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REVIEW

Chromatin remodelers: a concise introduction for biophysicists

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Abstract
Chromatin remodelers are molecular motors that act on nucleosomes: they move them along DNA or (dis-)assemble them. Despite the fact that they perform essential regulatory functions in cells—their deregulation can contribute to the development of cancers and lead to cell death—chromatin remodelers have only received meager attention in the biophysics community so far. In this short text, we attempt to present the key features of this interesting class of enzymes obtained with different experimental and theoretical methods, thereby providing a concise introduction for biophysicists to further stimulate interest in their properties.

Keywords Chromatin remodelers · Nucleosomes · Enzyme · Molecular motor

What are chromatin remodelers?

In order to introduce the concept of active chromatin remodelers to readers who have so far not taken notice of this class of enzymes/molecular motors, we have chosen a format similar to the nowadays ubiquitous FAQ pages in this short review: we hence group our material in a series of questions and answers. We begin with the simplest question.

The notion of *chromatin remodeling* describes an only vaguely defined concept. It is often employed in a very general sense as encompassing all processes that alter the structure of the chromatin fiber in the nucleus of a eukaryotic cell from a not entirely well-defined initial state to a final state. From a biophysical perspective, this notion can therefore be taken as a synonym for the part of chromatin fiber dynamics that involves the interaction of molecular partners with chromatin.

The notion of *chromatin remodelers* (in the following abbreviated by CRs) therefore encompasses in principle all molecules that interact with chromatin in this sense. There is, however, a distinct class of CRs that comprises molecular motors/enzymes that act upon nucleosomes under consumption of ATP. These active CRs (aCRs) are the subject of this review. Since we do not deal with other than active remodeling processes here, we drop the notion "active" from now on and also only use the abbreviation "CR' for these enzymes.

Although molecular motors became a topic of special interest in the biophysics/statistical physics community already some time ago, CRs have only gained a very limited attention in the biophysics community so far: most attention in the biophysics of chromatin has been paid to the nucleosome itself. We here try to help equilibrate the situation a little bit. Our ambition in the following is to summarize the key features of the structural and functional, i.e., biophysical, properties of active chromatin remodelers to help raise interest in this class of enzymes/molecular motors.

What is the molecular build-up of chromatin remodelers?

Chromatin remodelers are molecular motors whose motor domains derive from helicases. While helicases open up double-stranded DNA, CRs have evolved to remove the double-stranded DNA from the histone octamer, the central protein building block of nucleosomes. Apart from the motor domains that are common to all known variants of CRs, their main distinguishing feature is *accessory domains*,

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which lead to a sequence- or domain-based classification of CR "families." The current consensus on this classification is shown in Fig. 1, based on Clapier and Cairns (2009).

In this figure, the four families are listed with the acronyms that denominate them. These acronyms are historical and, e.g., refer to specific biological systems in which the corresponding remodeler has been first described; nowadays, the full names are usually not used explicitly in practice. Of key functional relevance in the domain composition are the motor domains (cores), which are conserved across the families, and are shown as dark blue blocks in the figure. The accessory domains are indicated by different colors (see the figure caption). These domains either interact with histone tails (bromo- and chromodomains), with DNA (SANT and SLIDE) or nuclear actin molecules (HSA). Bromo- and chromodomains recognize chemically modified histone tail residues: bromodomains are specific for acetylated histone tails, while chromodomains are specific for methyl groups present on the amino acids of the histone tails.

How do active chromatin remodelers engage with nucleosomes?

Knowing the sequence and domain composition of active CRs is one thing, yet another is the knowledge of the three-dimensional organization of the engagement of CRs with the nucleosome. Chromatin remodelers can be very large multiprotein complexes, see "What are the main physical characteristics of chromatin remodelers?." It is thus useful for the present purpose to restrain ourselves to only the engagement of the motor domains with the nucleosome. Figure 2 shows this for an exemplary case (Chittori et al. 2019).

From this figure, it can be clearly seen that while core 1 engages tightly with the upper gyre of the wrapped DNA, core 2 is placed more in between the two gyres. The resulting dynamics of the motor action is sketched in the third subfigure, which shows how the two cores are ratcheting on the nucleosomal DNA (left graph) (Blossey and Schiessel 2019). This action is translated into the progression of the two footprints $\mathbf{x_1}$ and $\mathbf{x_2}$ of the remodeler cores along DNA in the right graph, for three timesteps, t_0, t_1, and t_2. The notion "footprint" here refers to the contact area of the remodeler along the nucleosomal DNA, as can be seen in the middle figure of Fig. 2. In the dynamic action of the remodeler in displacing nucleosomes in order to facilitate nucleosome sliding, the motors first pull the DNA into the nucleosome($t_0 \rightarrow t_1$), while in the subsequent step, the added nucleosomal DNA has progressed around the histone core and is expelled from the nucleosome($t_1 \rightarrow t_2$).

What are the main physical characteristics of chromatin remodelers?

In 2014, Lavelle (2014) published a very nice paper collecting various biophysical quantities relevant for gene regulation. Chromatin remodelers do appear, if only as an extra. Already before the Lavelle paper, Cairns (2007) had collected the then available data from single-molecule experiments on chromatin remodelers. Since these experiments are very difficult, they have now been mostly superseded by FRET experiments, which provide interesting insights into the structural dynamics of the remodeling process but provide less direct physical information.

The first characteristic is the size or mass of the remodelers. ISWI, INO80, and Chd1 range from 1000, 1500, to 1700 amino acids. With an amino acid on average having a mass of 150 Da (or atomic mass units $u = 1.66 \times 10^{-27}$ kg), they range between 150 and 255 kDa. The remodeling complex RSC is considerably bigger, being composed of multiple subunits that have at least about 500 amino acids, hence 75 kDa.

The second characteristic is remodeling speed. In magnetic tweezer assays, an RSC complex has been observed to move at about 200 bp/s under conditions of a low tension imposed on the substrate (DNA) of 0.3 pN. At higher tensions, the remodeling speed slows down, until in optical tweezers the stalling

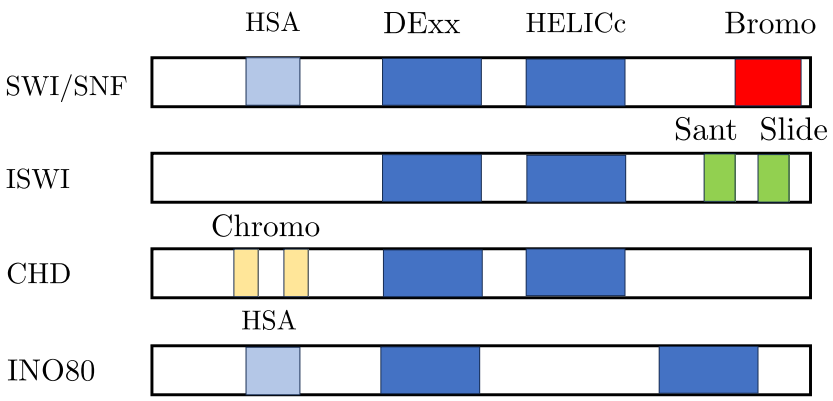

Fig. 1 Schematics of the four remodeler families as defined by domain composition. All remodelers contain two ATPase domains (DExx, HELICc), shown in dark blue, and accessory domains of regulatory purposes: the bromodomain (red), chromodomain (yellow), SANT-SLIDE domains (green), and the actin-binding domain HSA (light blue). Redrawn after Clapier and Cairns (2009)

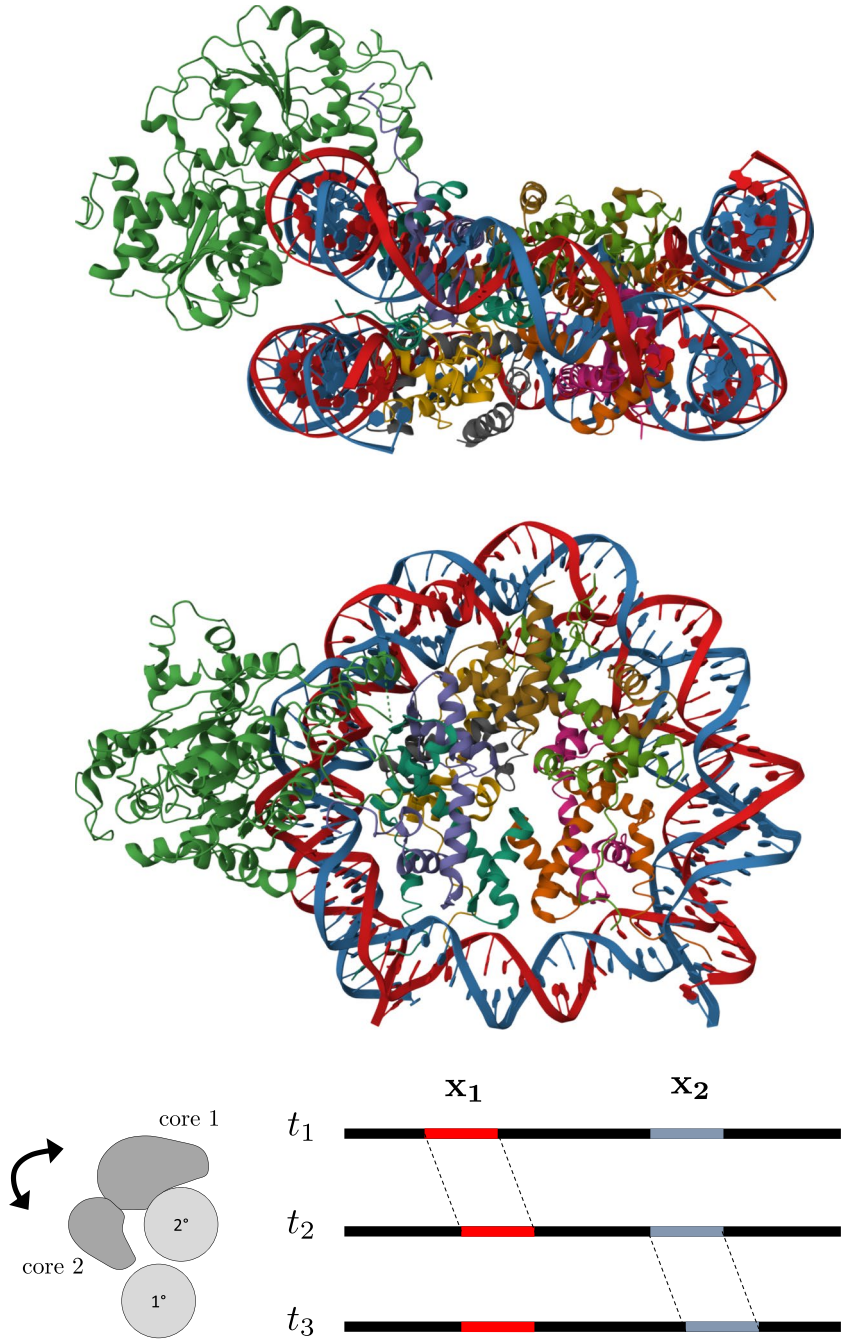

Fig. 2 Cryo-EM structure of the ISWI-ATPase-nucleosome complex discussed in Chittori et al. (2019). Taken from the PDB, entry 6PFW. The top image shows the side view, in which the two domains, or cores, are clearly discernable. The middle image shows the top view of the nucleosome-remodeler complex. The bottom image illustrates the mapping of the remodeler action on the nucleosome to the molecular motor model of a Brownian dimer. $\mathbf{x_1}$ (red) and $\mathbf{x_2}$ (blue) are the footprints of the remodeler cores on the DNA. This figure is redrawn after (Blossey and Schiessel 2019)

force of 12 pN is reached. The processivity of the remodeler, i.e., how many base pairs it advances during one continuous remodeling action, is fairly low, lying at around 20 bp.

How are chromatin remodelers recruited to nucleosomes?

A key question in the understanding of chromatin remodelers is how they can find their nucleosomal target for remodeling. In principle, this could be just the result of a random selection assuming that their action was fairly unspecific—a choice in fact sometimes made by biophysicists (Padinhateeri and Marko 2011). However, what stands against this idea is the presence of the histone tails on nucleosomes, and their multiple possible tail modifications, often summarized under the notion of the "histone code" (Strahl and Allis 2000). Otherwise, why would remodelers have accessory domains that are indeed specific to histone tails, and to specific modifications at that?

This key feature of CR structure has been built into a kinetic proofreading scheme for chromatin remodeling

(Blossey and Schiessel 2008). The idea for kinetic proofreading goes back to the 1970s and was developed originally to explain the specificity of mRNA translation; it meanwhile has found numerous other applications (Boeger 2022). In the kinetic proofreading scenario by Blossey and Schiessel, the binding of remodelers to nucleosomes is determined by the combination of the binding of the motor domains to the two gyres of the DNA in combination with the "proper" histone tail state of the nucleosome, i.e., the presence or absence of chemical modifications on the histone tails. The presence of the proper state dictates whether this binding is successful: this is the transition of the state *TN*, the binding to the nucleosome-transcription factor complex, towards the state *I*; if the remodeler has found the "correct" substrate, it will proceed to state I^*; otherwise, it will disengage again (return to state *N*). This remodeler-recruitment picture is rendered more complex due to the presence of the pioneer transcription factor *T* that can help the binding of the remodeler by adding further specificity to the interaction as well as combinatorial complexity. This is expressed in the two different scenarios of Fig. 3. In Fig. 3i, the bound transcription factor helps in the recruitment of the remodeler, but then unbinds from the complex, while in Fig. 3ii, it stays bound during remodeler action. Figure 3 is taken from Schiessel and Blossey (2020), which has been the latest update on the original scenario by the authors from 2008.

What is known about the sequence dependence of chromatin remodelers?

The kinetic proofreading scenario sketched above does not contain any direct specific sequence dependence; this is certainly an oversimplification of reality. Where then does the sequence play a role?

Chromatin remodelers do not have a direct sequence dependence by themselves: their domains can be specific for DNA, as obviously are the ATPase domains, and like the SANT/SLIDE domains, but not for specific target sequences. Since nucleosomes have base pair sequence preferences for their positioning (Schiessel 2023), it is expected that the remodeler-nucleosome complex shows a sequence dependence itself. However, it is not immediately clear whether active repositioning helps nucleosomes to equilibrate in the passive landscape or whether it rather leads to different sequence preferences altogether. The question of where the sequence dependence lies in chromatin remodeling is actually a complex topic.

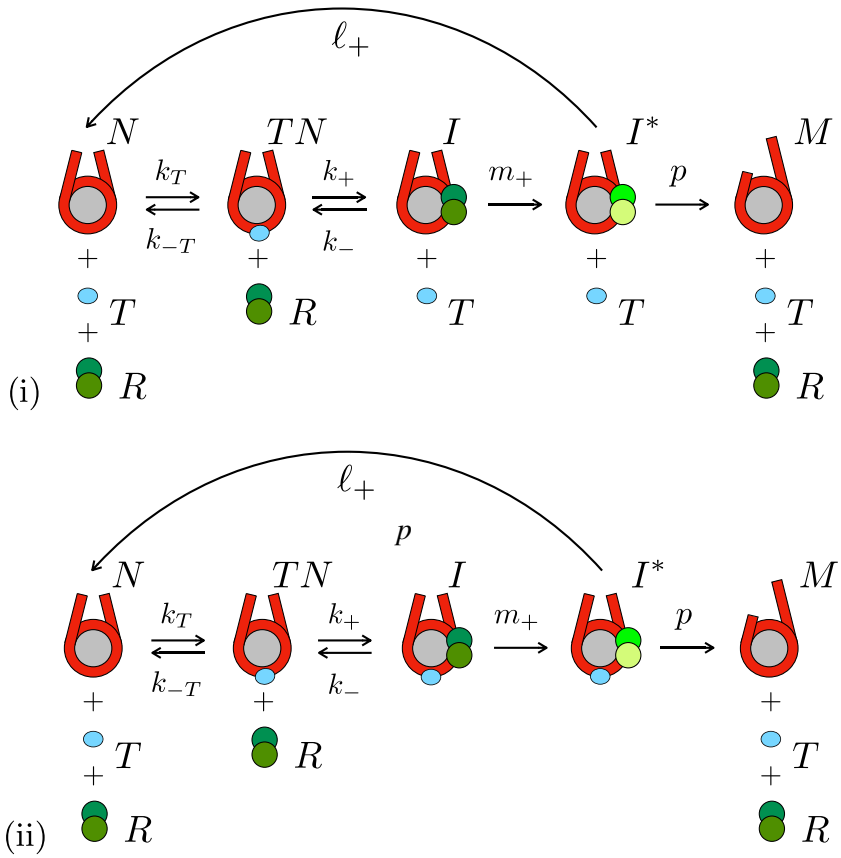

Fig. 3 Kinetic proofreading scenarios **i** and **ii** of chromatin remodeling in its latest version. *N* denotes the nucleosome; *T* is a pioneer transcription factor; *R* is the remodeler; *I* and I^* are remodeler-nucleosome complexes; and *M* is the mobile nucleosome. For the interpretation, see the main text. Reprinted with permission from the American Physical Society (Schiessel and Blossey 2020)

A clear experimental demonstration of sequence-dependent chromatin remodeling has been provided by work on chromatin remodeler Chd1 (Winger and Bowman 2017). Chd1 was originally shown to move a nucleosome positioned asymmetrically on a short DNA template toward the center, i.e., that Chd1 has the tendency to push the nucleosome in the direction of the longer free DNA section (Stockdale et al. 2006; McKnight et al. 2011). That also the involved base pair sequence can affect the outcome of remodeling became apparent when using a symmetric template where the nucleosome was positioned in the middle, surrounded by two free DNA sections of the same length (Winger and Bowman 2017). Despite the symmetry, Chd1 tended to shift the nucleosome always in the same direction. What could be the underlying reason?

Remarkably, the nucleosome positioning sequence 601 used in this experiment is known to behave highly asymmetric even in the absence of remodelers or other active processes. For instance, nucleosomes show thermally induced spontaneous unwrapping from both ends of the wrapped DNA, but for the 601 nucleosome, it has been observed that this unwrapping occurs much more frequently from one end than the other (Anderson and Widom 2000; Mauney et al. 2018). It was also found that the 601 nucleosome preferentially unwinds at one of its ends when exposed to an external force (Ngo et al. 2015). These observations have been explained by the highly asymmetric nature of the mechanical properties of the two halves of the 601 base pair sequence (Culkin et al. 2017; van Deelen et al. 2020; de Bruin et al. 2016).

The experiments with Chd1 acting on the 601 nucleosome indicate that the asymmetry of the physical properties of the 601 DNA leads also to an asymmetric activity of the Chd1 remodeler. Especially, the sequences around superhelical positions ±2 (defined as two DNA superhelical turns away from the dyad, the center of the wrapped DNA portion) appear to be important (Winger and Bowman 2017), as they are known to be the possible places where the remodeler can bind and induce a local deformation on the DNA which in turn leads to a one base pair repositioning step of the whole nucleosome. Obviously, as the nucleosome is shifted to new positions, also, the sequences around ±2 change, which complicates interpreting the outcome of sequence-dependent nucleosome remodeling action.

To create a well-defined array of nucleosomes might even require the sequential action of a whole set of remodelers. An example is a study that demonstrated that the in vivo nucleosome arrangement around promoters can be achieved in a minimal reconstituted system by the sequential action of various remodelers (Krietenstein et al. 2016). At least some of these remodelers might be guided by mechanical cues of the underlying base pair sequences, and different remodelers might respond to these cues in different ways.

The complex interplay of array-forming CRs like ISWI, Chd1, and INO80 has recently been investigated in very detailed experiments, e.g., by Oberbeckmann et al. (2021) on INO80.

What models for chromatin remodeling have been discussed in the biophysics modeling literature so far?

As mentioned at the beginning of the review, so far, chromatin remodelers have received only modest interest in the biophysics community. We refer here to two types of problems that were addressed by modeling—without claiming completeness in such a short text. The first type concerns the effect of remodelers on the positioning of single nucleosomes on DNA, the second the positioning of multiple nucleosomes.

The solution to the first problem, the positioning of single nucleosomes, has benefitted decisively from single-molecule FRET-based techniques which allow to determine the position of a nucleosome relative to a DNA sequence (Racki et al. 2009). The corresponding data for the position of a 601 nucleosome have been re-analyzed from the experiments within statistical physics-based molecular motor models: firstly, on the basis of a master equation approach (Vandecan and Blossey 2012) and, subsequently, with the help of the Fokker-Planck equation (Vandecan and Blossey 2013). Experiments and models are based on the variant ACF of the ISWI remodeler, which acts as a dimer and whose function is to centrally position the nucleosome on the DNA with the help of the SANT/SLIDE domains. The synchronization of the two motors in the dimer in pulling the nucleosome in opposite directions is one of the key features addressed in the theoretical models. This coordination between motor units bears some similarity to the action of the two ATPases of a single motor as shown in Fig. 2. Figure 2 (bottom right) depicts the mapping of the two units on the motion of a Brownian dimer along the DNA; see the discussion in "How do active chromatin remodelers engage with nucleosomes?" (Blossey and Schiessel 2019). A much more detailed model derived from molecular dynamics simulations has been developed in Brandani and Takada (2018).

This basic capacity to centrally position a nucleosome has been exploited in a kinetic MC study of a nucleosomal array (Florescu et al. 2012) that demonstrated that the coordinated positioning of nucleosomes leads to a much more precisely defined nucleosomal array than the fundamental statistical positioning effect originally described in Kornberg and Stryer (1988). Differences between ISWI and ACF were addressed in Schram et al. (2015). Earlier work on nucleosomal positioning in arrays by Padinhateeri and Marko (2011) had not included a specific positioning

mechanism. As the experiments on INO80 in Oberbeckmann et al. (2021) clearly show, more detailed models would be required to cover details down to the sequence level. Such attempts have so far not been undertaken and would thus be of enormous interest.

Conclusions

In this short review, we have highlighted the key features of active chromatin remodelers, enzyme/molecular motors that play distinctive roles in the organization of nucleosomes along the chromatin fiber. We identified such properties: the different enzyme families, as defined by the accessory domains that interact with histone tails; the molecular composition (size) of the CRs; the forces they exert as well as the speed of remodeling. The recruitment of remodelers to nucleosomes can be captured by kinetic proofreading scenarios in which equilibrium recognition steps to DNA and histone tails, the involvement of DNA sequence-dependent transcription factors ("pioneer transcription factors") conspire with the irreversible process of ATP consumption by the CR motor domains. The role of DNA in the remodeling actions itself, missing from the kinetic proofreading model, is currently being elucidated in advanced in vitro experiments and will likely yield a more profound understanding. And it can be expected that further surprises lie along the road: there are, e.g., recent data on the tentative involvement of histone tails and their epigenetic states on the positioning of nucleosomes even without remodeler involvement (Nikitina et al. 2023).

Readers whom we have been able to motivate to dive much deeper into this exciting field and who are, in particular, interested in learning considerably more about the structure-function properties of chromatin remodelers are recommended to have a look at the very recent review by Eustermann et al. (2023).

Author contribution Sophie Klempahn, Helmut Schiessel, and Ralf Blossey contributed equally to the manuscript.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Ethical approval This article does not contain any studies associated with animals or with human participants.

Consent for publication The authors have received consent to publish.

Conflict of interest The authors declare no competing interests.

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