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Nucleosome sliding: facts and fiction

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Nucleosome sliding is a frequent result of energy-dependent nucleosome remodelling *in vitro*. This review discusses the possible roles for nucleosome sliding in the assembly and maintenance of dynamic chromatin and for the regulation of diverse functions in eukaryotic nuclei.

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Introduction

All fundamental processes with chromatin substrate in eukaryotic nuclei, be it the replication of the genome, the transcription of genes, the sensing and repair of DNA damage, or the generation of genetic diversity through recombination, are initiated and regulated by DNA-binding proteins that scan the chromatin fibre in search of their preferred recognition sequences. Examples where active transcription factors are present in nuclei but are hindered from interacting with regulatory elements (Becker *et al*., 1987) highlight the discriminating role of the chromatin organization for factor access. Inaccessible chromatin is commonly characterized by DNA methylation and distinct patterns of histone modification. Rendering genes accessible involves unfolding of higher order structures through targeting of enzymes that alter these modifications (Jenuwein and Allis, 2001). At the level of the chromatin fibre, a second type of remodelling enzyme is needed; ATP-dependent nucleosome remodelling factors modulate chromatin structure in more subtle ways. They use the chemical energy freed by ATP hydrolysis to transiently disrupt the histone–DNA interactions that characterize canonical nucleosomes (Gregory *et al*., 2001; Becker and Hörz, 2002; Narlikar *et al*., 2002). Their action increases the accessibility of nucleosomal DNA and facilitates the relocation of histone octamers to adjacent DNA segments ('sliding'), and may even lead to displacement of a histone octamer to a different DNA segment. Short-range nucleosome movements *in cis* seem to be a particularly attractive principle by which the overall packaging of DNA is maintained, yet rendered 'transparent' through stochastic exposure of individual DNA segments in the more accessible linkers between nucleosomes. Energy-dependent nucleosome remodelling not only serves to open chromatin structure, but is also involved in gene repression, chromatin assembly and the maintenance of higher order chromosome structure. Here, I will collect the available evidence for catalysed nucleosome sliding and speculate on the possible contributions of nucleosome sliding for chromatin dynamics *in vivo*.

Nucleosome sliding: early observations

As the DNA double helix spools around the histone octamer to create a nucleosome core particle, it contacts the histone surface at 14 sites with clusters of hydrogen bonds and salt links (Luger and Richmond, 1998). Collectively, these weak interactions render the nucleosome a rather stable particle. Yet passive (non-catalysed) movement of histone octamers on DNA has been observed at moderately elevated temperature and ionic strength (Beard, 1978; Pennings *et al*., 1991; Meersseman *et al*., 1992). Dislocation of nucleosomal DNA requires that all interactions are broken and reformed. Disrupting all bonds at the same time would presumably lead to a prohibitive free energy penalty. Current models for passive histone octamer movement on DNA therefore assume that only segments of DNA (involving only few histone–DNA contacts) are peeled off the histone surface at any given time (Van Holde and Yager, 1985; Widom, 1999; Schiessel *et al*., 2001). The DNA at the 'edge' of the nucleosome comes off the histone surface most easily. Thermal twisting or other distortion of this DNA, such as bending it into a tight loop or 'bulge' will lead to the reformation of equivalent but non-identical histone–DNA interactions (Figure 1A), and the nucleosome would then contain a segment of distorted DNA (a 'defect in stored length'; Schiessel *et al*., 2001) 'looping' from the nucleosome. Diffusion of this distortion over the particle until it emerges on the other side will lead to complete translocation of the DNA relative to hallmarks on the octamer (Figure 1A).

Nucleosome sliding catalysed by ATP-dependent nucleosome remodelling factors

Low levels of spontaneous nucleosome mobility may occur under physiological conditions, but it seems that the cell does not take chances. Rather, it invented nucleosome remodelling enzymes that lower the energy barrier, which limits spontaneous nucleosome movements, by coupling the disruption of histone–DNA contacts to ATP hydrolysis. The ATP-dependent ('active') sliding of nucleosomes over distances of up to 100 bp in arrays with physiological properties was first observed during the characterization of chromatin reconstituted *in vitro* in *Drosophila* embryo extracts (Varga-Weisz *et al*., 1995). During the following years, a zoo of ATP-consuming activities involved in chromatin metabolism were identified in these extracts, such as the nucleosome remodelling

factor (NURF; Tsukiyama and Wu, 1995; Tsukiyama *et al*., 1995), the ATP-utilizing chromatin assembly and remodelling factor (ACF; Ito *et al*., 1997a) and the chromatin accessibility complex (CHRAC; Varga-Weisz *et al*., 1997). The shared subunit of these three complexes, the ATPase ISWI, endows these machineries with the ability to catalyse nucleosome sliding (for a review, see Längst and Becker, 2001b).

ISWI belongs to the large SWI2/SNF2 family of ATPases, members of which are involved in all prominent nuclear processes (Eisen *et al*., 1995). According to distinctive structural features, these ATPases define subfamilies, the prominent ones being represented by the bromodomain-containing SWI2/SNF2, by ISWI with C-terminal SANT-like modules and the chromodomain ATPase Mi-2 (Becker and Hörz, 2002; Narlikar *et al*., 2002). Despite the very different domain organization of the remodelling ATPases and their association with a variety of other subunits, all remodelling complexes are able to induce the movement of intact histone octamers on DNA *in cis* (Hamiche *et al*., 1999; Längst *et al*., 1999; Brehm *et al*., 2000; Guschin *et al*., 2000; Jaskelioff *et al*., 2000). However, whereas for ISWI-containing factors nucleosome sliding seems to be the predominant outcome of nucleosome remodelling, ATPases related to yeast SWI2/SNF2 may also catalyse the disruption of histone–DNA interaction without relocation of the octamer or, at the other extreme, the complete dislocation of a histone octamer to free, competing DNA (Lorch *et al*., 1999; Phelan *et al*., 2000; Narlikar *et al*., 2001).

Whether, under physiological circumstances, nucleosomes will move on DNA *in cis* (sliding) or be shuffled to acceptor DNA *in trans* will undoubtedly depend on the nucleosome density and the availability of free DNA of suitable length close-by. My bias is that the former reaction is more likely to occur and that the inherent flexibility of the fibre (Woodcock and Dimitrov, 2001) will permit significant, short range nucleosome sliding.

Nucleosome sliding, chromatin assembly and nucleosome fibre folding

We envision global needs for nucleosome mobility, endowing the chromatin fibre with 'fluidity' and transparency. A first task may be posed by replication, when the nucleosomes of the parental strand are randomly distributed to the daughter strands and the resulting gaps in the fibre are filled by assembly of new octamers. Discontinuities of the chromatin fibre may also arise throughout the cell cycle when DNA-binding regulators vacate their targets. It is unknown how the continuity of the nucleosomal fibre is assured *in vivo*, but in cell-free model systems, regular nucleosomal arrays are generated by an energy-dependent process that can be catalysed by some (but interestingly not all) nucleosome remodelling factors of the ISWI-type (Ito *et al*., 1997b; Varga-Weisz *et al*., 1997; Tsukiyama *et al*., 1999). Uniformity of internucleosomal distances may define a low-energy state of the system since gaps in nucleosome arrays prevent the folding of the fibre (Fletcher and Hansen, 1996). Although counter-intuitive at first glance, it appears that the same factors that render DNA in chromatin accessible also have the potential to improve the folding of chromatin into higher order structures through their 'spacing' capability. A role for ISWI in the maintenance of chromosome integrity has recently been inferred from a particular phenotypic aspect of flies lacking ISWI. Analysing the polytene chromosomes of *Drosophila* larvae that die due to lack of ISWI, Tamkun and colleagues found the X chromosomes of male larvae massively deformed, consistent with a global impairment of chromatin folding (Deuring *et al*., 2000).

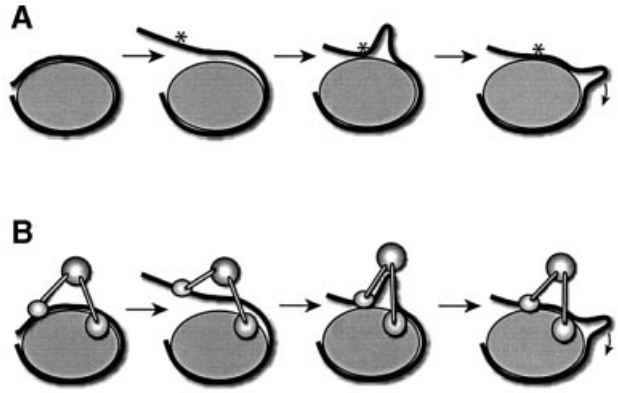

Fig. 1. Loop propagation model for passive (**A**) and active (**B**) nucleosome sliding. The nucleosome is represented by a grey ellipse around which the DNA (black string) winds. The initial steps of nucleosome mobilization are depicted. The asterisk represents a hallmark on the DNA. The remodelling machinery, of which no structure is known, is represented schematically by rod-connected spheres.

Once the nucleosomal fibre is properly assembled, 'nucleosome spacing' factors such as CHRAC and ACF may then continue to keep it in a 'vibrant' state, flexible to permit the interaction of DNA-binding regulators. Even movements of DNA relative to the histone surface over very short distances may have significant impact on factor binding. Some regulators are able to interact with DNA bent over the histone octamer, if their short recognition sequence faces outward from the histone surface (Beato and Eisfeld, 1997). Translocating a histone octamer by just 5 bp will expose any given sequence that was previously occluded by the histones. More profound movements will further change the accessibility; the closer a given DNA sequence to the nucleosome edge, the more accessible it will be. An important consequence of the existence of principles that assure global transparency of chromatin is that any DNA-binding regulator may profit, regardless whether its function is to activate or to repress, to open or to close chromatin.

Nucleosome sliding, nucleosome positioning and promoter architecture

Specific positioning of nucleosomes with respect to the underlying DNA sequence (as opposed to random localization of histone octamers in a population of genomes) is frequently observed close to regulatory elements (Wallrath *et al*., 1994). Are these positioned nucleosomes subject to the same kind of short distance motion or are they somehow exempt from energy-dependent mobilization? High resolution mapping after *in vivo* cross-linking revealed that even nucleosomes that appear tightly positioned at first glance, display a continuum of

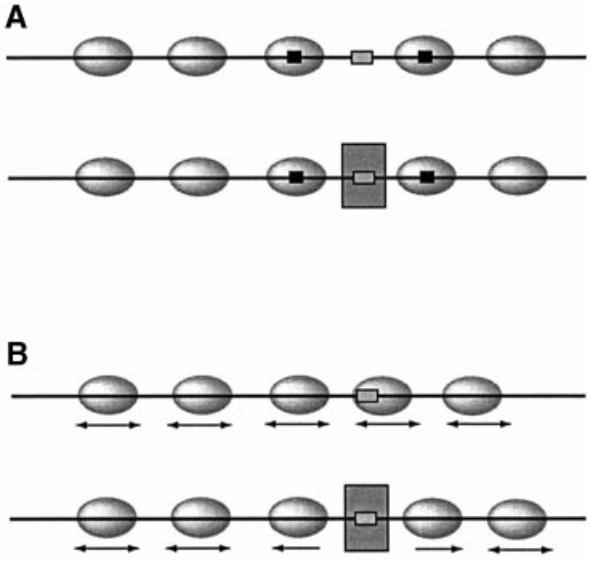

Fig. 2. Two models for the creation of promoter architecture. (**A**) Nucleosomes (ellipsoids) are positioned due to dedicated sequence elements (black boxes) such that the binding site (small grey box) for a regulator (large grey box) is left accessible. (**B**) Nucleosomes are not positioned but mobile. Due to statistical movement, the binding site for a regulator is transiently exposed. The interaction of a regulator brings about a positioning of adjacent nucleosomes.

translational positions around preferred sites (Buttinelli *et al*., 1993; Fragoso *et al*., 1995; Tanaka *et al*., 1996). Presumably, these positions are in constant exchange *in vivo* due to nucleosome sliding and the mapping procedure captured a 'snapshot' of the equilibrium at the time of cross-linking.

It is often assumed that the DNA structure around critical regulatory sites has a defining effect on nucleosome positions, such that, for example, binding sites for regulators are left nucleosome-free (Figure 2A). Since, at least *in vitro*, nucleosome remodelling ATPases are able to slide nucleosomes off even the strongest nucleosome positioning sequences (G.Längst, J.Widom and P.B. Becker, unpublished data), an alternative scenario must also be considered. Energy-dependent nucleosome mobilization may assure that histone octamers adopt all possible positions on a given DNA segment for a fraction of the time. A DNA-binding regulator may take advantage of the 'window of opportunity' to interact with its binding site when it is transiently exposed. Importantly, its binding will create a 'boundary', further constraining nucleosome movement. Nucleosome mobility will allow optimizing nucleosome positions according to the tendency of the system to avoid molecular clashes while maximizing the neutralization of DNA (Figure 2B). Adjustments of neighbouring nucleosomes in the array will lead to 'nucleosome phasing' with respect to a boundary. This principle, by which non-random nucleosome positions are brought about by an essentially stochastic mechanism, has already been envisioned early on by Kornberg and Stryer (1988), and supported by experiments in cell-free systems (Varga-Weisz *et al*., 1995; Kang *et al*., 2002) and is also consistent with *in vivo* observations (Fedor *et al*., 1988; Lomvardas and Thanos, 2001).

Targeting nucleosome lubricants

While the proposed global functions of ATP-dependent nucleosome remodelling factors are still speculative to date, there is good evidence for the targeting of these enzymes to specific sites. Numerous interactions between sequence-specific transcription regulators and components of nucleosome remodelling complexes have been described. Direct or indirect recruitment by DNA-binding regulators along with effects on transcription suggests roles for ATP-dependent nucleosome remodelling factors in gene activation as well as repression (for reviews, see Peterson and Logie, 2000; Becker and Hörz, 2002; Narlikar *et al*., 2002). In some cases, targeting of remodelling factors to promoters has been directly correlated with changes in nucleosome positions *in vivo* (Goldmark *et al*., 2000; Kent *et al*., 2001; Lomvardas and Thanos, 2001). A particularly illustrative example is the targeting of the yeast Isw2 complex to the *REC104* promoter via the DNA bound repressor Ume6p, leading to shifts in nucleosome positions towards the repressed state of the promoter (Goldmark *et al*., 2000). Other targeting principles may include interactions with components of constitutive heterochromatin (Bozhenok *et al*., 2002), and methylated DNA (Wade *et al*., 1999).

The workings of nucleosome sliding

The mechanisms by which nucleosome remodelling factors induce the sliding of histone octamers on DNA are still unknown. However, the ongoing analysis of different nucleosome remodelling factors in cell-free systems is providing a rich phenomenology from which general outlines can be derived. It is conceivable that catalysed nucleosome sliding is mechanistically related to passive nucleosome movements. For example, in the context of the model for passive nucleosome movement discussed above (Figure 1A), each of the following steps may be facilitated by enzymes: the peeling off of a segment of DNA from the histone octamer surface, the distortion of this DNA into a bulge, as well as the propagation of this DNA deformation over the histone octamer (Figure 1B).

Since nucleosome remodelling factors are very different in terms of subunit and domain composition, an interesting question is whether a unified mechanism for nucleosome sliding exists or whether individual machineries have their own approach to altering histone–DNA interactions. A common reaction catalysed by various ATPases is the distortion of DNA leading to torsional stress within a constrained domain (Havas *et al*., 2000; Gavin *et al*., 2001; Längst and Becker, 2001a; Liu *et al*., 2001). Notable differences in nucleosome remodelling phenomenology are particularly obvious if ISWI-type and SWI2/SNF2-type ATPases are compared (for a review, see Flaus and Owen-Hughes, 2001): (i) octamer transfer to competing DNA so far has only been observed in reactions driven by SWI2/SNF2-type ATPases; (ii) these ATPases cause obvious alterations of histone–DNA interactions within mononucleosomes, whereas such an 'altered path' of DNA has not been observed during ISWI-catalysed nucleosome sliding; (iii) a stable 'remodelled state' that can be best described as 'nucleosome dimers with partially peeled off

DNA' (Schnitzler *et al*., 2001; and references therein) can be observed after remodelling with SWI/SNF, but not with ISWI; and (iv) ISWI requires the N-terminus of histone H4 for a productive ATPase cycle, whereas SWI/SNF-type enzymes can deal with nucleosomes lacking these domains. To date, all phenomenology related to reactions catalysed by ISWI can easily be explained by assuming that the sliding of intact histone octamers is the main outcome of the remodelling reaction. By contrast, some aspects of remodelling by SWI2/SNF2 (BRG1) points to changes in histone–DNA interactions without nucleosome movement.

Even though these distinctions are obvious, it may be premature to conclude about fundamentally different remodelling strategies. Conceivably, a overall similar *in vitro* remodelling reaction could lead to differential accumulation of intermediates, dead-end products or bona fide end products, depending on the reaction conditions. Intermediates of a nucleosome sliding reaction, such as looped-out DNA on the surface of a histone octamer may be stabilized under some circumstances and accumulate, leading to the observation of a stably altered path. Depending on the rate and directionality of propagation of these DNA distortions, nucleosome sliding or remodelling' without relocation may be observed (for a more detailed discussion, see Becker and Hörz, 2002).

Controlling nucleosome movements

It is likely that the activity of nucleosome remodelling factors will be regulated, and the first regulatory principles are emerging. While nucleosome remodelling ATPases alone can function *in vitro*, their activity is modulated by associated subunits in the physiological complexes (Ito *et al*., 1999; Phelan *et al*., 2000; Eberharter *et al*., 2001; Xiao *et al*., 2001). The modulation of stability and activity of Brg1 and hBrm by phosphorylation (Muchardt *et al*., 1996) is presumably only the first of many regulatory modifications to be discovered.

Not surprisingly, remodelling enzymes are also sensitive towards the modification status of exposed N-terminal 'tails' of the histones (Clapier *et al*., 2002; Corona *et al*., 2002). Interaction of the yeast SWI/SNF complex with chromatin is strengthened by histone acetylation (Hassan *et al*., 2001) and functional interaction between ATP-dependent nucleosome remodelling and histone acetylation is widely observed (for a review, see Becker and Hörz, 2002). Combinations of histone modifications are thought to determine the functional status of chromatin (Jenuwein and Allis, 2001), which obviously includes the degree of nucleosome mobility.

The ease with which nucleosomes can be moved on DNA also depends on the folding of the chromatin fibre. Association of histone H1 with nucleosomal linker DNA 'seals' the two DNA segments at the nucleosome edges into a 'stem' structure (Bednar *et al*., 1998) that restricts passive nucleosome movement (Pennings *et al*., 1994) as well as catalysed remodelling of nucleosomal arrays by enzymes of all major subclasses (Horn *et al*., 2002). Most interestingly, phosphorylation of histone H1 relieves these constraints, presumably due to weakened interactions with DNA (Horn *et al*., 2002). It is likely that the interplay between various linker-binding factors is a decisive determinant of chromatin fluidity. Remarkably, interaction of the abundant non-histone protein HMGB1 with linker DNA at the strategic nucleosomal edge, overlapping the ISWI interaction site not only is compatible with nucleosome sliding, but also facilitates mobilization of a nucleosome by ACF (T.Bonaldi, G.Längst, R.Strohner, P.B.Becker and M.E.Bianchi, submitted). *In vivo*, competition of HMGB1 with H1 for nucleosomal interaction may be facilitated by H1 phosphorylation.

The restrictive role of further levels of chromatin organization, such as the presence of heterochromatin components has not yet been defined. However, the recent observation of an inhibitory effect of a polycomb complex on nucleosome remodelling by Brg1 suggests that repressive chromatin structures are also characterized by reduced nucleosome mobility (Francis *et al*., 2001).

Conclusion

ATP-dependent, catalysed and regulated nucleosome sliding is likely to make important contributions to the plasticity and transparency of chromatin. Elucidation of the functional diversification of chromatin remodelling machines, their targeting, regulation and mechanism of action remains a worthwhile goal for the years to come.

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