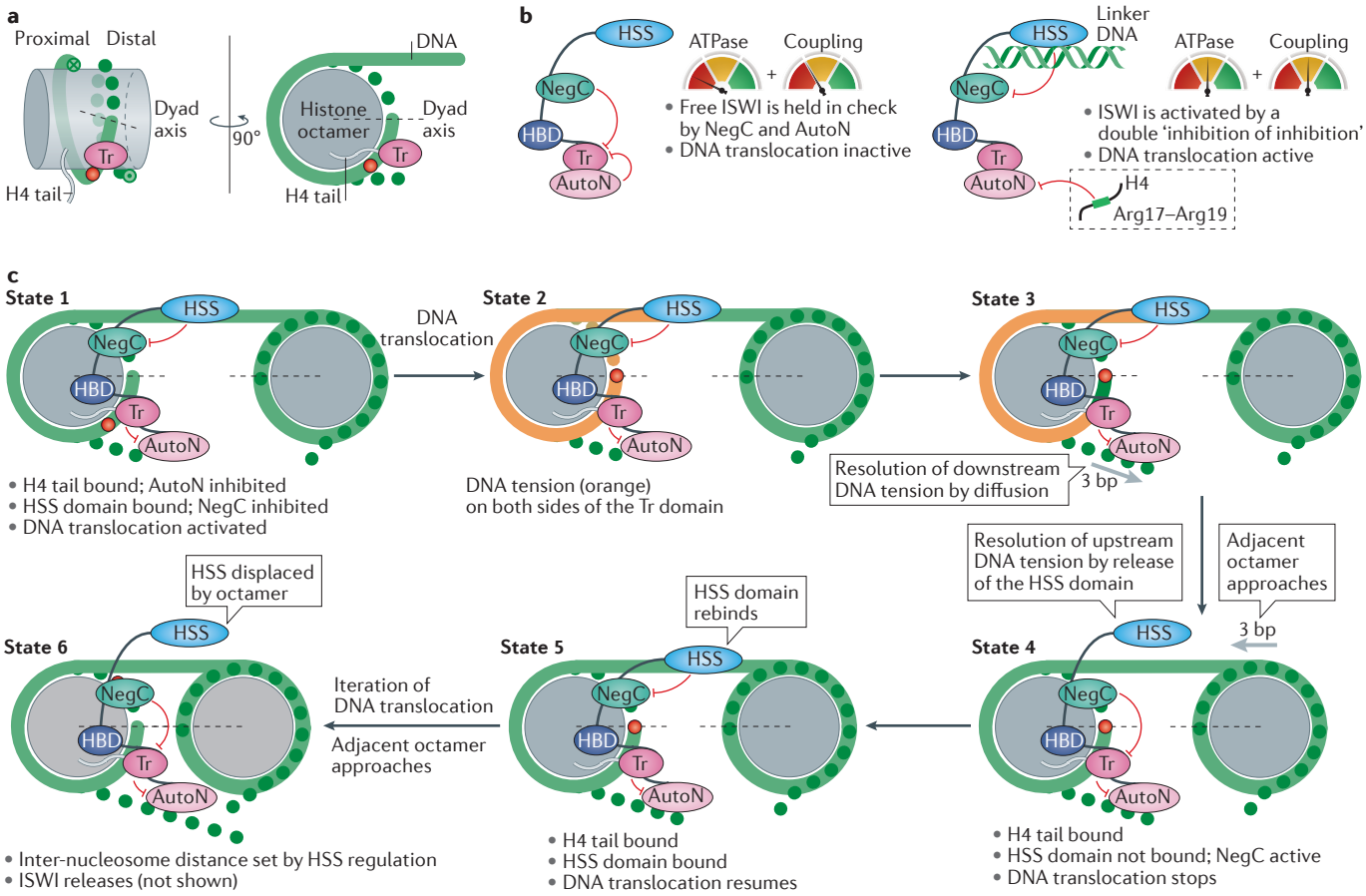

Figure 2 | **Model of the regulation of DNA translocation leading to precise nucleosome spacing by ISWI subfamily remodellers.** **a** | The nucleosome is shown with the left-handed wrapping of DNA around the histone octamer (grey transparent cylinder). The DNA colour changes from light green to dark green when passing the nucleosome dyad (from the proximal side to the distal side), to distinguish the second gyre. The location where a remodeller ATPase–translocase (Tr) domain will bind on the nucleosome, as well as one H4 tail, is also depicted. A red circle serves as a reference point to trace DNA translocation. **b** | Schematic of the domain architecture of *Drosophila melanogaster* imitation switch (ISWI). Regulation of *D. melanogaster* ISWI: in the left-hand diagram, the autoinhibitory N-terminal (AutoN) and negative regulator of coupling (NegC) domains inhibit the ATPase activity and coupling of the translocase domain, respectively, thus inactivating DNA translocation. In the right-hand diagram, ISWI is activated by a double 'inhibition of inhibition' by the Arg17–Arg19 patch of the histone H4 tail and by linker DNA, which antagonize AutoN and NegC, thereby increasing ATPase activity and coupling, respectively, and activating DNA translocation. **c** | Precise spacing of nucleosomes by ISWI subfamily remodellers. The ISWI remodeller interacts with the nucleosome two DNA helical turns away from the dyad via its ATPase–translocase domain and is anchored to the surface of the octamer by a histone-binding domain (HBD). The H4 tail binds to the remodeller, releasing AutoN inhibition and activating ATPase activity. In parallel, the HAND–SANT–SLIDE (HSS) domain binds to linker DNA, releasing NegC inhibition and reinstating efficient coupling (state 1). The translocase domain translocates 3 bp of DNA along the surface of the nucleosome (state 1 to state 2), generating DNA tension (orange) on both the proximal and the distal sides of the translocase domain, owing to the lack or excess of DNA, respectively (state 2). On the distal side, DNA tension is resolved (restoring green DNA colour) by one-dimensional diffusion of the 3 bp of excess DNA (implemented as three 1 bp steps), which moves around the distal side (2nd half) of the nucleosome in the form of a small wave, and then resolves in the distal linker (state 2 to state 3). On the proximal side, DNA tension is resolved by DNA from the proximal linker entering the nucleosome, 3 bp at a time, which requires the release of the HSS binding (state 3 to state 4). Consequently, the adjacent nucleosome approaches by 3 bp (state 4) and the HSS re-binds linker DNA in its new position (state 5). This process is reiterated, resulting in the progressive approach of the adjacent nucleosome (state 5 to state 6), until the approaching octamer prevents the HSS from re-binding the linker DNA, thereby reinstating inhibition by NegC (state 6). DNA translocation then ceases, and the remodeller is released from the nucleosome (not shown), setting a precise inter-nucleosome distance. Multiple occurrences of this process result in nucleosome arrays with precise, regular spacing (Supplementary information S7 (movie)).

on the proximal side of the translocase domain[51] (Supplementary information S6 (movie)), especially if DNA movement is constrained (Supplementary information S7 (movie)). Of note, the translocase domain also functions as an internal ratchet to ensure directional movement of the DNA. We explore below how remodeller subfamilies regulate DNA translocation differently to achieve their specialized outcomes.

Differential regulation of translocation

In isolation, several remodeller ATPase domains are intrinsically active, although not necessarily maximally active, and it is becoming clear that the regulation of ATPase activity is carried out by domains that flank the ATPase domain and/or by associated proteins through one of three modes: 'gating', ATP turnover, or 'coupling'. A fourth mode, regulated affinity, is related

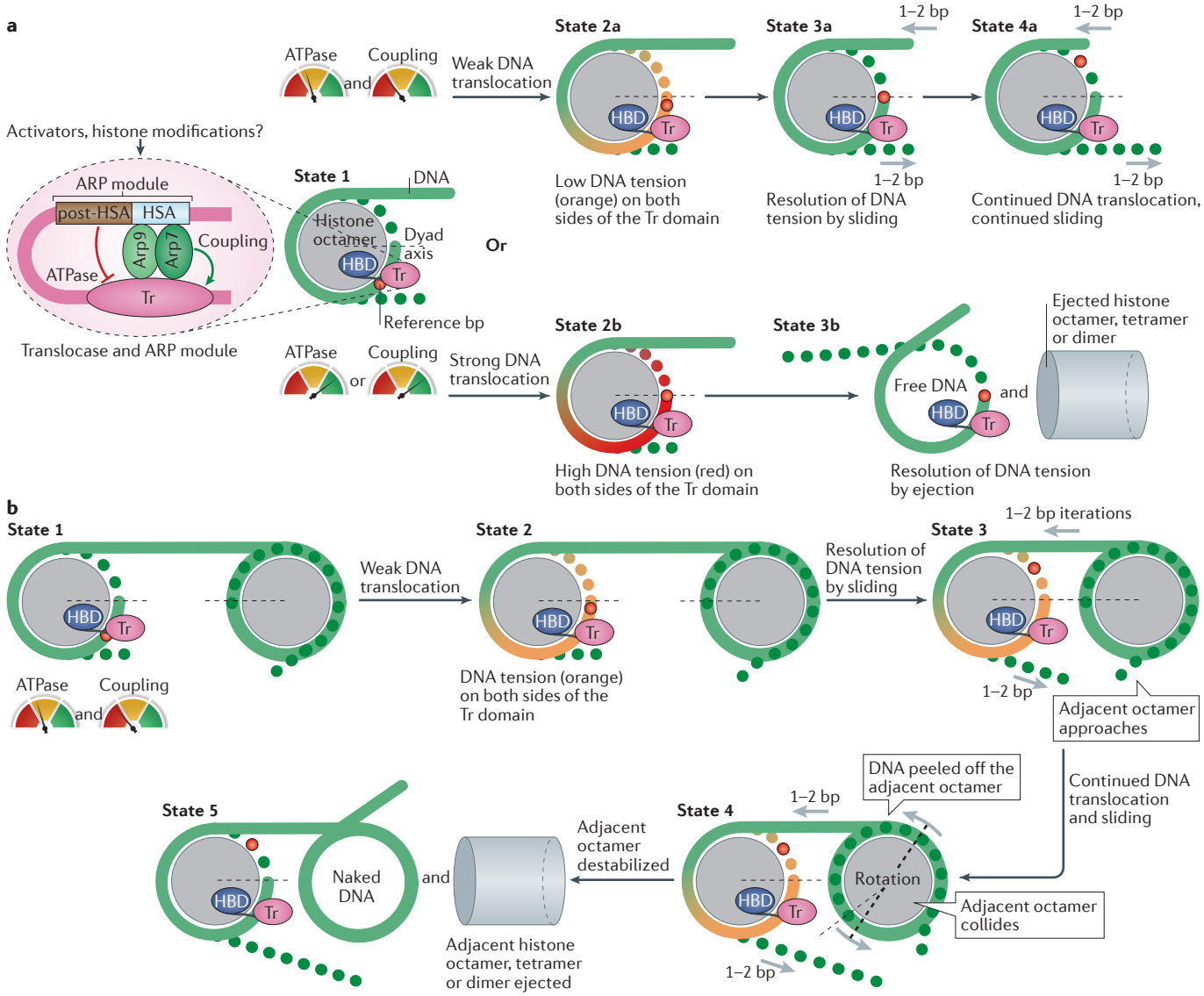

Figure 3 | **Models of nucleosome ejection by SWI/SNF subfamily remodellers. a** | Regulation of DNA translocation, leading to nucleosome ejection by switch/sucrose non-fermentable (SWI/SNF) subfamily remodellers. The actin-related protein (ARP) module regulates both the ATPase and the coupling activities of the ATPase–translocase domain (Tr), which interacts with the nucleosome two helical turns away from the dyad (state 1), anchors to the surface of the octamer via a histone-binding domain (HBD) and translocates 1–2 bp of DNA along the surface of the nucleosome (state 1 to state 2), thereby generating DNA tension on both the proximal and the distal sides of the translocase domain. Low-to-moderate ATPase activity and coupling leads to weak DNA translocation and low DNA tension (orange; state 2a) that are resolved by sliding (restoring green DNA colour; state 3a). Continued DNA translocation results in continued sliding, the progressive displacement of the histone octamer with respect to the DNA (state 4a). Alternatively, SWI/SNF can generate high coupling (by the helicase/SANT-associated (HSA)–Arp7–Arp9 module) and high ATPase activity (by post-HSA), leading to strong DNA translocation and high DNA tension and disruption of histone–DNA contacts (red; state 2b), which results in histone ejection (state 3b; see Supplementary information S9 (movie)). **b** | Nucleosome ejection by spooling during remodelling by SWI/SNF subfamily remodellers. As shown in part **a**, the ATPase–translocase domain of the SWI/SNF subfamily remodellers can generate low-to-moderate DNA tension (state 1 to state 2) that is resolved by sliding. By iterations, continued DNA translocation and sliding lead to the approach of an adjacent octamer (state 3) that ultimately collides with the remodeller-bound nucleosome, resulting in the DNA being peeled off the adjacent octamer (state 4) and eventually in the ejection of the adjacent nucleosome by 'spooling' (state 5).

to remodeller targeting and substrate selectivity and is not discussed here, except when it also affects enzymatic activity.

Gating refers to the ability of the substrate nucleosome to access the ATPase active site. A prominent example involves the yeast Chd1 remodeller, which has N-terminal chromodomains positioned to interfere with the path of DNA through the DNA-binding cleft, thereby requiring a conformational change to allow DNA binding[48]. An alternative form of gating regulates the Swi2/Snf2 subfamily ATPases and involves the non-productive positioning of the two RecA-like lobes without DNA, which requires a regulated conformational change to form a proper cleft for DNA interaction and ATP hydrolysis[49].

The regulation of ATP turnover determines how quickly the enzyme conducts the ATP-binding–hydrolysis-driven conformation cycle — the successive conformations that an enzyme adopts during the ATP hydrolysis cycle — and thus how fast the RecA-like 'mittens' move along DNA (Supplementary information S3,S5,S6 (movies)).

Coupling refers to the efficiency of this process — the probability that ATP hydrolysis will result in DNA translocation (or the amount of DNA that is translocated per ATP hydrolysis cycle). Thus, coupling can represent the ability of the mittens to properly grip and release during the conformation cycle, and so may help to implement force. For each remodeller subtype, we describe below the domains and proteins that are known to regulate gating, ATPase activity or coupling, and how they collaborate to determine the remodelling outcome.

Mechanisms and regulation of chromatin assembly. Nucleosome assembly and spacing is primarily conducted by ISWI and CHD subfamily remodellers, although sliding and spacing activity has also been reported for an INO80 subfamily member[57]. Replication presents a challenge to chromatin organization, as nucleosomes are initially randomly deposited in the wake of DNA replication. First, pre-nucleosomes form, which are histone octamers upon which the DNA is not fully or properly wrapped (~80 bp rather than 147 bp)[12,13]. The remodeller may assist in the formation of fully mature and wrapped nucleosomes, and may subsequently use ATP-dependent nucleosome sliding activities to achieve ordered spacing[12,13] (FIG. 1a).

The key to spacing involves the separate regulation of the ATPase and the coupling components of DNA translocation. ISWI and CHD remodellers each use a DNA-binding domain (DBD), HAND–SANT–SLIDE (HSS) and DBD, respectively (FIG. 1b), as a 'molecular ruler' that binds to linker (extranucleosomal) DNA and that measures the distance between nucleosomes[58]. HSS binding to linker DNA leads to the binding of the ATPase domain on the proximal side, two helical turns away from the nucleosome dyad (FIG. 2a), and to the promotion of coupling, by antagonizing the negative regulator of coupling (NegC) domain, which physically bridges the two RecA-like lobes, and negatively regulates coupling. Before nucleosome binding, NegC prevents productive DNA translocation by uncoupling ATP hydrolysis from translocation, imparting a form of autoinhibition[33] (FIG. 2b). Binding of the HSS to linker DNA relieves NegC autoinhibition, thereby restoring coupling and enabling DNA translocation (FIG. 2c, state 1 and state 5). This interplay and inhibition of the inhibition of catalytic activity together provide an alternative regulatory mechanism to the previously suggested 'power stroke' models in which the HSS pushes DNA into the nucleosome[33,59]. The active translocase domain pulls in DNA, causing tension on both sides of the domain (FIG. 2c, state 2). This tension is resolved in two temporal phases: on the distal side, tension is resolved by wave propagation, as described above (FIG. 2c, state 3). On the proximal side, the tension constrained between the translocase and the HSS domain is retained until the HSS releases the linker DNA (FIG. 2c, state 4). In fact, single-molecule FRET experiments have suggested that the HSS remains bound during the translocation of 3 bp of DNA. This results in 3 bp of DNA exiting first from the distal side of the nucleosome via wave propagation, 1 bp at a time. Next, the 3 bp of undertwisted DNA is relaxed and drawn into the nucleosome[51], which we interpret as resulting from the HSS domain releasing this undertwisted DNA (FIG. 2c, state 4; see Supplementary information S7 (movie)). Thus, ~1 bp of sliding occurs per ATP hydrolysis, which is executed in 3 bp successive steps. Iterations of this cycle will draw the adjacent nucleosome ever nearer (FIG. 2c, state 5 and state 6), progressively shortening the linker DNA, until the adjacent nucleosome interferes with binding by the HSS domain through steric hindrance (FIG. 2c, state 6). When the HSS domain can no longer re-bind linker DNA, it fails to antagonize NegC and the translocation ceases (FIG. 2c, state 6), leaving the adjacent nucleosome at a fixed distance from the substrate nucleosome. Sequential application of the spacing process to all nucleosomes on the template will produce an array in which all nucleosomes are separated by the same distance. This entire process is depicted in Supplementary information S7 (movie).

Of note, the ISWI complex ATP-utilizing chromatin remodelling and assembly factor (ACF) contains a protein (Acf1) that extends the length of the DNA bound by the HSS and the DBD domains and thus yields a nucleosome array with a longer average linker[16], in keeping with the model described above. Moreover, Acf1 contributes to the mechanism of sensing the length of linker DNA through an interesting interplay with the histone H4 tail and the autoinhibitory N-terminal (AutoN) domain (see below)[60]. We note that a DNA-bound transcription factor (or a strongly positioned nucleosome) can function as a boundary element, against which unidirectional sliding and spacing events occur, thereby facilitating the formation of an array of regularly spaced nucleosomes[46,61–64].

In addition to regulated coupling, regulated ATPase activity is also a feature of ISWI. A small basic patch (Arg residues 17–19) of the histone H4 tail activates chromatin-assembly remodellers, such as ISWI[65–68], by helping to orient the ATPase domain on the nucleosome to two helical turns away from the dyad[69] and inducing an allosteric

change in the ATP-binding pocket[70]. The N terminus of ISWI contains a 'mimic' of the H4 tail basic patch known as AutoN (FIG. 1b), which inhibits ATPase activity[33] and provides a form of autoinhibition (analogous to that of NegC) that is antagonized by the authentic H4 tail basic patch. Of note, the human ACF1 protein also contributes allosterically to this regulation when not binding to linker DNA by sequestering the histone H4 tail[60]. Thus, ISWI activity is regulated at two levels, ATPase and coupling, which both involve the relief of intrinsic autoinhibition by nucleosomal epitopes[33]. The recently published structure of *M. thermophila* ISWI[50] both strongly supports and extends prior biochemical and genetic research. This work confirms that the AutoN domain and the H4 tail basic patch exhibit mutually exclusive binding to the surface of lobe 2 (see also Note added in proof), and the AutoN domain has been shown to extend past its original length to include an additional inhibitory element. In parallel, NegC was confirmed to act allosterically to respond to extranucleosomal DNA length. Thus, ISWI is a tightly and dynamically regulated motor; it is held in check by autoinhibition but, once relieved of its intrinsic brakes, it functions efficiently as an autonomous nucleosome remodeller[33,71].

Studies suggest a similar mechanism of nucleosome spacing by the yeast CHD subfamily, based in part on their NegC and similar HSS DNA-binding domains[16] (see Note added in proof). However, CHD remodellers contain one or more chromodomains in their N terminus rather than a clear AutoN domain, suggesting slightly different modes of regulation. Of note, the CHD subfamily has greatly expanded in mammals, but has had more limited mechanistic characterization.

Interestingly, certain ISWI complexes (for example, human SNF2H (also known as SMARCA5)) can operate via a 2:1 rather than a 1:1 remodeller:nucleosome stoichiometry[31,72]. The 2:1 ratio involves a second SNF2H complex binding in a symmetrical position on the opposite side of the nucleosome, without a steric clash with the first complex. As the DNA translocation mechanism is directional (propelling towards the dyad), two SNF2H complexes on opposite sides may alternate in activity, enabling octamer movement in alternative directions[72]. Furthermore, SNF2H dimerization enhances remodelling, and a conformational change in SNF2H that occurs upon ATP analogue binding may affect the sensing of linker DNA length and translocation[73]. This work is consistent with the regulatory mechanisms described above, as ISWI conformational changes during an ATP hydrolysis cycle may affect HSS–linker interactions.

Mechanisms and regulation of chromatin access. Chromatin access can be accomplished by specialized remodellers in all four subfamilies but is most strongly associated with SWI/SNF remodellers. Biochemical and structural studies with SWI/SNF subfamily remodellers strongly support a 1:1 remodeller:nucleosome stoichiometry, and reveal a striking binding pocket with almost perfect mononucleosome dimensions[74–80] (Supplementary information S2 (figure)). Access of the nucleosome to this pocket may involve conformational changes and can be regulated by histone tail modifications[74,77,78,80], which might be recognized by one of the many histone-interacting domains in SWI/SNF complexes. We consider this to be consistent with the idea of histone modifications gating access to the pocket.

A key question about SWI/SNF remodellers is how sliding versus ejection is regulated. Recent work has identified several DNA translocation regulators: three domains that reside on the catalytic subunit (helicase/SANT-associated (HSA), post-HSA and protrusion 1, which is located within the insertion between the two RecA-like lobes), and two actin-related proteins (ARPs) that directly bind to the HSA domain[35] (FIG. 3a). ARPs are important functional members of two of the four remodeller subfamilies, SWI/SNF and INO80 (Supplementary information S8 (box)). In the yeast SWI/SNF subfamily, the associated ARPs facilitate sliding and enable ejection[35]. Mechanistically, these ARPs greatly improve coupling by folding back and functionally interacting with protrusion 1 within the translocase domain (FIG. 3a). By contrast, the post-HSA domain has no effect on coupling, but instead strongly inhibits ATP hydrolysis. These ATPase and coupling activities are integrated by the translocase domain to determine the velocity and efficiency of DNA translocation[35]. With low-to-moderate DNA translocation efficiency, proportional nucleosome sliding occurs, whereas with higher DNA translocation efficiency, histone ejection occurs[35] (FIG. 3a; see Supplementary information S9 (movie)). Of note, direct interaction of the post-HSA region with the protrusion 1 domain was demonstrated in a recent structural study[49], reinforcing the idea that interaction of the ARP–HSA–post-HSA module with protrusion 1 is a conserved feature that is used for ATPase and/or coupling regulation.

We propose two non-mutually exclusive models to explain how DNA translocation could lead to nucleosome ejection. In the first model, the disruption of multiple histone–DNA contacts by efficient and forcible DNA translocation might directly facilitate histone loss (FIG. 3a), and might additionally enable histone chaperones and/or specialized proteins on particular remodellers to gain access to assist in the removal of the underlying histones. Considering the position of the translocase domain, the H2A–H2B dimer should be the most susceptible to ejection, and, indeed, SWI/SNF remodellers may destabilize and remove H2A–H2B dimers as the first step in ejection[81–84]. Of note, the use of DNA translocation by SWI/SNF for the removal of H2A–H2B dimers may be a feature that is shared with editing remodellers, although only editing remodellers replace canonical H2A–H2B dimers with histone variant dimers (see below).

In the second model, the nucleosome adjacent to the one that is undergoing remodelling is the nucleosome that will be ejected, rather than the nucleosome that is bound by the remodeller. In this case, the act of processive DNA translocation on the bound nucleosome initially draws the available linker DNA into the bound nucleosome and, when linker DNA availability is exhausted, the remodeller 'spools' the DNA off the adjacent

DNA translocation efficiency
Quantified by measuring coupling, it describes the amount of DNA that is translocated per ATP hydrolysis and/or the probability that the enzyme conducts a DNA translocation step per ATP hydrolysis cycle.

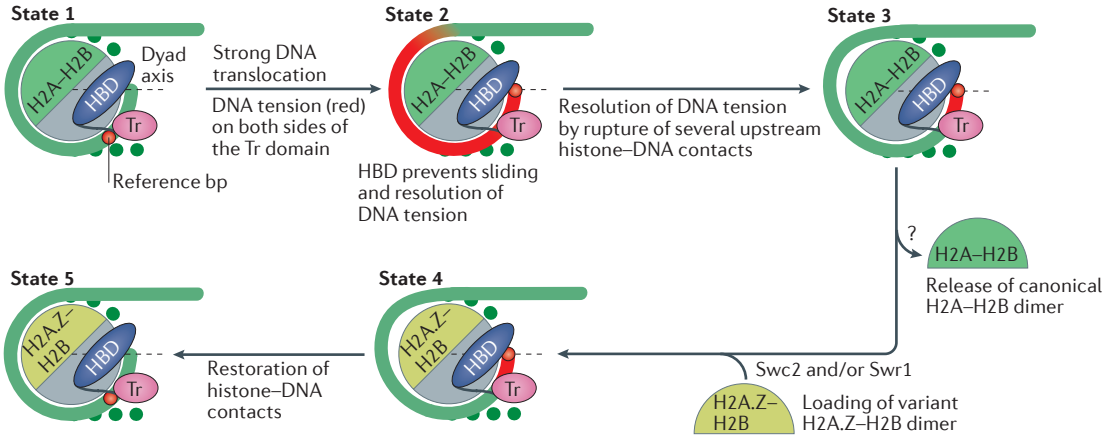

Figure 4 | **Model of histone exchange by the remodeller SWR1C.** As in the case of imitation switch (ISWI) and switch/sucrose non-fermentable (SWI/SNF) subfamilies, the ATPase–translocase domain (Tr) of the yeast INO80 subfamily remodeller Swr1 complex (SWR1C) interacts with a nucleosome two helical turns away from the dyad (state 1), is anchored to the surface of the octamer via a histone-binding domain (HBD) and strongly translocates 1–2 bp of DNA at the surface of the nucleosome (state 1 to state 2), thereby generating high DNA tension (red DNA; state 2). On the distal side, resolution of DNA tension by DNA propagation may be prevented by the binding of the HBD (state 2). On the proximal side, DNA tension is resolved by the disruption of several upstream histone–DNA contacts (restoring green DNA colour; state 3), allowing the release of one canonical histone H2A (H2A)–H2B dimer and the loading of a variant H2A.Z–H2B dimer assisted by the Swc2 and/or Swr1 subunits (state 3 to state 4). Histone–DNA contacts are restored following the histone exchange (state 5; see Supplementary information S10 (movie)).

nucleosome, which leads to octamer ejection[85,86] (FIG. 3b). This model is supported by studies of yeast SWI/SNF using templates with two nucleosomes[87,88]. Of note, SWI/SNF remodellers display higher levels of DNA translocation efficiency than ISWI remodellers, which may explain why only SWI/SNF remodellers can eject nucleosomes[35]. Finally, a key unanswered question is how SWI/SNF remodellers are instructed to implement high levels of DNA translocation, which enables nucleosome ejection.

Regulation of nucleosome editing. Nucleosome editing, which involves the incorporation or the removal of histone variants, is mostly carried out by members of the INO80 subfamily; nucleosome editing allows construction of specialized chromatin regions in a replication-independent manner. Among the key variants to be incorporated is the H2A variant H2A.Z. Elegant work has shown that the yeast INO80C subtype SWR1C removes canonical H2A–H2B dimers and replaces them with H2A.Z–H2B dimers[19]. Of note, SWR1C does not slide nucleosomes[34], whereas INO80C can slide nucleosomes, as well as catalyse the eviction and replacement of H2A.Z–H2B dimers[89–91]. Thus, the INO80C subtype has both access and editing activities. Of note, in yeast, an H2A.Z-contaning nucleosome is less stable than a canonical nucleosome[92]. This property may be used for regulating genes and heterochromatin properties[93–95], but is not discussed further here.

A remodeller specialized for editing must be able to stabilize the hexasome during remodelling and incorporate a specific variant dimer to generate a variant-containing nucleosome. Thus, editing remodellers must discriminate between substrate and product nucleosomes. For example, yeast SWR1C contains proteins that are specialized for H2A.Z–H2B recognition[96,97], and conducts dimer replacement in a stepwise and unidirectional manner, one dimer at a time, first generating heterotypic nucleosomes (with one canonical H2A–H2B dimer and one variant H2A.Z–H2B dimer), and then generating homotypic H2A.Z nucleosomes[98]. However, as SWR1C binds with comparable affinity to both H2A- and H2A.Z-containing nucleosomes, substrate discrimination is complex[34]. We hypothesize that the translocase domain of SWR1C only interacts productively with an H2A-containing nucleosome (or with a heterotypic nucleosome), and not with a homotypic H2A.Z-containing nucleosome, thereby specifying H2A–H2B dimer replacement (FIG. 4). Interestingly, as ATPase activity is stimulated by H2A nucleosomes, and is activated further by the addition of free H2A.Z–H2B dimers, free H2A.Z–H2B acts as both a regulator and a substrate molecule[98]. With regard to gating, H2A.Z–H2B, or a SWR1C subunit that recognizes H2A.Z, may gate the interaction of the translocase domain with nucleosomal DNA near the dyad. Domain swapping experiments have identified H2A.Z residues that block dimer exchange by SWR1C, providing candidates for a gating domain[34].

Structural studies of yeast INO80C and SWR1C have revealed their similar architecture, which is characterized by a compact 'head' domain, which contains ruvB-like protein 1 (Rvb1) and Rvb2 in a heterohexameric ring, and a flexible 'tail' domain[99–101] (Supplementary information S2 (figure)). Both enzymes show remarkable structural heterogeneity, with a continuum of extended and compact forms. The INO80C complex may adopt an extended form that sandwiches a nucleosome between

Hexasome
Nucleosome that lacks one histone H2A–H2B dimer.

the tail and the head domains[100] (Supplementary information S2 (figure)), whereas the compact form blocks nucleosome binding, potentially providing an additional gating mode of regulation.

Similarly to SWI/SNF subfamily remodellers, INO80 subtypes use ARPs for nucleosome editing[102] (Supplementary information S8 (box)). In the case of yeast INO80C, one Arp8–Arp4–actin module binds to the HSA domain and promotes high-affinity nucleosome binding[101] (Supplementary information S2 (figure)). A second ARP-containing module, Ies6–Arp5, interacts with the ATPase insertion domain. The Ies2 subunit facilitates Ies6–Arp5 interaction with and activation of the Ino80 ATPase[103,104]. This module also promotes nucleosome binding[104], with Arp5 coupling ATPase activity to nucleosome mobilization[103–105]. Research on the reconstituted human INO80C core complex confirms the roles described above for the human homologues of Ies2 (INO80B) and Ies6–Arp5 (INO80C–ARP5)[106]. Finally, human INO80 has a C-terminal domain that has the hallmarks of NegC, as its removal markedly increases ATPase activity[104].

Yeast SWR1C also seems to use DNA translocation to facilitate H2A–H2B removal and subsequent H2A.Z–H2B deposition; SWR1C interacts with DNA approximately two helical turns away from the nucleosome dyad, and histone exchange is blocked by an adjacent 2 bp gap, which is consistent with an essential role for DNA translocation in nucleosome editing[34]. Of note, the amount of translocation involved may not be extensive, as a DNA gap located 3–4 helical turns away from the nucleosome dyad does not inhibit SWR1C[34]. As SWR1C does not reposition the H2A.Z-containing nucleosome product, how does SWR1C impose DNA translocation without sliding the nucleosome? We suggest that SWR1C functions like other remodellers: it engages nucleosomal DNA near the dyad (FIG. 4, state 1) but translocates only a few base pairs, thereby creating a region of localized DNA translocation and twist between the translocase and the proximal DNA entry–exit site (FIG. 4, state 2). However, unlike enzymes that catalyse sliding, SWR1C does not allow propagation of the twist and translocation wave to the distal side of the nucleosome, but instead holds this torsion in order to selectively destabilize DNA that is bound to the adjacent H2A–H2B dimer (FIG. 4, state 3). Following H2A exchange with H2A.Z, the DNA would then re-wrap, resulting in a nucleosomal product with an unchanged translational position (FIG. 4, state 5; see Supplementary information S10 (movie)).

Regulation by targeting epitopes

We discuss below how nucleosomal epitopes, transcription factors and chromatin factors interact with remodeller domains to help to target and also to regulate chromatin remodellers.

Remodeller targeting and regulation by histone modifications and variants. Multiple studies have linked histone modifications to the targeting and regulation of chromatin remodellers[107]. Remodellers of all four subtypes contain proteins and/or domains that bind to to histone modifications (for example, bromodomains, bromo-adjacent homology (BAH) domains, chromodomains, plant homeodomain (PHD) domains, Pro-Trp-Trp-Pro (PWWP) domains and tryptophan-aspartic acid (WD40) domains). Furthermore, chromatin-modifying enzymes and complexes cooperate with remodellers, especially at environmentally regulated genes[108]. For example, the yeast Spt-Ada-Gcn5-acetyltransferase (SAGA) complex commonly functions with SWI/SNF to promote gene activity, and can assist SWI/SNF recruitment to gene promoters[109].

In principle, a histone modification (or variant) could influence (either positively or negatively) remodeller targeting or activity. Indeed, the remodeller domains and motifs listed above selectively engage nucleosomes that have particular modifications, and can enhance their affinity (targeting) or activity. To affect activity, the histone modification or variant should subsequently regulate the functions of the ATPase domain or the histone chaperones. To affect targeting, histone modifications are predicted to function as combinations of modifications, or cooperate with gene-specific activators and repressors[110], as isolated remodeller motif–modification interactions are typically of low-to-moderate affinity (mid-to-high micromolar range)[111–118]. Another aspect of selectivity is how remodellers avoid binding and/or acting on the nucleosomes that they should normally avoid, which may involve modifications that prevent remodeller binding (or, alternatively, 'shielding' the nucleosome by recruiting another factor[119]), or inhibiting remodeller activity through an allosteric mechanism.

Interactions exist between particular histone modifications and all four remodeller subfamilies; below, we provide a selective list. In the ISWI subfamily, a PHD or a PWWP domain is used for targeting methylated histones: the *Drosophila melanogaster* nucleosome remodelling factor (NURF) remodelling complex binds to trimethylated histone H3 Lys4 (H3K4me3)[112,120,121], and the yeast ISW1b complex binds to H3K36me3 (REF. 122). In the CHD subfamily, the chromodomain or chromodomains can similarly bind to methylated histones[123,124]. In the SWI/SNF subfamily, the bromodomain located at the C terminus of the yeast Snf2/Swi2 ATPase promotes the targeting of SWI/SNF activity to nucleosomes that are acetylated on histone H3 (REFS 110,111,125–127). The yeast Snf2/Swi2 bromodomain can also regulate the binding to and remodelling of acetylated nucleosomes by SWI/SNF through an intramolecular interaction with an acetylated residue within the Swi2/Snf2 subunit[128,129]. Similarly, the tandem bromodomain located on the yeast remodel the structure of chromatin (RSC) complex subunit 4 (Rsc4) shows specificity for binding to acetylated histone H3 Lys14 (H3K14ac), and this single acetylated residue is sufficient to enhance RSC binding to nucleosomes *in vitro*[130]. In the yeast INO80 subfamily, the double bromodomain-containing subunit bromodomain-containing factor 1 (Bdf1) promotes H2A.Z deposition by SWR1C on nucleosomes acetylated on either histone H4 or H2A[131].

In addition to roles in targeting, histone modifications and variants also regulate remodelling activities. For example, nucleosomes containing the H2A.Z variant stimulate the ATPase and remodelling activities of ISWI, but not the activities of SWI/SNF subfamily members[132]. For the SWI/SNF subfamily members, site-specific H3 acetylation was shown to enhance the remodelling activities of yeast RSC and SWI/SNF, without increasing their nucleosome-binding affinities[110,125]. Intriguingly, acetylated H3 peptides open the nucleosome-binding cavity within RSC[78]. The enhancement of remodelling activity required the Snf2/Swi2 bromodomain[110], implying a regulatory role beyond targeting for bromodomain–histone tail interactions.

The H4 tail stimulates the *D. melanogaster* ISWI ATPase and remodelling activity[65–67], and most studies have suggested that acetylation of the H4 tail attenuates this stimulation[33,50,125,133,134]. Acetylation of H4K12 or H4K16 may weaken the ability of the H4 tail to compete with the AutoN domain. Of note, H4K16ac does not inactivate ISWI, but instead the ATP-dependent mobilization of nucleosomes is slowed by ~1.5-fold to 4-fold[50,125,133,134]. Furthermore, a recent study has suggested that the ability of *D. melanogaster* ISWI to properly space nucleosome arrays is not sensitive to H4K16ac[135].

In addition to those in histone tails, many post-translational modifications occur on the globular surface of the nucleosome. Of particular interest are two lysine residues (sometimes targeted for acetylation), H3K56 and H3K64, which are located on the lateral surface where DNA enters the nucleosome. In yeast, H3K56ac enhances the ability of SWI/SNF and RSC to mobilize nucleosomes in *cis*[136], whereas H3K64ac enhances the sliding activity of Chd1 but not of RSC[137]. How these two acetylation marks can have distinct effects on different remodelling enzymes is not yet clear. H3K56ac also has a striking effect on the nucleosome-editing activities of yeast INO80 subfamily members — it enhances the editing activity of INO80C but disrupts nucleosome discrimination by SWR1C, thereby allowing both H2A- and H2A.Z-containing nucleosomes to stimulate its ATPase activity[92]. How H3K56ac disrupts nucleosome discrimination is not known, although it has been suggested to function together with the H2A.Z-binding subunit Swc2 (REF. 92).

Remodeller targeting and regulation by DNA-binding proteins. Alongside their important roles in recruiting remodellers and mediating enhancer-promoter looping[138], transcription activators can directly interact with remodellers and can affect remodelling activities; for example, interactions between yeast SWI/SNF and a DNA-bound activator promotes nucleosome eviction *in vitro*[139–141]. We speculate that — beyond recruitment — DNA site-specific transcription activators and repressors (in combination with histone modifications and variants) interact in a specific manner with remodeller domains and proteins, regulate DNA translocation parameters, and influence both remodelling efficiency and outcomes[142]. Therefore, the cell type-specific compositional diversity of remodellers may exist to interact with the cell type-specific activator and repressor repertoire to regulate remodeller targeting and remodelling activities.

The hourglass model

Considering the current data, we suggest that ATP-dependent chromatin remodellers align with the following conceptual framework: first, compositional diversity, to specify both targeting and regulation; second, a unifying mechanism that involves a histone-anchored ATPase that conducts directional DNA translocation two helical turns away from the dyad; and third, functional specialization through proteins and domains that regulate how DNA translocation generates the alternative outcomes of chromatin assembly, access and editing. This framework resembles an hourglass, where the narrow neck represents the aspect of least variance among remodellers — the unifying implementation of histone-anchored DNA translocation within the nucleosome (FIG. 5).

This model also provides an intuitive path for the evolution of chromatin remodellers. An ancient protein that moved along DNA could have evolved into a DNA translocase within a chromatin remodeller by acquiring histone-anchoring capacity, which enables the propelling of DNA around nucleosomes — placing it at the narrow part of the hourglass. From there, evolution could have then shaped how the ATPase is regulated, with autoinhibition representing a particularly common mode[33,143,144]. In this case, domains that flank the ATPase domain inhibit ATPase activity or efficiency, which is reversed by particular histone epitopes or associated proteins, thereby enabling DNA translocation. Intuitively, these ATPase regulatory domains could have then co-evolved with histone modifications and variants to regulate and to specialize the enzyme — and to have co-evolved further with DNA-binding transcription activators and repressors to regulate targeting — resulting in the expansive remodeller families and remodeller functions that we have now.

Perspectives and future directions

As discussed above, many remodellers are built in a modular mode, with cell-type-specific subunits that tailor interactions with and regulation by cell-type-specific activators and repressors. Going forwards, we envision much attention being paid to how these specific interactions provide a varied targeting repertoire, and also how they enable particular remodeller outcomes at specific locations. An additional question is how certain factors promote novel remodelling activities; for example, how SWI/SNF evicts the heterochromatin protein Sir3 from nucleosomes[145]. Metazoan SWI/SNF remodellers can evict Polycomb repressive complex 1 (PRC1) and PRC2 (REF. 146), but can also function synergistically with them *in vivo* to achieve cellular states such as pluripotency[147]. Remodeller activities may be further influenced by remodeller subunits that recognize histone modifications and variants. For the SWI/SNF- and INO80 subfamily remodellers, the roles of ARPs will be

of particular interest based on their demonstrated ability to control ATPase activity, coupling, or both[35,106], as well as their known interactions with histones. For the INO80 subfamily in particular, the precise mechanistic roles of the enigmatic Rvb AAA+ ATPases and their relationship to the remodeller ATPase cycle is of great interest as they have an additional ATP-dependent activity. Although the composition of yeast ISWI and CHD subfamily remodellers is simple (Supplementary information S1 (figure)), it is much more complex in mammals, with a wide variety of associated proteins and candidate regulatory domains flanking the ATPase domain, making these remodellers ripe for future studies.

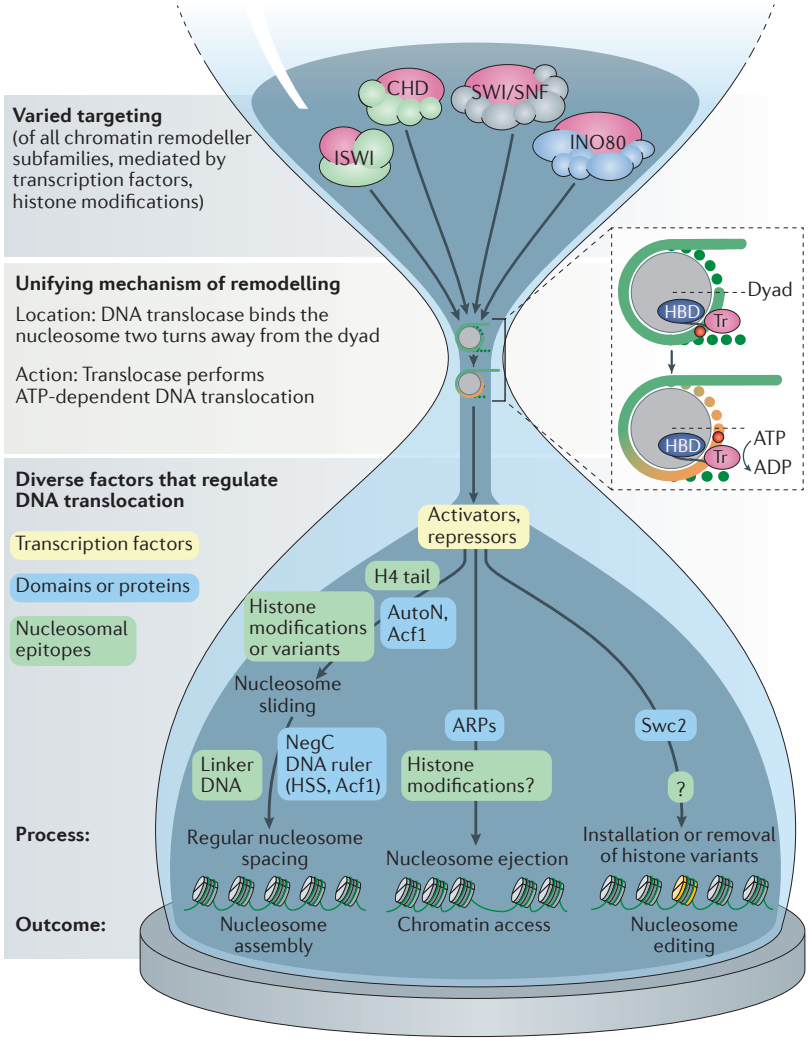

Figure 5 | **The hourglass model of chromatin remodelling.** Remodeller diversity (top) serves a variety of nucleosomal processes (bottom), but all might funnel through a unifying mechanism: an ATPase ('motor') subunit that is anchored to the histone octamer two helical turns away from the dyad that carries out DNA translocation (centre). At the top of the hourglass, the compositional diversity of remodellers enables specific interactions with particular transcription factors and/or histone modifications to specify targeting. The funnel depicts the implementation of ATP-dependent DNA translocation by the ATPase–translocase (Tr) domain from a fixed location at the nucleosome, anchored by a histone-binding domain (HBD). At the bottom of the hourglass, the various nucleosome-remodelling outcomes are depicted (assembly, access or editing), which are achieved through separate processes. Each process involves particular regulatory domains and/or proteins (blue boxes) on each remodeller, and their interactions with specific transcription factors and chromatin features, such as histone modifications, variants and linker DNA (green boxes). ARPs, actin-related proteins; AutoN, autoinhibitory N-terminal; CHD, chromodomain helicase DNA-binding; HSS, HAND–SANT–SLIDE; NegC, negative regulator of coupling.

The field will greatly benefit from high-resolution structural studies of the ATPase–translocase domain interacting with regulatory domains or proteins and the nucleosome, along with mutant versions that confer conformational changes that inform about regulatory mechanisms. The characterization of the disease-causing mutations of remodeller subunits — in particular, those mutations that cause cancer and developmental disorders — will continue to draw much effort. As a first step, it will be important to characterize remodeller assembly in the cell of origin and determine whether a mutation solely affects remodeller targeting, or remodeller activity, or both, as well as its effect on transcription and genome stability.

Additional subjects for future study include how histone chaperones cooperate with remodellers to install or evict specific histones[11,148,149], how remodellers from different subfamilies may synergize or may antagonize each other to dynamically remodel chromatin states[122,150,151], and how non-coding RNAs might influence remodeller targeting and regulation[152–155]. Furthermore, we currently understand only a portion of the mechanistic details of orphan remodellers, such as the autoinhibitory mechanism that regulates the ATPase activity of the human transcription-coupled nucleotide excision repair protein ERCC6 (REFS 143,144), and the use of histone chaperones to specify the interaction of the human α-thalassaemia/mental retardation syndrome X-linked (ATRX) remodeller with H3.3 (REFS 21,156). It will be of great interest to determine whether these orphan enzymes share similar mechanistic and regulatory principles with the four main remodeller subfamilies.

We conclude this Review by emphasizing that the genomic chromatin landscape is sculpted by remodellers that do not simply conduct a standard task once targeted, but that instead function as 'smart' machines that are informed by their nucleosome substrate and resident proteins about whether or how to remodel, through the regulation of their common ATPase–DNA translocase activity.

Note added in proof

Recent work demonstrates that octamer plasticity promotes nucleosome sliding by SNF2H[192]. A study using electron microscopy has resolved the structure of the *S. cerevisiae* chromatin remodeller Snf2 bound to a nucleosome, and confirms that the ATPase–translocase lobes bind two DNA helical turns away from the nucleosomal dyad. The study also confirms and extends our understanding of the DNA translocation mechanism and its regulation[193]. Crosslinking studies reveal that the AutoN domain of SNF2H and the basic patch of the histone H4 tail bind in close proximity on the surface of lobe 2 of SNF2H[194]. The chromatin remodeller Chd1 binds to both DNA gyres of the nucleosome[195].

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Acknowledgements
This work was supported by the Howard Hughes Medical Institute (HHMI) (C.R.C. and B.R.C.), the US National Institutes of Health (NIH) (GM60415 to B.R.C.; GM054096 and GM049650 to C.L.P.).

Competing interests statement
The authors declare no competing interests.

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