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An Engine for Nucleosome Remodeling

Minireview

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In the eukaryotic nucleus, the structural context for proteins involved in transcriptional regulation, DNA replication, and DNA repair is a nucleosome array. Activation of transcription is frequently accompanied by a reorganization of the chromatin structure facilitating the access of the required DNA-binding proteins. Conversely, repression is accompanied by the restoration of the array. These local changes involve the disruption or reformation of nucleosomes and can be mediated by large multiprotein assemblies, termed chromatin remodeling complexes (Felsenfeld, 1996; Workman and Kingston, 1998).

The first remodeling complex to be identified was the 11-subunit yeast SWI/SNF assembly, which is required for the relief of chromatin repression and the activation of a set of inducible genes. One subunit of this complex, SWI2/SNF2, is homologous to DNA helicases, and it was consequently suggested that this protein might perform a similar function in nucleosome disruption. Further homologs to this subunit are present in *Drosophila* (Brm), in humans (BRG1 and hBrm), and another in yeast (Sth1 in the RSC complex). These complexes possess the common property of facilitating the access of transcription factors to nucleosomal DNA in a reaction requiring ATP. A related class of remodeling complexes, termed NURF (nucleosome remodeling factor), CHRAC (chromatin accessibility complex), and ACF (ATP-utilizing nucleosome assembly and remodeling factor) have been isolated from extracts of *Drosophila* embryos (Pazin and Kadonaga, 1997). These complexes not only stimulate transcription factor binding but also, to a greater or lesser extent depending on the complex, promote nucleosome mobility (i.e., the repositioning of the histone octamer on a DNA sequence). The increased mobility permits the formation of regularly spaced nucleosome arrays in the presence of CHRAC or ACF but not NURF. The different complexes are thus functionally distinguishable in vitro. All the complexes isolated from *Drosophila* contain ISWI, a protein that also contains the helicase motif but lacks the C-terminal bromodomain characteristic of the Swi2/Snf2 protein (Tsukiyama et al., 1995) (Figure 1). Homologs of ISWI are present in both humans and yeast but have not yet been shown to be present in a remodeling assembly. A further class of related proteins implicated in chromatin remodeling are the CHD polypeptides. Again these contain a helicase motif but also contain two chromodomains, a motif believed to be involved in protein–protein interactions in heterochromatic chromatin structures, and either a PHD (plant homeodomain) domain or another DNA-binding domain (Figure 1). Unlike the ISWI- and Swi2/Snf2-containing complexes, at least certain of the complexes containing CHD are associated with repressive chromatin remodeling (Tong et al., 1998; Zhang et al., 1998).

Molecular Mechanisms for Chromatin Disruption

How do these complexes effect nucleosome disruption? Both the SWI/SNF complexes and to a lesser extent NURF of the ISWI complexes increase the accessibility of nucleosomal DNA to DNase I and other nucleases, although this property has yet to be demonstrated for CHRAC. In addition, SWI/SNF substantially reduces the negative superhelical turns constrained by nucleosome arrays. Both this topological change and the change in accessibility to DNase I indicate an extensive unwrapping of DNA from the histone octamer. This conclusion is also consistent with the observation that mutations in histone H4 which eliminate a particular contact with nucleosomal DNA, and hence lower the affinity of the octamer for DNA, suppress a mutation in one component of the SWI/SNF complex. More detailed studies show that the remodeling by the SWI/SNF-related complex RSC proceeds via an activated intermediate containing both RSC and core histones together with nucleosomal DNA (Figure 2). The DNA associated with this complex has a greatly enhanced sensitivity to exo- and endonucleases with a pattern of DNase I cleavage similar to that observed with naked DNA (Lorch et al., 1998), showing that the DNA in this complex is on average fully accessible in contrast to wrapped nucleosomal DNA. On removal of RSC, the nucleosome remains in an altered state with the associated DNA retaining a slightly increased accessibility to DNase I relative to normal core particles, although somewhat decreased relative to the activated intermediate complex. A similar stable altered state is generated by the action of the human SWI/SNF complex on mononucleosomes (Côté et al., 1998; Schnitzler et al., 1998). These “altered” nucleosomes behave physically as a dinucleosome and contain a full complement of core histones, yet it is unclear whether this particle is the “natural” product of nucleosome remodeling. In principle it could be generated from a change in conformation of adjacent histone octamers leading to a rearrangement of internucleosomal interactions or, alternatively, from the processive unwrapping of DNA from a terminus of one nucleosome (Pazin and Kadonaga, 1997), which then might reassociate with the exposed core histones of another similarly disrupted particle. A precedent for such a mechanism is the rebinding of DNA by a nucleosome displaced from the same core particle by a transcribing RNA polymerase, thus resulting in a shift in the position of the octamer (Studitsky et al., 1997).

One prediction of the latter mechanism is that free DNA molecules should act as acceptors for the octamer DNA-binding sites freed by unwrapping of the nucleosomal DNA. In accordance with this prediction, Lorch et al. (1999) (this issue of *Cell*) have demonstrated that the yeast RSC complex can indeed catalyze the transfer of a histone octamer from a nucleosome core particle to a separate naked DNA, and that this transfer proceeds via the activated RSC-nucleosome intermediate. In the

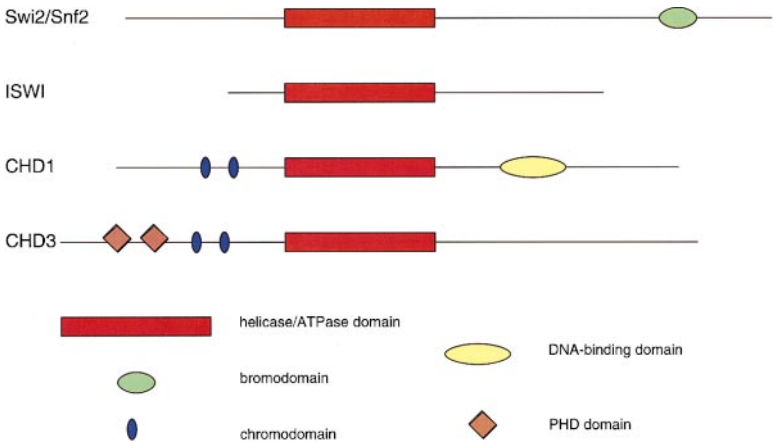

Figure 1. Structures of the Swi2/Snf2 Superfamily of Remodeling Proteins

The relative lengths are averages and do not represent specific family members.

context of chromatin, the acceptor is likely to be DNA that is closest to the disrupted core particle, with the resulting transfer leading to a shift in the octamer position along the DNA. This mechanism thus readily accounts for both the nucleosome mobility and enhanced DNA accessibility induced by remodeling complexes, particularly those containing the ISWI protein. It is unknown whether the stable altered "dinucleosomal" particle can exist, however transiently, in vivo, and thus its biological role remains moot. It is nevertheless conceivable that such a particle could contribute to a highly localized disruption of the array.

The Remodeling Engine

Although it has been assumed that ATPase activity of the subunit with helicase homology provided the motor necessary for nucleosome disruption, it was unclear whether the other subunits were also required for this process. However, recent experiments using isolated protein show that at least the ISWI or Swi2 polypeptides are sufficient and thus constitute the engine of the remodeling machine. Using the human homologs of the Swi2/Snf2 protein, Phelan et al. (1999) demonstrate that

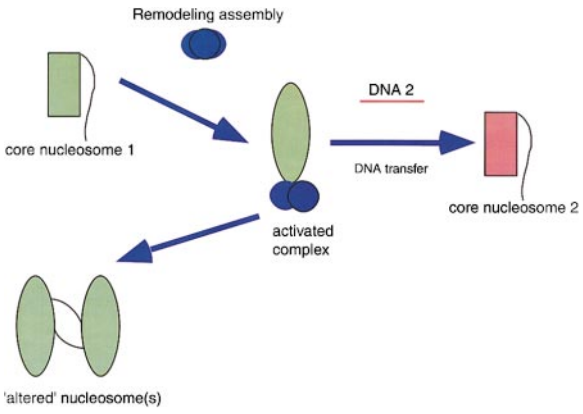

Figure 2. Mechanism for Chromatin Remodeling and Octamer Transfer

The action of a remodeling complex on a core nucleosome results in the formation of an activated complex with altered histone–DNA contacts. The octamer in this complex can serve as an acceptor for either a free DNA molecule or unwrapped DNA from another activated particle (adapted from Lorch et al., 1999).

either BRG1 or hBRM individually can, in an ATP-dependent manner, increase the accessibility of nucleosomal DNA to DNase I to a level comparable to that attained with the complete assemblies. Similarly both proteins can elicit the same change in DNA topology of nucleosome arrays as the hSWI/SNF complex itself. These results show that the mechanism of disruption by the isolated Swi2 polypeptide must be very similar to that of the assembly. However, the isolated BRG1 subunit is considerably less efficient than the complex, particularly in effecting the topological change. This activity could be enhanced to normal levels by the inclusion of three additional components, IN1, BAF170, and BAF 155, of the hSWI/SNF complex. All these subunits contain coiled-coil domains, but their precise role remains to be established. Whether the inefficiency of the isolated subunit is a consequence of a reduced extent or rate of reaction is also unknown.

In another set of experiments, Corona et al. (1999) show that the isolated ISWI protein can by itself reproduce the functions of the three ISWI-containing complexes. In particular, like NURF and CHRAC, isolated ISWI facilitated the access of the activator protein GAGA, to its binding sites in the hsp26 promoter on a chromatin, but not a naked DNA, template. By contrast, like CHRAC, which efficiently remodels nucleosome arrays, but unlike NURF, isolated ISWI improved the regularity of nucleosome spacing. Finally, isolated ISWI mimicked the activity of ACF in NAP-1 (nucleosome assembly protein 1) dependent assembly of chromatin from histones and DNA. This study indicates that ISWI is sufficient for each of these processes but that in the remodeling machines its precise function is modulated by its environment.

The ATPase activities of the complexes containing ISWI and hSwi2 differ functionally in one important respect. Whereas that of the ISWI-containing complexes respond only to nucleosomes, hSwi2 is stimulated by both nucleosomes and free DNA. It is very striking that in this respect the ligand preferences of the individual engines qualitatively reflect that of the NURF and SWI/SNF complexes, respectively, and thus these properties must be determined in large part by the engine subunits. By contrast, the inhibition of isolated ISWI activity by the N-terminal tails of the different histones differs from that of the NURF complex. Whereas for ISWI the most

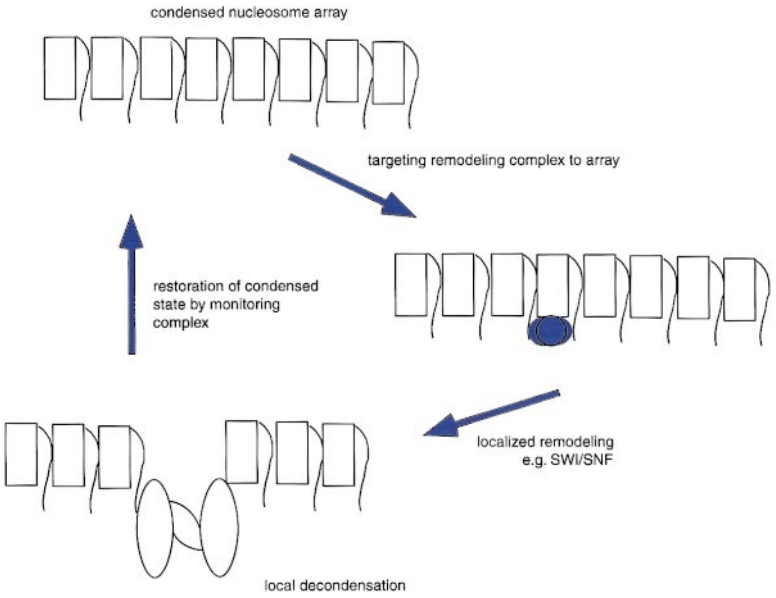

Figure 3. A Cyclic Mechanism for Disruption and Reformation of Nucleosome Arrays

The model postulates that different remodeling complexes are required for nucleosome disruption, permitting the binding of transcription factors and the reformation of nucleosome arrays after the dissociation of the factors.

effective N-terminal tails are those of histones H2A and H2B with little inhibition by the N-terminal tails of H3 and H4, the opposite pattern is observed for the NURF complex (Georgel et al., 1997). While it remains possible that this difference is a consequence of trivial variations in methodology, it seems possible that this change in selectivity could result from additional recognition determinants being provided by other polypeptides in the NURF complex. In particular, one component of NURF (Martinez-Balbas et al., 1998) has homology to the mammalian protein RbAp48, which binds to helix 1 of histone H4, implying that Swi2, but not ISWI, may interact directly with the H3 and H4 tails while ISWI binds the H2A and H2B tails. Similarly, the bromodomain present in Swi2, but absent from ISWI, selectively binds the N-terminal tails of histones H3 and H4 (Ornaghi et al., 1999). Differences such as these in the chromatin targets of the subunits of the remodeling complexes could reflect the nature of their substrates. For example, if the chromatin is condensed, any interactions between adjacent nucleosomes would require disruption prior to any remodeling involving alteration of the core histone–DNA contacts. By contrast, remodeling of chromatin in an open configuration requires simply the recognition of an isolated core particle. Whatever the precise interactions involved, it is clear that the context of the engine in a particular complex can modulate its functionality and integrate its activity with other modular functions. For example, the CHRAC complex contains a topoisomerase II dimer that could be required in vivo for mediating changes in DNA topology associated with remodeling.

Chromatin Remodeling—Cyclic or Reversible?

In vitro all the chromatin remodeling activities containing ISWI or Swi2/Snf2 can increase the accessibility of nucleosomal DNA to transcription factors or other DNA-binding proteins. In the case of the SWI/SNF complex, there is substantial genetic and biochemical evidence that complex mediated transcriptional activation is accompanied by nucleosome disruption in vivo and in vitro. However, it remains unclear whether disruption rather than restoration is the principal in vivo function of the majority of the other complexes. In vitro both RSC and SWI/SNF complexes catalyze an equilibrium between altered and unaltered states of the nucleosome and therefore in principle could act either to disrupt or restore a nucleosome array or, alternatively, could perform both functions. A pertinent question in this context is whether, say, the remodeling processes associated with the activation and repression of a particular promoter are mediated by the same or different remodeling complexes. In many other biological processes, a greater precision in regulation is accomplished by balancing two opposing activities to determine the directionality of a reaction (Figure 3). The substantially greater abundance of RSC compared to the SWI/SNF complex in yeast suggests that while the latter can mediate local, possibly targeted, increases in accessibility, RSC may have a more general monitoring function in the maintenance of particular chromatin structures. A further indication of the potential bidirectionality of remodeling processes is the isolation of a large human multiprotein complex containing both the dermatomyosotis-specific autoantigen Mi2b, a putative remodeling engine of the CHD3 class, and the histone deacetylases HDAC1/2 (Zhang et al., 1998). Since histone deacetylation is strongly correlated with transcriptional repression and the stabilization of condensed nucleosome arrays, the implication is that this complex acts to decrease the accessibility of chromatin to transcription factors or other DNA-binding proteins. Although it is ostensibly paradoxical for chromatin condensation to require prior nucleosome disruption, a possible rationale for the engine in this case is to provide access for two associated histone-binding proteins, RbAp48/46, which contact the DNA-binding helix 1 of histone H4 (Verreault et al., 1996).

Overall the picture is one of multiple chromatin remodeling machines of disparate function that are related by a common mechanism to unravel nucleosomes. The precise biological roles of each of these complexes remain to be unraveled during the course of future investigations.

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