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The Latest Twists in Chromatin Remodeling

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ABSTRACT In its most restrictive interpretation, the notion of chromatin remodeling refers to the action of chromatin-remodeling enzymes on nucleosomes with the aim of displacing and removing them from the chromatin fiber (the effective polymer formed by a DNA molecule and proteins). This local modification of the fiber structure can have consequences for the initiation and repression of the transcription process, and when the remodeling process spreads along the fiber, it also results in long-range effects essential for fiber condensation. There are three regulatory levels of relevance that can be distinguished for this process: the intrinsic sequence preference of the histone octamer, which rules the positioning of the nucleosome along the DNA, notably in relation to the genetic information coded in DNA; the recognition or selection of nucleosomal substrates by remodeling complexes; and, finally, the motor action on the nucleosome exerted by the chromatin remodeler. Recent work has been able to provide crucial insights at each of these three levels that add new twists to this exciting and unfinished story, which we highlight in this perspective.

The nucleosome, the basic structural unit of the chromatin fiber, remains a key subject of interest for chromatin biologists and physicists. A key basic insight of recent years was the (indirect) sequence dependence of its positioning along DNA (1). It had been noticed already, much earlier, that the nucleosome structure is a flexible, dynamic structure with an intrinsic, thermally driven mobility (2). In the context of many chromatin-related processes, the nucleosome needs to be actively displaced or removed. The molecular machines that organize this process are called chromatin remodelers (3), commonly grouped into four distinct families (see Fig. 1) (4,5). Chromatin remodelers also are increasingly understood as key factors in the development of diseases due to their deregulation of gene expression, such as in cancer (see, e.g., (6)). The definition of chromatin remodeler families relies on the basic motor unit, the ATPase, which derives from helicases, and the positioning of additional regulatory subunits around the ATPase.

How can we picture a chromatin remodeler working on a nucleosome? Being researchers in the low countries (the Netherlands and French Flanders), we allow ourselves to resort to an analogy drawn from a favorite transportation means in our regions, the bicycle. Man-powered bikes may still be the most frequently used type of bikes, but additional power is built in in the ever more popular eBikes. For those who want to have the best of both worlds, there are the "clip-on" motors: if one wants to go faster, one fixes a small add-on motor to power the bike. An example is shown in Fig. 2.

Chromatin remodelers, within this analogy, are nothing but motors that can be "clipped on" to nucleosomes. However, they do not propel the nucleosome in a linear fashion, as many molecular motors do that simply transport cargo. Chromatin remodeling motors displace the DNA wrapped around the histone octamer, and this obviously is a much more complex task than linear transport. Our simplistic analogy, however, also makes us ask simple questions, such as, "where are these motors actually fixed on the nucleosome?" "How do they pull on the DNA?" "How is the DNA transported around the nucleosome?" Recent research has given at least partial answers to these basic questions.

Before turning to the topic of the motor action, we will address the two additional levels of chromatin regulation concerning the nucleosome mentioned in the Abstract. The first and most fundamental one is the positioning of the nucleosome along the fiber, which is dictated in a complex way by the DNA sequence—or, rather, by the physical properties associated with the stacking of the basepairs. The second level is the problem of how the machinery recognizes the right nucleosome at the right time. Some time ago, we postulated a "kinetic proofreading" scenario for this process, for which some experimental justification became available shortly afterward. New high-throughput data that have been published only very recently lend

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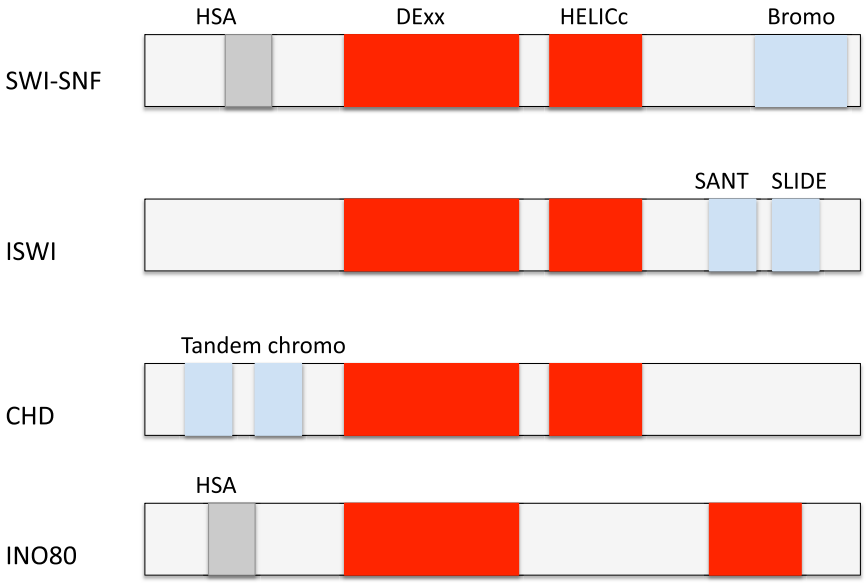

FIGURE 1 Definition of the remodeler families according to (4). DExx and HELICc (*red online*) are ATPase domains; *Bromo*, SANT and SLIDE, and *Tandem chromo* (*blue online*) are accessory domains that recognize specific histone-tail modifications, or DNA. Adapted from (4). To see this figure in color, go online.

experimental support to our idea. Finally, regarding level three, recent progress in the understanding of the action of remodeling motors has become available through new experimental techniques that allow tracing of the dynamics of the remodeler-nucleosome complexes, which we highlight as we discuss some new results. Key in this field have been the substantial advances in cryo-electron microscopy (cryo-EM), freshly honored with the Nobel prize in Chemistry in 2017 for the pioneers of this technique. In the following sections, we step through recent insights regarding these three levels.

FIGURE 2 Top: a "clip-on" motor that turns a bike into an eBike; the bottom figure shows how the motor is fixed on the bike. The photo is courtesy of add-e, an Austrian ebike company (https://wwww.add-e.at/de/). To see this figure in color, go online.

Nucleosome positioning

In a nucleosome, about one persistence length of DNA is wrapped one and three quarter turns around an octamer of histone proteins, which amounts to a substantial amount of bending energy ($\sim$60 k_BT (7)). On the other hand, the elasticity and geometry of the DNA double helix depends on the underlying sequence of basepairs (8,9). It is thus to be expected that the affinity of a given stretch of DNA to be complexed in a nucleosome varies strongly with sequence. Moreover, the binding of the DNA to the octamer occurs mainly at 14 patches where the minor groove of the DNA touches the surface of the octamer (10). As the sugar-phosphate backbones do not change with the underlying basepair sequence, the pure binding energy (mainly based on charge-charge interactions between the DNA phosphates and histones (11)) is expected to be only weakly sequence dependent. Taken together, these observations suggest that the nucleosome performs an indirect readout of the basepair sequence, with the affinity reflecting the overall ability of 147 basepairs to wrap around the octamer.

Nucleosomes indeed show characteristic sequence preferences (1,12), e.g., high-affinity sequences feature an increased occurrence of GC dinucleotides (a G followed by a C) at locations where the minor groove faces outward, whereas AA, TT, and TA dinucleotides peak in between, where the minor groove faces inward toward the histone octamer (i.e., at the binding sites) (see Fig. 3 *a*). These preferences have been proposed to constitute a "genomic code

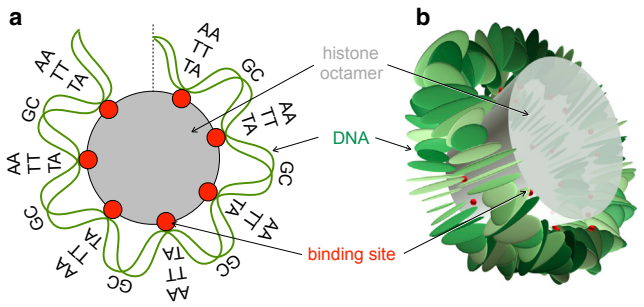

FIGURE 3 (*a*) Nucleosome positioning rules (1): key dinucleotides are shown relative to one-half of the symmetric nucleosome. (*b*) A coarse-grained computational model of the nucleosome as employed in (18)–(20). To see this figure in color, go online.

for nucleosome positioning" (1) (for earlier versions of this idea, see, e.g., (12,13)). In fact, the sequence preferences of the nucleosome give rise to two types of positional preferences: rotational and translational positioning. Rotational positioning results from the fact that DNA is attached at its minor groove to the octamer. Therefore, when a nucleosome is repositioned 1 bp step at a time, the DNA needs to perform a corkscrew-like motion. As a given wrapped stretch of DNA has typically a preferred bending direction (even for a completely random basepair sequence), there is a minimum in the bending energy every 10 bp, causing the rotational positioning of the nucleosome. The second type of preference, translational positioning, reflects an overall preference of nucleosomes to sit on DNA stretches with high GC content and to avoid certain motifs, such as poly(dA:dT) tracts.

Nucleosomes have been mapped genome-wide in vivo and in vitro (in the latter case, nucleosomes are reconstituted on DNA from their pure components) using a variety of methods, e.g., digestion by nuclease (1) or a chemical cleavage technique (14). Such nucleosome maps have taught us that indeed non-random mechanical cues can be found written along genomes. This becomes especially clear by focusing on particular locations, e.g., transcription start sites (TSSs), and then averaging over all such locations (e.g., over the TSSs of all genes of an organism). Such studies have revealed that yeast shows on average a depletion of nucleosomes just in front of genes (1,14). But does this depletion reflect nucleosome sequence preferences or is it caused by other mechanisms, e.g., the action of chromatin remodelers (15)? In general, this is a complex question and the answer clearly depends on the organism at hand.

To answer this question, it is necessary to develop methods that allow estimation of nucleosome sequence preferences along DNA molecules. Bioinformatics models trained on experimental nucleosome maps provide a common approach (1). Deeper insight into the relation between DNA mechanics and nucleosome positioning can be gained from coarse-grained computer models of nucleosomes that give fairly reliable estimates of sequence preferences (16–18) (see, e.g., Fig. 3 *b*). These models, however, typically tend to be too slow to perform, e.g., genome-wide averages of the DNA mechanics around TSSs. The recently developed mutation Monte Carlo method (18) overcomes this problem as it allows determination of the sequence preferences of a given model nucleosome that in turn can be used to build probabilistic models (19,20). Such models are similar to the above-mentioned bioinformatics approaches but ultimately are based on specific microscopic models with well-known ingredients. Starting from an already fairly efficient coarse-grained nucleosome model, this approach leads to an $\sim 10^5$-fold speedup of performance (19). When we applied this technique to TSSs of yeast (21), we found excellent agreement with experimental data. As the approach is based on a purely mechanical model, this suggests that nucleosome depletion at TSSs in yeast is indeed caused by sequence-dependent DNA mechanics.

An exciting question to ask is to what extent genomes position nucleosomes. This turns out to be a tricky question. For instance, in (1), it was claimed that ~50% of the nucleosomes on the yeast genomes can be "explained solely by sequence preferences." However, this statement has to be taken with a grain of salt, as it does not automatically mean that there are dedicated locations for 50% of the nucleosomes directly encoded into the DNA sequence. When one looks at the in vivo nucleosome maps of yeast, it seems that nucleosomes are well positioned along the beginning of each gene such that one can count them, one after the other (one speaks indeed of the +1 nucleosome, the +2 nucleosome, and so on (14)). But when one calculates the average positional preferences of the nucleosomes around the TSSs (21), one finds mainly an "anti-positioning" element just in front of genes, an AT-rich piece of DNA that repels nucleosomes. The appearance of clearly distinguishable "positioned" nucleosomes along the beginning of genes in yeast is then, in fact, just a statistical effect caused by the relatively large density of nucleosomes and the presence of a boundary constraint, as suggested in the classical work of Kornberg and Stryer (22). For the much lower density of nucleosomes obtained via in vitro reconstitution, these seemingly well-defined peaks vanish completely (23) (the situation is in fact a bit more complex; for details we refer the reader to the excellent review by Struhl and Segal (15)).

Even though nucleosomes seem not to be positioned individually in yeast, the statistical ordering of nucleosomes caused by the presence of a boundary can still be said to be "explained" by nucleosomal sequence preferences. But the more exciting question remains: whether there are also examples of nucleosomes that are specifically positioned by sequence at certain genomic locations. There are indeed numerous examples. In fact, the genomes of many organisms attract nucleosomes to TSSs. A rule that seems to be generally true (at least for the 35 eukaryotic genomes we analyzed (21)) is that genomes of unicellular organisms repel nucleosomes

from TSSs, whereas multicellular life forms show a region that attracts nucleosomes. For instance, nematodes like *Caenorhabditis elegans* have (on average) a strongly positioned nucleosome just at the entrance to their genes (21). Mammals (e.g., mice, chimpanzees, and humans) show a broad region with high overall nucleosome affinity (21).

What is the biological function of those various motifs? At this point, one can only speculate. For yeast, the encoded nucleosome depletion "may indicate that eukaryotic genomes direct the transcriptional machinery to functional sites by encoding unstable nucleosomes over these elements, thereby enhancing their accessibility" (1); the same would be true for all unicellular lifeforms (21). In *C. elegans*, one finds a single well-positioned nucleosome at the beginning of many genes in vitro and in vivo, as predicted by our mechanical model (21), and this might function as a mechanism for TSS selection for RNA polymerase (24). In humans, the situation is complex. The high nucleosome occupancy encoded by the sequence at promoters (21) has been speculated "to restrict access to regulatory information that will ultimately be utilized in only a subset of differentiated cells" (25). However, the in vivo nucleosome occupancy does not correlate well with that intrinsic nucleosome affinity, possibly reflecting transcription-related processes (26). A possible explanation is that the mechanical cues serve here a different purpose, namely, to determine which nucleosomes are retained in sperm cells (where most nucleosomes are replaced by protamines), allowing the transmission of paternal epigenetic information. In fact, the mechanical cues correlate well with the nucleosome retention score in sperm cells (21,26). However, this does not mean that there are no mechanical cues for nucleosomes in somatic human cells. A spectacular example is 6×10^6 nucleosomes mechanically positioned around nucleosome-inhibiting barriers, but the biological function has yet to be determined (27).

We finally mention two more important points that are not yet well understood. The first is that the nucleosome density varies with cell type or developmental state, even though all cells of an organism have the same DNA sequences. This is not inconsistent with the idea of mechanical cues on DNA molecules, as regions of nucleosomes might act as "nucleosomal switches" (28). Another complication is the presence of higher-order chromatin structures that might influence nucleosome positioning, a subject that to our knowledge has not yet been addressed.

Sequence-dependent DNA mechanics is thus one of several players that determine nucleosome positions along genomes. We turn now to another key mechanism: the action of chromatin remodelers.

Nucleosome recognition by remodelers

Chromatin remodelers have a very high affinity for DNA, so that they will "remodel" even a naked DNA molecule, and this even without ATP (29). This basic background mechanism therefore needs to be tuned such that the remodelers act on the right objects (the nucleosomes) at the right place (e.g., near a TSS), and at the right time.

A mechanism by which the remodelers identify their targets has been proposed by us in 2008 (30). It is a variant of the famous kinetic proofreading mechanism originally proposed by John Hopfield in the context of mRNA translation (31). In the context of chromatin remodeling, histone tail modifications placed by "histone writers" can be read by accessory subunits of the chromatin remodelers that are sensitive to these states. Essentially the same idea was put forth shortly afterward by Geeta Narlikar for the ISWI/ACF system, based on her very detailed experiments (32,33).

Very recently, a high-throughput analysis confronting different remodelers with the different possible histone tail modifications lends very strong support for the correlation between histone tail states and the outcomes of remodeler actions (34). Although the results have not been interpreted within the proofreading scenario, the observations themselves are clearly in support of it. Apart from the recognition of histone modifications, a key element of the kinetic proofreading scenario, there are also additional levels of recognition encoded that provide alternative means of regulation. Since ISWI recognizes the H4-tail only without modifications, there is an additional level embedded in this system, as a "basic patch" on the tail enters into competition with a like patch on the remodeler itself: the remodeling motor is inhibited by some of its own domains (called AutoN and NegC), an inhibition that is only relieved in the presence of the histone tail (35). Recently, the multivalency of bromodomains of the BAF chromatin remodeling complex has been elucidated, as they bind to both DNA and the histone-tail modification H3K14ac (36). These insights show that even within the interaction of a specific remodeler type with a nucleosome, a rich network of recognition mechanisms has evolved for the fine tuning of remodeler action. These developments are clearly important for more general predictive models of remodeler recruitment on large scales similar to those for sequence-directed nucleosome positioning. Statistical physics-based models in this direction have already been put forward (37,38).

Chromatin remodeler action

Motor engagement

Three recent studies have provided new key insights into the engagement of chromatin remodeling motors on the nucleosome; as they consider remodelers from different families, the insights they yield nicely complement each other.

In a study by Liu et al. (39), summarized by Wigley and Bowman (40), the interaction between the ATPase unit of Snf2 (also called SWI-SNF) and the nucleosome was

studied by cryo-EM. The study reveals that the ATPase is bound to an internal site on superhelical location 2 (SHL2). As the structure is nucleotide free, the ATP-binding cleft is in an open conformation, which, by comparison with the closed conformations, allows us to conclude that the closure of the cleft would push 1 bp of DNA toward the nucleosome dyad. An important insight from this study is that in addition to the binding site of the ATPase at SHL2, an acidic patch on the first lobe of the ATPase contacts the DNA 90 bp away. Upon ATP binding and closure of the cleft, the second lobe can move the DNA duplex toward the dyad axis across the histone octamer. After ATP hydrolysis, lobe 2 would need to reset without sliding the DNA back with it. This study therefore provides an answer to the question we asked in the introduction. On the eBike, the "clip-on" motor on the nucleosome needs to be fixed at a position on the frame, and it then contacts the rolling wheel of the bike to transmit the power. In the case of the ATPase, the remodeler remains attached with its lobe 1 at SHL2, whereas lobe 2 dynamically resets upon translocation (see the schematic illustration in Fig. 4). Very similar findings on the workings of the remodeler ATPase were obtained by Nodelman et al. (41) in their work on the Chd1 remodeler, which has also been studied by the Bowman group in much detail (42,43). Chd1 is a (smaller) remodeling complex that plays a key role in nucleosome positioning over coding regions (44).

The third study we refer to is the work by Sundaramoorthy et al. (45), which also considers Chd1. Like other remodelers, Chd1 belongs to the Snf2-family and contains two helicase-like domains for which previous structural information was available for the ATPase domain associated to N-terminal chromodomains, which serve to recognize methylation states of the histone tails. Chd1 resembles ISWI in one important aspect, as it also contains a C-terminal DNA-binding domain composed of the SANT and SLIDE domains. The structural information available for all these structures, however, was limited to these subdomains, not reaching to the level of the full structure. In the experiments described in (45), SAXS data obtained on full Chd1 complexes (without the nucleosome) showed that Chd1 is a monomeric complex. To obtain higher-resolution data, the complex was studied with pulsed electron paramagnetic resonance after cysteine-serine replacements. The mutant protein showed unmodified remodeler activity. Reintroduction of specifically chosen labeled cysteine pairs allowed determination of distances in the complex, which can be related to the crystal structure. The resulting distance distributions reveal the possible dynamics of the structure through their difference from residue distances in the crystal structure. Together with docking poses, these data thus allow us to develop an idea of the dynamic contacts the complex can undergo. These results were also corroborated in a very recent structural study on the Chd1-nucleosome complex published by the Cramer group (46).

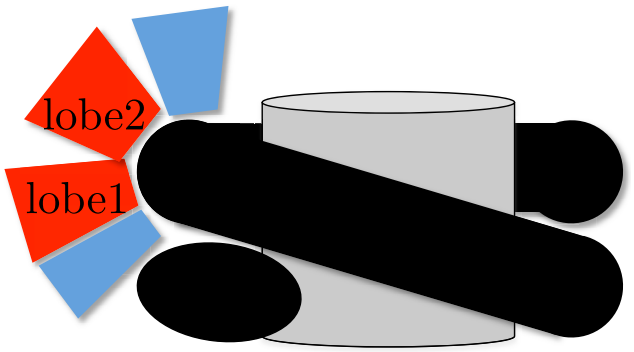

FIGURE 4 Schematic drawing of the remodeler engagement for the Snf2-construct, following Fig. 3 *a* from (39) and Fig. 2 from (40). The color scheme is as follows: light gray, histone octamer; black, nucleosomal DNA; lobe 1, lobe 2: ATPase units. The remaining trapezoids sketch accessory remodeler domains. To see this figure in color, go online.

Further insights into the role of the N-terminal tail in the regulation of remodeler activity were made by performing mutations in several regions and assessing their effect on the repositioning of remodelers. Finally, the engagement of the remodeler with the nucleosome was studied by cryo-EM. These highly detailed studies allow substantial insights into the different contacts the remodeler domains make with nucleosomes during remodeling.

A dynamical role for the histone octamer

In most studies of chromatin remodeling, the histone octamer is considered as a rather static bystander of remodeling events: it is essentially the spool around which the DNA is wrapped and hence unspooled or transported around this protein structure. A recent study by Sinha et al. (47) challenges this purely "passive" role of the histone octamer. The findings by Sinha et al. have been summarized by Flaus and Owen-Hughes (48). The key idea of this work has been first to introduce artificial modifications in the histone octamer structure, and then to correlate the direct observations of the effect of these modifications on NMR spectra of nucleosomes bound to a remodeler with positioning assays of nucleosomes under the action of remodelers.

Specifically, the authors studied ^{13}C-isotope modifications in the methyl groups of buried H4 side chains and detected the structural changes these modifications induce via NMR spectroscopy. The nucleosomes were bound to an Snf2-remodeler. The observed changes appeared prominently in the H3-H4 dimer near superhelical location 0 (SHL0), close to the center of the nucleosome, which is distant from the location SHL2 where the remodeler is expected to bind the nucleosome. In a separate set of experiments, the authors engineered disulfide linkages between H3 and H4 to restrict their flexibility. In accord with the NMR data, such cross-links in the vicinity of SHL0 led to a statistically significant number of disrupted nucleosomes,

whereas cross-links near SHL2 showed no significant effect. By studying remodelers from different families—ISWI, INO80, and RSC—differences between the remodelers became apparent: the cross-linking near SHL2 affects both ISWI- and RSC-remodeled nucleosomes but shows no relevant effect on INO80.

These results clearly show that the full structure of a nucleosome-remodeler complex features dynamical behavior in all of its subunits. Remodeling has become yet more dynamic than previously thought.

Nucleosomes and CRISPR-Cas

As a final point of this perspective article, we address the relevance of chromatin remodeling for what is currently the hottest topic in DNA biology, CRISPR-Cas9. In a recent study involving one of the co-inventors of the CRISPR technology, the role of nucleosomes on the chromatin fiber undergoing the genome editing process was investigated in the presence and absence of chromatin remodelers (49). In biochemical assays in which the preferred positioning of nucleosomes on the 601-sequence was used in specifically constructed sequences, the authors could establish that the efficiency of the Cas9 enzyme in cutting the DNA is consistent with the well-known nucleosome breathing behavior (50). According to this mechanism nucleosomal DNA unpeels temporarily from the ends, favoring the interaction of enzymes with sites that are close to the nucleosomal flanks. This was shown first for restriction enzymes (50,51) and can now be observed more directly via fluorescence resonance energy transfer (52,53). In addition, Cas9 efficiency is promoted by the presence of chromatin remodelers that displace the nucleosomes from the cut sites. Therefore, due to these two mechanisms, the CRISPR-Cas9 system can reach efficiencies in eukaryotes that equal those in bacterial systems, in which the DNA is more readily accessible.

The authors of (49) also point out that the design of CRISPR-Cas9 systems can be optimized by taking into account the intrinsic nucleosome positions. But to what extent can such a prediction be made? If nucleosome positions are known, coarse-grained models can predict the sequence-dependent accessibility of proteins to DNA target sites inside nucleosomes (50,51), as recently demonstrated (54). However, as mentioned earlier, not all nucleosomes are positioned by mechanical signals alone (see, e.g., our discussion of nucleosome positioning at human TSSs). We therefore expect that all three levels of chromatin regulation of the nucleosome need to be taken into account to arrive at reliable predictions of Cas9 efficiency.

Conclusions

We have provided an overview of recent developments in understanding how nucleosomes give limited access to their DNA. One important aspect is the sequence-dependent DNA elasticity, which can be tuned over evolutionary timescales to create regions of high or low nucleosome stability. We discussed how in the context of transcription start sites this might give access to regulatory information or, depending on the organisms, might determine nucleosome retention in sperm cells. We then turned to chromatin remodelers and first discussed new detailed experimental evidence as to how remodelers might recognize the "right" nucleosomes for their action. Finally, we discussed how very recent work begins to provide detailed insight into how the motor activity of remodelers translates to nucleosome repositioning. The high level of understanding of the microscopic details of these three mechanisms that influence nucleosome positioning and dynamics makes us hopeful that a comprehensive picture of how nucleosomes influence gene expression might be within reach in the near future. In this perspective, we have focused on the very recent developments that, in our view, significantly advance the field. Obviously, we have not been able to cover here all aspects in which progress has been made in the last years. For an extended description covering earlier work, we refer the reader to the recent review by Lai and Pugh (55).

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