Nucleosome remodelers on track

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Two recent studies address how chromatin-remodeling enzymes alter nucleosomes and suggest that they anchor on the particle while translocating on the nucleosomal DNA.

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The organization of eukaryotic genomes as chromatin serves two seemingly opposing functions. The need to stow large genomes within the small confines of eukaryotic nuclei, to protect them from damage and to prevent inadvertent expression of genes, requires a compact and rather strict organization. Use of genetic information, however, be it for gene expression, duplication or repair, demands that structures be flexible. Flexibility of chromatin structure is largely the result of the action of enzymes that alter the structure of the basic unit of chromatin, the nucleosome. Two recent papers[1,2] provide new insights into the mechanisms of 'nucleosome remodeling' and collectively suggest that remodeling enzymes function as specialized DNA translocases that track on nucleosomal DNA while remaining anchored at the particle.

The repeating fundamental structure of chromatin is the nucleosome, consisting of 147 base pairs of DNA wound around an octamer of histones in 1.67 turns. The DNA helix touches the histone surface at 14 sites grouped into clusters of interactions, many of them water mediated[3,4]. Despite these many interactions, the nucleosome is a dynamic particle, as segments of DNA detach transiently from the histone surface to expose DNA and histones to the solvent[5]. At slightly elevated ionic strength or temperature, histone octamers can slide on DNA[6]. Although these observations suggest that chromatin has 'built-in' flexibility, nature has not left the unwrapping of DNA to chance. Rather, a family of nucleosome-remodeling enzymes exist as active components of multiprotein complexes, functioning to remodel nucleosomes in a controlled manner. The term 'nucleosome remodeling' subsumes alterations of DNA-histone interactions that render nucleosomal DNA or histones accessible for interactions that are otherwise precluded. Extreme outcomes of nucleosome remodeling may, for example, include the complete disassembly of the particle by transfer of the histones to cooperating chaperones or the relocation (sliding) of intact histone octamers on DNA[7,8]. Given the organization of the nucleosome, it comes as no surprise that remodeling requires energy in the form of ATP hydrolysis.

In the simplest terms, alteration of canonical nucleosomal structure might involve contacts of a remodeling ATPase with the

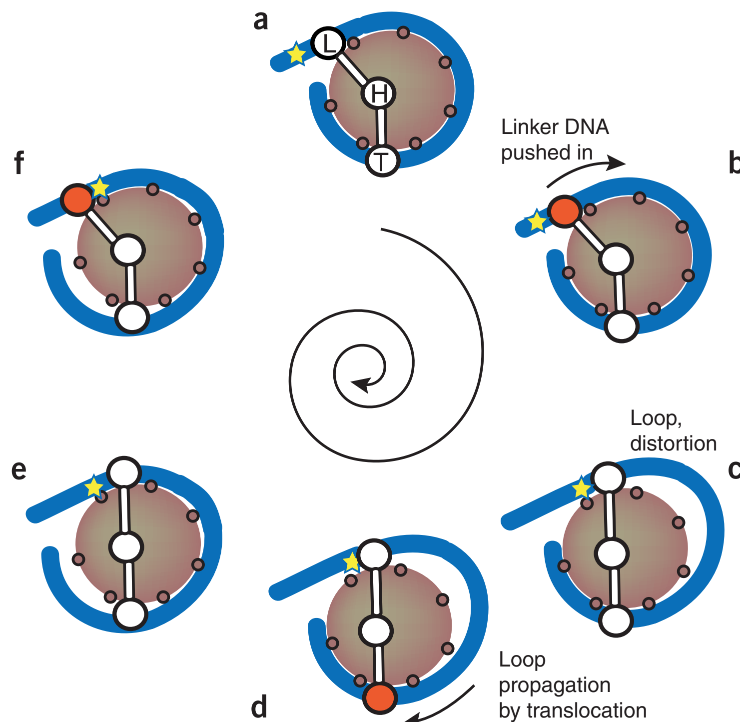

Figure 1 A model for ATP-dependent remodeling, integrating information provided by publications referred to in the text. (**a**–**f**) Hypothetical steps in a nucleosome remodeling reaction, DNA (blue) is wound around the histone octamer (brown) and held by clusters of interactions (small black circles). Only one turn of the DNA duplex is shown. The remodeling machinery is shown as consisting of three connected domains, a linker-binding domain (L), a translocase domain (T) and a histone contact (H). Red indicates domains that are changing conformations and translocating DNA; stars mark one segment of DNA to illustrate translocation.

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DNA and histone moieties of a nucleosome, followed by a conformational change of the enzyme, triggered by ATP binding or hydrolysis, that dislocates DNA relative to histones. An early model followed the observation of Richmond and Davey that nucleosomes can accommodate variable lengths of DNA[9]. The model suggested that remodeling involves twisting of the DNA helix over the histone octamer surface in a base-by-base reaction. In this twisting model the DNA remains largely in contact with the histone surface. Early experiments suggested that this model was not universally applicable, as single-stranded DNA nicks, abasic sites and bulky adducts that should inhibit DNA twisting did not inhibit remodeling by several enzymes[10–12]. Strohner *et al.*[1] present an extreme version of this experiment: they modified the nucleosomal DNA by attaching a large paramagnetic bead, which did not interfere with remodeling by the ATPase ISWI in the context of the ACF complex. They have also provided evidence that fairly large DNA segments at the nucleosome edge are at least transiently detached from the histone surface during ISWI-dependent nucleosome remodeling. These data are in agreement with studies on the SWI/SNF complex showing that large segments of DNA are rendered accessible on the nucleosome surface upon remodeling[13]. Collectively, these results suggest that the twisting model is incorrect.

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Crucial insight into the mechanism of nucleosome remodeling came from the realization that remodeling ATPases may function as specialized DNA translocases[14,15]. A series of elegant experiments by Saha *et al.*[2] now suggest that the nucleosome-remodeling ATPase Sth1 tracks along one DNA strand on the nucleosome surface. However, in contrast to the related movements of DNA helicases and type II restriction enzymes[16], Sth1 remains anchored at the histone octamer. DNA translocation with anchoring at the histones leads to relocation of DNA relative to a histone reference point.

Understanding the nucleosome remodeling reaction requires precise knowledge of contacts between the enzyme and the nucleosome. Studies on the remodeling complex ACF by Strohner *et al.*[1] suggest that the remodeler can interact with the DNA at its entry into the nucleosome (**Fig. 1a**, L). This is a strategic site, as it is where segments of DNA can be lifted off the histone surface most easily. Tracking toward the linker DNA would effectively push the linker into the realm of the nucleosome. Accordingly, the 'loop recapture' model proposes that ACF pushes a segment of linker DNA into the nucleosome, thereby lifting DNA off the histone (**Fig. 1b**). Depending on the nature of further interactions, the detached DNA will either appear as a loop on the nucleosome surface or be propagated to relocate the DNA relative to the histones (**Fig. 1c**).

Saha *et al.*[2] present a set of data that leads them to propose that Sth1 tracks on DNA not at the edge of the nucleosome but at a fixed site deep inside the nucleosome, about two DNA helical turns off the dyad axis of the nucleosome (**Fig. 1a**, T). This site seems also to be important for nucleosome remodeling by the ATPase ISWI. Schwanbeck *et al.*[17] found that the absence of nucleosides at this position interfered with nucleosome remodeling by the ISWI-containing NURF complex. The yeast Isw2 complex also makes a crucial contact at this site[18]. A unique feature of this position is the pass of the histone-H4 N terminus between the two gyres of nucleosomal DNA. Deletion of a patch of basic residues within the H4 tail prevents remodeling by ISWI-containing enzymes[19,20]. Schwanbeck *et al.* therefore hypothesized that these H4 residues may induce ISWI, tethered at this site, to translocate toward the nucleosome linker.

Saha *et al.*[2] present a model whereby directed DNA translocation within the nucleosome leads to a movement of DNA relative to the histone octamer. However, to explain the common observation that large segments of DNA apparently become accessible to nucleases during remodeling, an active detachment of DNA at the nucleosomal entry seems necessary. It is possible that the initial loop formation (**Fig. 1a–c**) is independent of the internal translocation, but that the latter activity contributes to propagating the detached DNA over the nucleosome surface (**Fig. 1c–e**).

It is clear that the interactions of remodeling enzymes with the nucleosome substrate are likely to be more complex. The simple, two-subunit remodeling factor ACF has four DNA binding sites, as defined by fluorescence techniques[1]. Interactions of remodelers with histones[21] are likely to contribute to the anchoring of the remodeling factors to the histone moieties (**Fig. 1**, H). The first electron microscopic images of the SWI/SNF complex suggest that the remodeling factor may enclose the nucleosome substrate almost entirely[22]. However, the progress documented in recent work shows that we are on the right track toward deciphering the mysterious mechanism of nucleosome remodeling.

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