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Restraining and unleashing chromatin remodelers – structural information guides chromatin plasticity

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Chromatin remodeling enzymes are large molecular machines that guard the genome by reorganizing chromatin structure. They can reposition, space and evict nucleosomes and thus control gene expression, DNA replication and repair. Recent cryo-electron microscopy (cryo-EM) analyses have captured snapshots of various chromatin remodelers as they interact with nucleosomes. In this review, we summarize and discuss the advances made in our understanding of the regulation of chromatin remodelers, the mode of DNA translocation, as well as the influence of associated protein domains and remodeler subunits on the specific functions of chromatin remodeling complexes. The emerging structural information will help our understanding of disease mechanisms and guide our knowledge toward innovative therapeutic interventions.

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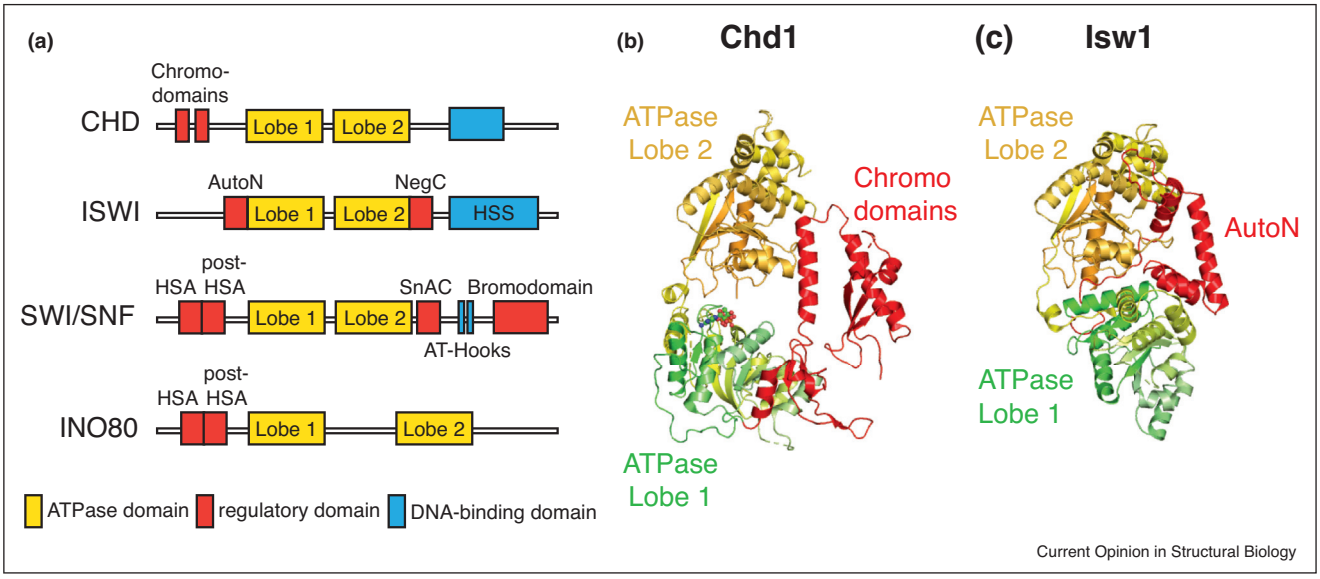
The diversity of different cell types is key to life, underpinning the ability of organisms to thrive in diverse environments. Cells also constantly adapt to endogenous and exogenous stimuli, reacting to sudden or chronic environmental changes, all while maintaining their identity [1]. To execute gene programs, cells need to alter their gene activity, which first and foremost involves accessing the DNA and regulating the structure of chromatin, the packaging of eukaryotic DNA in nucleosomes [2]. While inactive, untranscribed regions of the genome are compacted by the tight folding of nucleosomes into a densely packed chromatin structure, active regions show a more open structure [3]. Key to the transitions and dynamics in chromatin structure and gene activity are chromatin remodeling enzymes, which establish and/or reorganize chromatin structure during DNA replication, transcription and repair [4].

Chromatin remodelers contain a molecular engine that consists of two conserved RecA-like ATPase lobes, which slide DNA along the nucleosome in a mechanism powered by ATP hydrolysis [5]. Generally, these enzymes contain additional DNA-binding and regulatory domains, which vary widely in their roles and biological function and allow us to classify remodeling enzymes into four distinct classes: SWI/SNF, CHD, ISWI and INO80 family members [6] (Figure 1a). Chromatin remodelers are usually part of multi-subunit complexes, which impact their recruitment to specific genome regions and define the outcome of the nucleosome sliding reaction, resulting in the eviction or spacing of nucleosomes, or the exchange of histones [7].

Interestingly, more than 20% of cancers show changes in the function of chromatin remodeling complexes, resulting from loss-of-function point mutations, gene deletions and amplifications of remodelers and associated subunits [8–10]. Chromatin remodeling complexes have thus become novel targets for cancer therapy [11]. Because of their dynamic composition, large molecular size and complex regulation, chromatin remodelers have been inherently difficult to obtain structural information for. Detailed insights into their interaction with nucleosomes and regulatory mechanisms have thus been largely missing up to now, further challenging effective paths toward therapeutic intervention.

Yet, great progress has recently been achieved in three areas. Biochemical studies have dissected the mechanisms that regulate chromatin remodeler activity. Cryo-electron microscopy (cryo-EM) analyses have captured the interaction of various remodelers with nucleosomes, providing insight into the mechanisms of DNA translocation. Last but not least, we are beginning to decipher how mutations in remodelers contribute to or drive pathological changes in remodeler function, especially in human cancers.

Figure 1



Domain structures and auto-inhibited state of chromatin remodelers.
(a) Overview of the domain structures of the chromatin remodeler classes CHD, ISWI, SWI/SNF and INO80. Chromatin remodelers are highly conserved in their RecA-like ATPase domains (colored in yellow), while the different classes differ in their regulatory (red) and DNA-binding domains (blue). **(b),(c)** Crystal structures of the auto-inhibited states of (b) *S. cerevisiae* Chd1 (PDB: 3MWY) and (c) *M. thermophila* Isw1 (PDB: 5JXR) aligned to ATPase Lobe 2. The regulatory chromodomains (b) and AutoN motif (c) (both in red) hold the two ATPase lobes (green–yellow) apart to prevent ATP hydrolysis. Chd1 was crystallized in the presence of ATPγS, while the structure of Isw1 was obtained in the absence of ATP analogs.

In this review, we summarize advances made in understanding how remodelers engage with the chromatin substrate in a regulated manner. We explore how structural information guides our understanding of disease-causing mutations and sketch out a path that will further drive our understanding of their essential biological functions.

Abstinence and addiction – from self-inhibition in the resting state to essential oncogenes

Chromatin remodeling enzymes are powerful molecular machines capable of rapidly reorganizing chromatin structure. We now appreciate that their enzymatic activity is tightly regulated to avoid genome-wide deregulation of chromatin structure. Crystallization of remodeling enzymes and biochemical assays demonstrated that remodelers are held in self-inhibited 'resting' states when not interacting with chromatin [12•,13•,14–18]. Typically, the two ATPase lobes are positioned relative to each other in a way that holds residues critical for ATP hydrolysis apart [12•,13•,14], restraining their nucleosome remodeling activity. Moreover, regulatory domains in several remodelers fold back onto the ATPase engine, covering the DNA-binding interfaces and 'gating' the remodeler into an inactive conformation, as first described for the two globular histone-binding chromodomains of yeast Chd1 [12•] (Figure 1b). Linear motifs such as the AutoN and NegC in ISWI further contribute to a self-inhibited remodeler conformation [13•,15,16] (Figure 1c). In mammals, the nucleic acid poly-ADP-ribose (PAR) releases the globular macrodomain of ALC1/CHD1L from the ATPase motor, thus reactivating ATPase activity [17,18]. Intermolecular and intramolecular domain–domain interactions in remodelers and their complexes with allosteric ligands may thus act as a common mechanism to establish and regulate remodeler self-inhibition.

Modular allostery of this type, regulated by high-affinity ligands such as the histone H4 tail and extranucleosomal DNA in ISWI [15,16] or PAR for ALC1 [17,18], may also provide a mechanistic entry point for novel therapeutic solutions. At the genetic level, several chromatin remodelers become 'hyper-activated' and attain an essential function, including as oncogenes, when cancer cells become deficient in related remodelers. For instance, homozygous loss-of-function mutations in the SWI/SNF remodeler BRG1 occur in ~10% of non-small-cell lung cancers (as well as other tumors), rendering these tumors exquisitely dependent on the highly related remodeler BRM [19,20]. This dependency has led to efforts to target BRG1-mutant cancers using small-molecule inhibitors of BRM [21•]. The identified inhibitors bind close to the catalytic residue in a pocket within the N-terminal

ATPase lobe of BRM in direct proximity to the enzyme active site, thus blocking BRM's engagement with ATP. While reducing tumor growth in a BRG1-mutant lung-tumor xenograft, the compounds resulted in dose-limiting tolerability *in vivo* due to the high sequence similarity and thus dual inhibition of the motor domains of BRM and BRG1. This emphasizes that a more selective BRM-directed approach will be required.

Cancers can further become addicted to certain chromatin remodeling enzymes upon mutation of cellular signaling pathways. A prominent example is the dependency of PTEN-deficient prostate cancers on the helicase CHD1 [22]. While the phosphatase PTEN regulates the degradation of CHD1 under normal conditions, CHD1 is stabilized and transcriptionally activates NF-κB-signaling genes in its absence, thus promoting cancer cell proliferation and survival. Tumor cells deficient in the PTEN tumor suppressors are dependent on the function of CHD1, a so-called synthetic lethal relationship between these two gene pairs that could thus be exploited therapeutically. Considering our knowledge of the self-inhibited 'gated' structures that likely exist for all CHD family members, notably CHD1 and ALC1/CHD1L, small molecules that operate outside of the highly related catalytic motor domains may be found to disrupt this regulatory mechanism. Exploiting the modular allostery present in many chromatin remodelers may represent a tantalizing therapeutic opportunity in the development of drugs targeting chromatin remodelers outside of the conserved ATP-binding pocket in their helicase motor domains.

Chromatin remodelers caught in action during DNA translocation

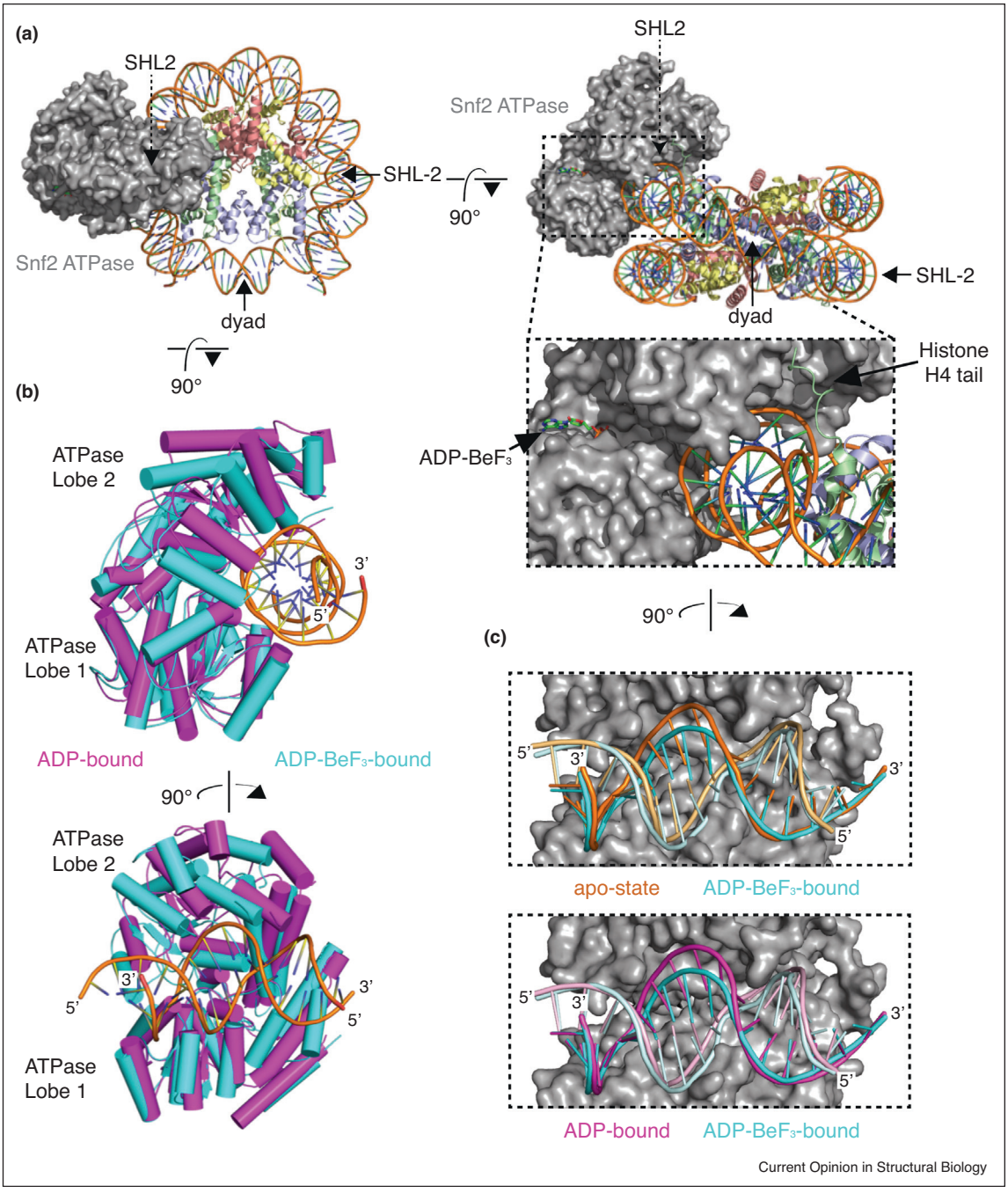
When engaged with chromatin, remodelers consume ATP to slide nucleosomes by translocating DNA, which can lead to rapid chromatin reorganization, as observed for the DNA-damage activated chromatin remodeler ALC1 [23–25]. A 'DNA wave/ twist diffusion model', in which ATP hydrolysis pushes DNA along the nucleosome in one to few base pair steps, has been suggested for DNA translocation [6,7]. However, structural information has long been missing.

Recent cryo-EM analyses of the yeast chromatin remodelers Snf2, Chd1 and Isw1 shed light on how these enzymes translocate nucleosomal DNA [26,27••,28•,29••,30•]. Upon nucleosome binding, the remodelers undergo large conformational changes. The two ATPase lobes reorient to form an interface which now allows binding to the phosphate backbone of one nucleosomal DNA gyre at superhelical location (SHL) ±2 (Figure 2a). Interestingly, the C-terminal ATPase Lobe2 has majorly been mapped to contact the 5′ strand, which has been assigned as the tracking strand for DNA translocation based on comparisons with the RNA helicase NS3 [26,29••,30•]. In contrast, the N-terminal Lobe1 seems to preferentially bind the complementary 3′ guide strand. Lobe1 additionally forms contacts at SHL ± 6 with the second DNA gyre (Snf2 and Chd1) [26,29••,30•] or the dish face of the nucleosome (Isw1) [28•], potentially anchoring the remodeler to the nucleosome during the remodeling reaction. The regulatory domains of Chd1 and Isw1 are folded away from the ATPase lobes in this conformation and contact either nucleosomal DNA (Chd1) [29••,30•] or the ATPase (Isw1) [28•], supporting the ungated remodeler conformation. In addition to DNA, the ATPase lobes grip onto the histone core and anchor the remodeler. The most conserved interaction occurs between an acidic patch on Lobe2 and the histone H4 tail, while Chd1 and Isw1 additionally engage with H3 [26,27••,28•,29••,30•]. These contacts are required for efficient chromatin remodeling, suggesting that tight histone contacts facilitate DNA translocation.

Intriguingly, the cryo-EM analyses have also captured Snf2 and Isw1 in different states — in the apo state, without the presence of nucleotides, as well as primed for catalysis, with a bound ATP analogue, or in a post-catalysis state with ADP [26,27••,28•]. The structures suggest a potential unified mechanism of translocation, which largely follows the suggested DNA wave/twist diffusion model. In the primed state, the ATPase lobes are in a closed conformation and the nucleosome in a relaxed state (PDB: 5Z3U, Figure 2b). After ATP hydrolysis, lobe2 rotates relative to lobe1, resulting in an open remodeler conformation. The rotation seems to result in a change of DNA-binding interactions of lobe2 on the tracking strand by 1 bp. The tracking strand therefore slides in from the entry site of the nucleosome and bulges at SHL2, whereas the guide strand retains its positions (Figure 2c). This results in base-pair twisting, extending all the way to the entry site. Binding of the next ATP relaxes the 1 bp DNA bulge by additional movement of the guide strand and release of the translocated DNA towards the exit site of the nucleosome, resulting in 1bp sliding for each ATP hydrolysis cycle. Interestingly, the ADP-bound state closely resembles the apo-state [26,27••], suggesting that DNA bulging is induced by the binding of the remodeler to nucleosomes, while ATP binding and hydrolysis result in full DNA translocation and generation of the next DNA bulge.

The suggested mechanism of DNA translocation is supported by biochemical observations and molecular simulations, which detect base twisting and DNA bulging along the nucleosome [31,32] and a low energy cost for this form of DNA translocation [33,34]. However, the results partially contradict the previously reported directionalities of nucleosome sliding. While Snf2 has been shown to preferentially slide nucleosomes towards the end of nucleosome arrays [35], Chd1 has been suggested

Figure 2



DNA translocation by the Snf2 ATPase.
(a) High-resolution structure of yeast Snf2 bound to the nucleosome at SHL2 in the ADP-BeF3-bound state (PDB: 5Z3U). Snf2, histones H2A, H2B, H3, H4 are colored in grey, yellow, red, blue and green, respectively. **(b)** Snf2 Lobe 2 (top) changes its orientation relative to Lobe 1 during the catalytic cycle. Lobe 1 of the ADP-BeF3-bound structure (cyan) was aligned to Lobe 1 of the ADP-bound structure (5Z3O, magenta). **(c)** The DNA tracking strand bulges at SHL2 in the apo-(5Z3O, orange) and ADP-bound states (magenta), but is relaxed in the ADP-BeF3-state (cyan). The guide strands (labelled in respective lighter colors) do not show major displacement. The entire remodeler-nucleosome complexes were aligned against each other. For clarity, only the ATPases in the apo state (top panel) and ADP-bound state (bottom panel) are shown respectively. The DNA end labelled in red corresponds to the 3′ end of the DNA.

to center nucleosomes [36]. In contrast, the almost identical cryo-EM structures of Chd1 and Snf2 suggest the same direction of DNA translocation. The directionality of DNA translocation in these structures is defined based on the superimposition with the distantly related single-stranded RNA helicase NS3 [37]. The assignment of the tracking strand is complicated due to contacts of the ATPase lobes to both strands of double-stranded DNA. In addition, the Chd1 state observed by cryo-EM has been suggested to inhibit ATPase activity [38]. Further refinements and analyses may therefore be required to obtain a comprehensive understanding of the nucleosome remodeling reaction.

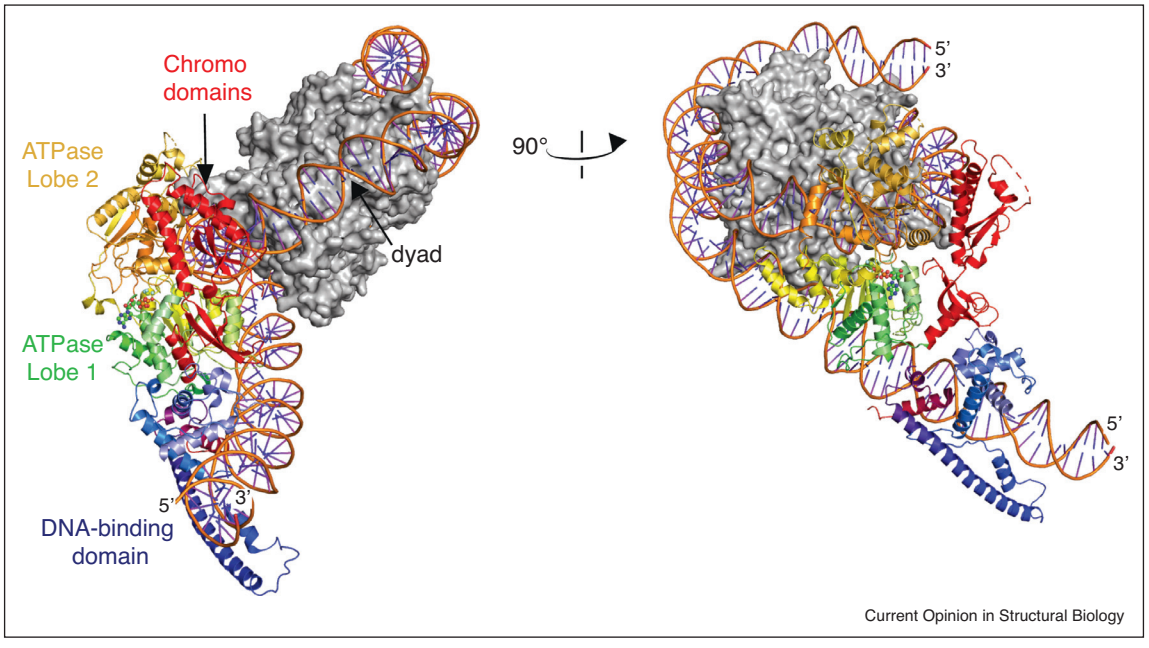
Fine-tuning remodeling through regulatory domains and subunits

While the ATPase motor of the remodelers performs the basic DNA translocation reaction, regulatory domains and associated subunits generally determine the outcome of the remodeling reaction. These domains/subunits target the remodelers to specific genomic locations and create a specific chromatin environment by nucleosome spacing, eviction or histone exchange [7]. Cryo-EM analyses of RSC [39••,40,41••], yeast SWI/SNF [42], SWR1 [43], INO80 [44,45] and the human BAF complex [46••] have significantly advanced our understanding of specific chromatin remodeling functions and their interactions with nucleosomes containing specific histone marks [30•,31,47]. Taking the CHD and SWI/SNF remodeler classes as examples, we will highlight below structural studies that shed light on chromatin plasticity.

Interactions that regulate transcriptional regulation for CHD-family remodelers

CHD family remodelers regulate transcription by repositioning and spacing nucleosomes throughout the transcription cycle [48]. Yeast Chd1 promotes transcriptional elongation through the repositioning of nucleosomes in gene bodies alongside RNA Polymerase II, while preventing cryptic transcription [49,50]. The cryo-EM structures of Chd1 in complex with the nucleosome core particle reveal that the protein detaches about two turns of DNA from the nucleosome at the exit site using its DNA-binding domain [29••,30•] (Figure 3). As the detached DNA is majorly extranucleosomal, the unwrapping of DNA may help to sense linker DNA length and space nucleosomes homogeneously. Interestingly, ubiquitination of H2B (H2BK120ub), a prominent mark in coding regions of genes that stimulates both transcription [51] and nucleosome repositioning by Chd1 *in vitro* [52], seems to distort one face of the nucleosome and may interact with the unwrapped DNA of Chd1 [30•]. It would be interesting to understand whether and how this interaction with H2BK120ub directly stimulates transcription mediated by Chd1. Conversely, DNA unwrapping is not observed in a structure of the human transcriptional

Figure 3

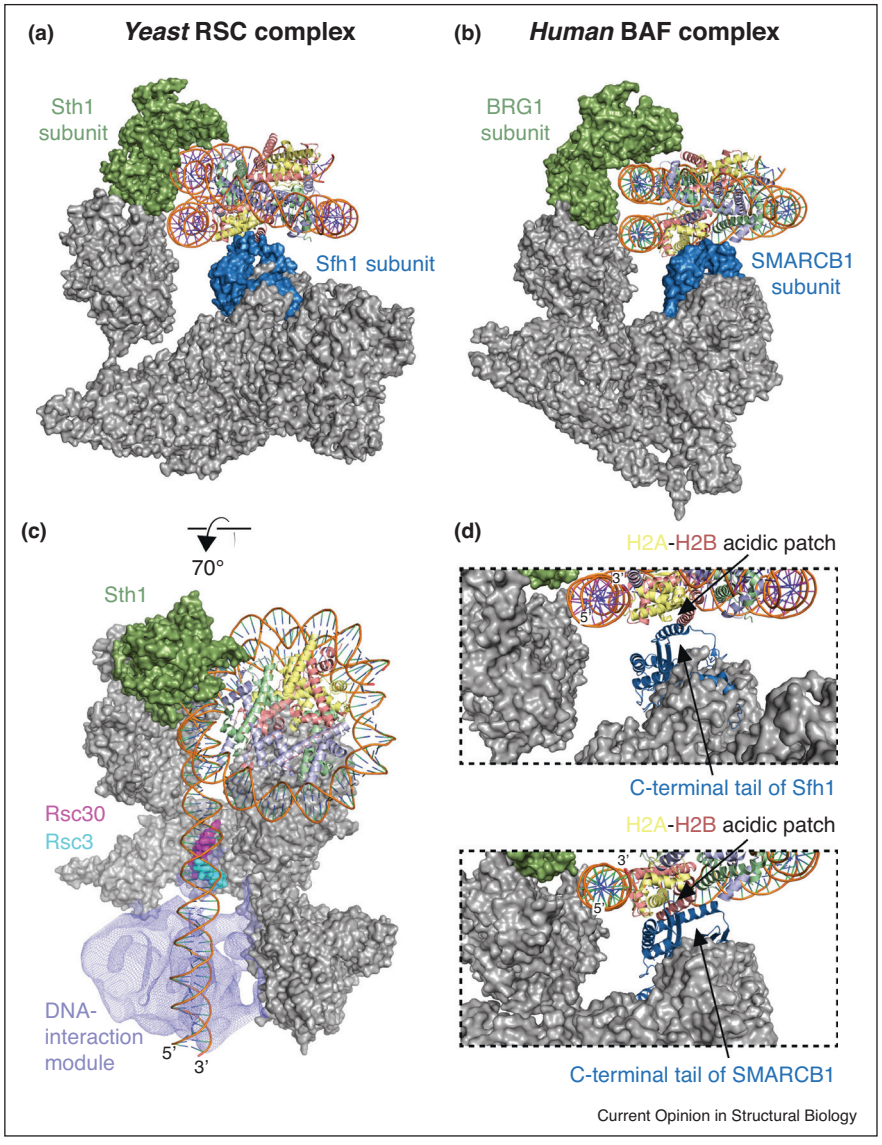


Nucleosome binding by the chromatin remodeler Chd1.
The Chd1 ATPase lobes (green and yellow) bind to SHL2, while the chromodomains (red) bind to SHL1. The DNA-binding domain (blue) engages with and distorts extranucleosomal DNA at the exit site. Lobe 2 was aligned to Lobe 2 of the auto-inhibited Chd1 structure in Figure 1b to emphasize the significant structural rearrangements the remodeler undergoes upon engagement with the nucleosome (see Figure 1). Chd1 PDB code: 5O9G. The DNA end labelled in red corresponds to the 3′ end of the DNA.

repressor CHD4, which lacks the DNA-binding domain [47]. This indicates that unwrapping could be specific to transcriptional activation. Notably, two molecules of Chd1 or CHD4 binding to a single nucleosome at both SHL2 and SHL-2 have also been captured [30•,47]. While the two molecules can bind without steric hindrance, the relevance of this observation on transcriptional regulation *in vivo* is not known and will require further analysis.

While CHD-type remodelers differ in their DNA-binding domains, the double chromodomain module is a common feature of most CHD remodelers, acting as an auto-inhibitory module as described above. The yeast Chd1 and human CHD4 structures show that the interaction of the chromodomains with the nucleosome is conserved [29••,30•,47]. The chromodomains contact nucleosomal DNA next to the ATPase lobes at SHL1.

Figure 4



Overview of the yeast and human SWI/SNF chromatin remodeling complexes.
(a),**(b)** High-resolution structures of the (a) yeast RSC complex (PDB: 6TDA) and (b) the human BAF complex (PDB: 6LTJ). The complexes were aligned using a nucleosome structure (PDB: 3AFA) as the target object. The ATPase modules are colored in green. Histones H2A, H2B, H3, H4 are marked in yellow, red, blue and green, respectively. The acidic patch targeting domains Sfh1 and SMARCB1 of RSC and BAF are shown in blue. **(c)** Overlap of the RSC cryo-EM structure with its electron density map shows an unassigned density (blue mesh, contoured at 3.5 sigma) that might correspond to the DNA interaction module containing Rsc3 and Rsc30. The DNA binding subunits Rsc3 and Rsc30 were not modelled, as only short fragments could be identified (see PDB: 6KW4; cyan: RSC3, magenta: RSC30). **(d)** Zoom-In onto the interactions of Sfh1 (RSC complex, top) and SMARCB1 (BAF complex, bottom) with the H2A–H2B acidic patch. The DNA end-labelled in red corresponds to the 3′ end of the DNA.

Interestingly, mutations in the DNA binding interfaces of the chromodomains are prominent in endometrial cancer and disrupt the ATPase and chromatin remodeling activities of the *Drosophila* CHD4 homolog Mi-2 [53•]. This highlights that the chromodomains not only act as an auto-inhibitory module, but further promote efficient remodeling of CHD-type remodelers through additional DNA contacts. It will be exciting to find out how cancer mutants in the chromodomains of distinct CHD remodelers affect transcription and other cellular processes.

The nucleosome acidic patch and SWI/SNF-type remodelers

SWI/SNF-type chromatin remodeling complexes are major regulators of gene transcription [54]. The yeast RSC and SWI/SNF complexes control the chromatin state at promoters by sliding or evicting the +1 and −1 nucleosomes, with RSC being ~10-fold more abundant than SWI/SNF [55,56]. Several cryo-EM structures of RSC and one structure of SWI/SNF have been solved recently [39••,40,41••,42], demonstrating the high similarity of the two complexes. The motor subunits Sth1 (RSC) and Snf2 (SWI/SNF) bind the nucleosome at SHL2 in the same manner as the isolated Snf2 ATPase module. Additionally, a DNA-interaction module possibly containing the RSC subunits Rsc3 and Rsc30 protects 20–40 bp of DNA at the exit site [39••,41••] (Figure 4a,c). Acting on the +1 nucleosome, DNA translocation would thus render promotor DNA more accessible and RSC could protect the generated nucleosome-free region through the action of Rsc3 and Rsc30. It would be interesting to investigate the effects of Rsc3 and Rsc30 on chromatin remodeling and transcription regulation in further detail and to find out whether the related SWI/SNF remodeler contains subunits with a similar mode of action. In fact, the presence of extranucleosomal DNA seems to be integral for SWI/SNF binding to the nucleosome, as the researchers did not obtain stable complexes when using only a nucleosome core particle [42].

In addition to the observed DNA interactions, the SWI/SNF complexes further seem to anchor the nucleosome by recognizing the H2A–H2B acidic patch through a highly conserved C-terminal helix of Sfh1/Snf5 on one side of the nucleosome [39••,41••,42] (Figure 4a,d). This interaction of Sfh1 does not seem to be required for efficient nucleosome sliding by RSC, but rather mediates nucleosome eviction [39••].

Intriguingly, the cryo-EM structure of the human BAF complex, the homolog of the yeast SWI/SNF complex, shows that the C-terminus of the human homolog of Sfh1/Snf5, SMARCB1, also binds the H2A–H2B acidic patch and that the remodeling complex sandwiches the nucleosome through this interaction [46••] (Figure 4b,d). The C-terminal α-helix of SMARCB1 is highly conserved and frequently mutated in rhabdoid tumors and intellectual disability syndromes [8,57]. A study investigating recurrent mutations of the intellectual disability syndrome Coffrin-Siris Syndrome lying in the C-terminus of SMARCB1 showed that the interaction with the nucleosome is lost when SMARCB1 is mutated [58•]. Genome-wide, the loss of this H2A–H2B acidic patch interaction results in reduced enhancer DNA accessibility and increased nucleosome occupancy, while the targeting of SWI/SNF complexes is unaffected. Further, in a cell model for neuronal differentiation, these disease mutations lead to developmental defects. This highlights the relevance of SMARCB1's function on intact SWI/SNF remodeling and nucleosome eviction. In addition to SMARCB1, almost all subunits of the SWI/SNF complexes are mutated in cancer [8]. With the high-resolution structure of the human BAF complex at hand, it will now be truly exciting to investigate how cancer mutations disrupt the function of these large multi-subunit remodeling complexes and seek to deduce disease mechanisms.

Concluding remarks

Chromatin remodeling complexes achieve highly dynamic, specific and diverse cellular functions, ranging from nucleosome repositioning, spacing and histone exchange. Structural studies of the ATPase polypeptide in the remodelers show the enzymes in self-inhibited, resting states. The basic mechanism of DNA translocation seems to be conserved across different remodeler classes and species, although the exact engagement of remodelers with nucleosomal DNA and histones diverges and the outcome of the remodeling reactions differs. Cryo-EM analyses of remodeling complexes provide new insights in remodeler function at the mechanistic level and helps rationalize how mutations impact remodeling activity. The future promises to further drive our understanding of chromatin plasticity at the structural level, particularly in the context of how chromatin modifications impinge on remodeler activity and by extending structural analyses from mono-nucleosomes to larger chromatin arrays, the physiological template on which chromatin remodelers unleash their power. Finally, additional structures of human remodelers will help to guide our insights into cancer-causing mechanisms and provide a structural basis for targeted inhibitor design toward novel cancer therapies.

Conflict of interest statement

Andreas Ladurner is co-founder and Chief Scientific Officer of Eisbach Bio GmbH.

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