

Mechanisms for ATP-dependent chromatin remodelling

Andrew Flaus* and Tom Owen-Hughes†

During the past year, major advances have been made towards understanding the function of ATP-dependent chromatin-remodelling activities both *in vitro* and *in vivo*. These suggest that ATP-dependent chromatin-remodelling activities are capable of both altering the structure of individual nucleosomes and acting in concert with other forms of chromatin-modifying enzymes, to regulate the formation and decondensation of chromatin fibres.

Addresses

The Wellcome Trust Biocentre, School of Life Sciences, University of Dundee, Dundee DD1 5EH, UK

*e-mail: a.flaus@dundee.ac.uk

†e-mail: t.a.owen-hughes@dundee.ac.uk

Current Opinion in Genetics & Development 2001, 11:148–154

0959-437X/01/\$ – see front matter

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Abbreviations

| | |
|---------|--|
| ACF | ATP-utilising chromatin assembly and remodelling factor |
| CHD | chromodomain ATPase |
| CHRAC | chromatin accessibility complex |
| ISWI | imitation switch |
| RSC | remodels the structure of chromatin |
| SAGA | Spt-Ada-Gcn5-Acetyltransferase |
| SANT | putative DNA binding domains in the SWI/SNF and ADA complexes, the transcriptional co-repressor N-CoR and TFIIIB |
| SWI/SNF | mating type switching/sucrose non-fermenting |
| TBP | TATA-binding protein |

Introduction

‘Chromatin remodelling’ is an ambiguous term used to encompass a range of structural transitions that occur during gene regulation. In many cases, these include a combination of, first, non-covalent alteration of chromatin structure mediated by the binding of transcription factors or the action of ATP-dependent remodelling activities [1]; second, modification of chromatin components by covalent post-translational modification [2]; and third, alterations to the non-core histone protein content of chromatin. The combined effect of these processes is to regulate the ability of transcription, replication and repair factories to gain access to their target regions of the genome. Although there is evidence that, at least in some cases, all of these processes may act in concert, here we focus upon recent advances to our understanding of the mechanisms for ATP-dependent remodelling of chromatin structure.

Helicase-like motifs

ATP-dependent chromatin remodelling complexes can be divided into three subfamilies on functional and sequence grounds [3]. The archetypes of these subfamilies are the yeast SNF2 *Drosophila* ISWI and mouse CHD1-containing complexes. All eukaryotes appear to possess multiple forms of these ATP-dependent chromatin-remodelling activities [4,5]. Their universally conserved feature is a catalytic

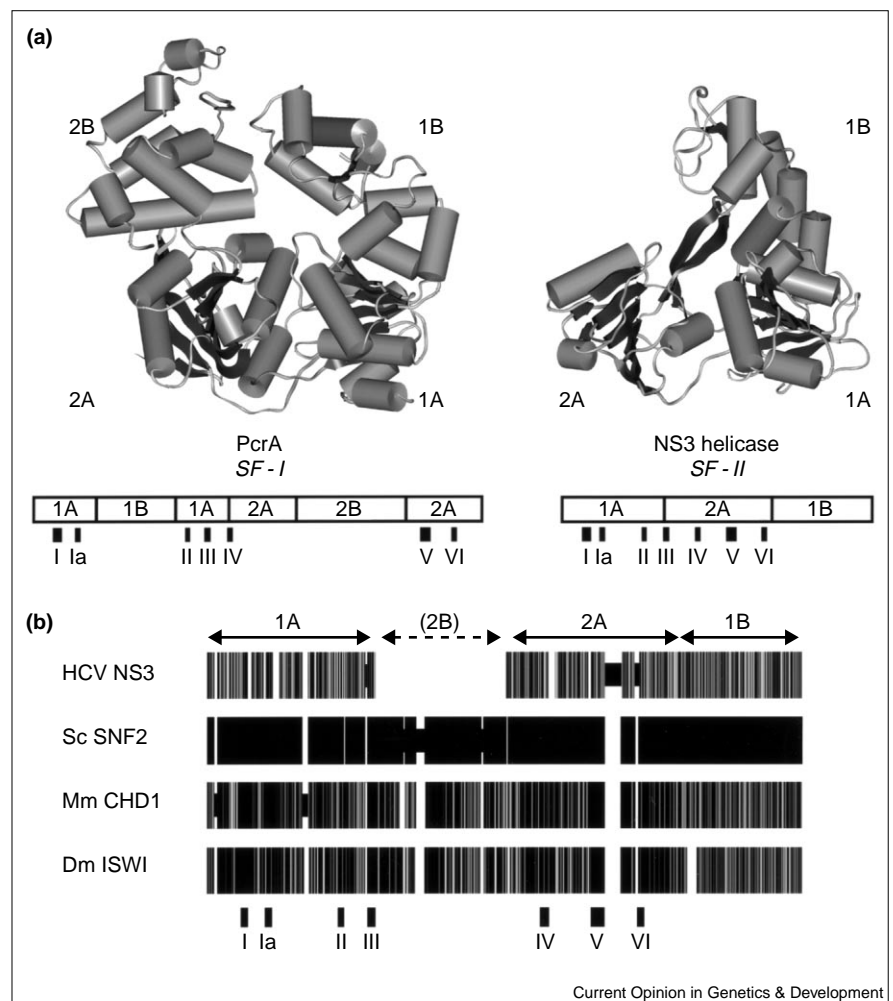
ATP-hydrolysing core that shares a region of homology with a broad collection of proteins, several of which have helicase activity. Defining this homology is an ordered series of seven short peptide boxes (Figure 1). Members of this large helicase-like grouping can be subdivided according to particular motif variations into two large subdivisions — superfamily I (SF-I) and superfamily II (SF-II) — plus a number of smaller groupings [6,7]. ATP-dependent chromatin-remodelling complexes belong to the SF-II superfamily. Recently, the crystal structures of the helicase region of a number of SF-I members, along with the SF-II member Hepatitis C virus NS3 RNA helicase, have been determined. Despite the superfamilial distinction, the SF-I and NS3 helicases have similar overall structures (Figure 1). The major differences are that NS3 lacks one of the four domains present in the SF-I structures and the order in which the structural features are threaded together is different. Alignment of helicase-like motifs of Snf2, ISWI and CHD1 with the NS3 RNA helicase reveals that the number of amino acids between motifs is generally similar in all cases except III–IV, where the remodellers have ~180 residues in place of the 37 in NS3 (Figure 1a). As the size of the 2B domain absent in NS3 but occurring in the SF-I structures is typically 160 amino acids, it is possible that the ATP-dependent remodellers contain an equivalent to this domain. Furthermore, secondary structure predictions of this region of SNF2 (residues 935–1106) are all-helical, consistent with the fold of domain 2B in SF-I structures (C Bond, personal communication).

Helicase motives?

A helicase is an enzyme that processively catalyses separation of DNA strands. Despite the similarity which catalytic subunits of ATP-dependent remodelling activities share with *bona fide* DNA helicases, none have been found that can function in classic strand-displacement assays for DNA helicase activity. What, then, could be the function of the SNF2-like ATPase motors? A clue may come from the DNA-translocating subunits of type I and type III restriction enzymes that are also SF-II members and do not possess helicase activity. Recently, a range of approaches have been used to show that the translocating HsdR subunits of type I enzymes spool DNA through them in an ATP-dependent manner which results in them moving or tracking along DNA [8,9*–13*]. Rotation is an inevitable outcome of DNA tracking by any processive enzyme as all regular binding surfaces on DNA are arrayed helically. In the case of type I restriction enzymes, this rotation is constrained between the DNA binding and translocating subunits, resulting in the accumulation of superhelical stress in the intervening DNA which has been detected through the use of eubacterial topoisomerase and atomic force microscopy [10*,11*]. The DNA repair protein Rad52 is more closely related to SWI/SNF and has also been found capable of altering local

Figure 1

(a) Structures of broadly homologous *Bacillus stearothermophilus* PcrA helicase (left) and Hepatitis C virus NS3 helicase (right), members of SF-I and SF-II respectively, with a schematic of their distinct domain organisations. PcrA from PDB entry 1PJR [58], NS3 helicase from entry 1HE1 [59]. After Korolev *et al.* [60]. (b) Alignment of SF-II NS3 helicase with archetypal ATP-dependent remodellers yeast SNF2, mouse CHD1 and *Drosophila* ISWI showing the large domain-like insertion between motifs III and IV. Aligned residues are plotted with grey level proportional to a structure-derived substitution score [61] compared to SNF2. Blossum62-weighted alignments were made using Multalin [62] after fixing helicase-like motifs as precisely as possible [7]. Gaps show as white, narrow bars represent stretches in a single polypeptide inducing a gap. The carboxy-terminal region of the NS3 helicase domain 1B is equivalent to the signal for a randomised polypeptide (data not shown), indicating minimal homology in this region.



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DNA topology [14^{*}–16^{*}]. Recently, we have detected the ability of a representative selection of ATP-dependent remodelling activities to generate unconstrained negative superhelical torsion in both DNA and chromatin [17^{**}]. This suggests that the ability to induce changes in local DNA twist may be shared by many of the SF-II members that do not have *bona fide* DNA-helicase activity.

One motor, many chassis

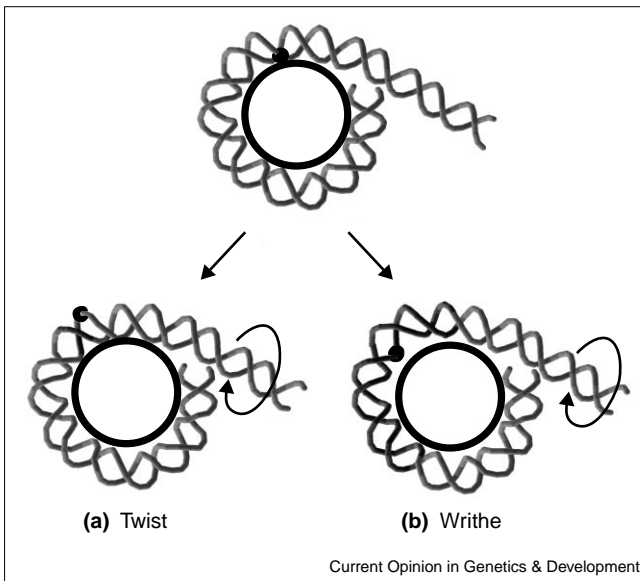
For all ATP-dependent remodellers characterised to date, single point mutations in the helicase-like motifs are sufficient to abolish their activity. Furthermore, recent studies have shown that at least some ATP-dependent remodellers maintain activity as individual polypeptides or minimal complexes [18^{*}–20^{*}], suggesting that the ATPase components are fundamental to the enzymatic action.

It is also clear that there are some differences in the activity of different ATP-dependent remodellers. For example, the activities of ISWI and Mi-2 are not stimulated by DNA alone but require histone components of nucleosomes as well. In the case of ISWI, this activity requires intact histone

tails, but for Mi-2 histone tails are not required [21^{*}–23^{*}]. These observations suggest that the catalytic domains of some remodellers interact with nucleosomal features that include both histones and DNA whereas others can interact with DNA alone. Studies of a less closely related ATPase (ADAAD) have shown that its ATPase activity is stimulated to a greater extent by single stranded/double stranded DNA transitions [24], and that of Mot1 is stimulated by TBP [25]. A simple interpretation of these observations is that the action of this family of helicase-like motors can be refined to recognise a range of different structural features.

Many ATP-dependent chromatin-remodelling activities contain other conserved motifs in addition to the helicase-like regions. Although these vary between different remodellers, they include bromodomains, SANT domains, chromodomains and AT-hooks. Many of these may provide means by which remodelling complexes may be targeted to regions of the genome with specific chromatin composition. There is also evidence to indicate that at least some remodelling activities contain components capable of directly interacting with transcription factors [26]. This provides another means by

Figure 2



Remodelled nucleosomes may accommodate superhelical tension as alterations to the localised twist and writhe of DNA. Part of the DNA backbone is illustrated wrapped around a schematic representation of the histone octamer. In each case, a single phosphate atom is coloured black as a reference point. (a) Where twist is generated, the DNA in the region of this phosphate group becomes over-rotated. (b) Where the torsion is accommodated as writhe, DNA is pushed off the surface of the nucleosome. Although most of the DNA histone contacts are not altered in each case, the accessibility of DNA in the region of the marker phosphate group is altered in both (a) and (b).

which these activities can be recruited to specific regions of the genome. *In vivo* different forms of recruitment may be combined to provide highly specific targeting.

Nucleosome mobilisation

Five research groups [27^{*}–31^{*}] have reported the ability of four different remodelling activities to alter the positions of nucleosomes along DNA, suggesting that nucleosome mobilisation may be an activity common to all remodellers. How, then, might Snf2-like motor proteins catalyse nucleosome mobilisation? The high-resolution structure of the nucleosome provides evidence in support of one means by which DNA may be moved over the surface of the nucleosome. Unequal lengths of DNA are wrapped on either side of the nucleosome, resulting in the underwinding of DNA over a region of 10bp on the shorter DNA half [32]. The application of torsion to DNA by a remodelling activity that is also tethered to a histone component of the nucleosome could result in the alteration of DNA twist on the surface of a nucleosome, as illustrated in Figure 2a. The propagation of this twist over the surface of a nucleosome would result in the movement of DNA over the surface of a nucleosome by twist diffusion as illustrated [33].

Twist diffusion is not necessarily the only consequence of applying superhelical stress to DNA on the surface of a nucleosome. Where both the torque generated by the

motor and the level to which histone DNA contacts on the surface of the nucleosome can constrain this torque are high, then DNA is likely to become distorted by a writhe component in addition to twist. This could have the effect of pushing DNA off the surface of the nucleosome (Figure 2b). As thermal fluctuations have been shown to result in the exposure of DNA sequences on the edge of nucleosomes in a similar fashion [34], it seems reasonable that remodelling activities should be able to increase the rate and extent of this exposure. Once DNA has come off the surface of the nucleosome, re-association at a different site on the octamer surface will result in the generation of a bulge or loop of DNA not bound to the octamer. This could be transmitted around the surface of the octamer by writhe diffusion as illustrated [33]. This is similar to a mechanism proposed for the transit of RNA polymerases through nucleosomes [35] and provides an alternative means to alter the positions of nucleosomes along DNA. As twist and writhe are interchangeable expressions of a change in topological linking number, it would be predicted that both forms of distortion could be combined.

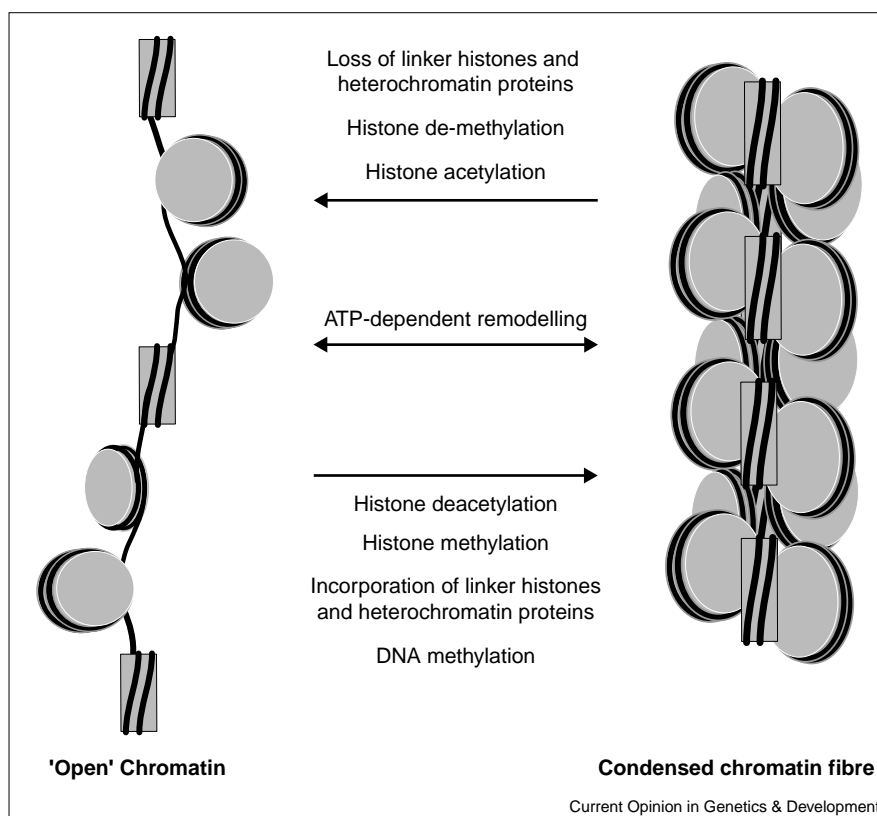
If nucleosome mobilisation occurs via pathways similar to those described above, then it would be expected that, in addition to nucleosomes at different locations, remodelled chromatin might consist of intermediates in the translocation process. Many of the properties of 'remodelled chromatin' are consistent with this. For example, the ability of nucleases and transcription factors to gain access to such distorted nucleosomes would be increased. Perhaps most strikingly it would be expected that nucleosomes remodelled in this way would have an altered ability to constrain supercoils. This is indeed the case, the linking number of DNA on these nucleosomes is altered by an average of approximately half a turn per nucleosome [36^{*}].

Recently, another form of remodelled chromatin has been characterised as having many of the properties expected for a dinucleosome [37^{*},38^{*}]. Such species could be generated as the result of the association of nucleosomes that have been moved to the end of DNA fragments such that DNA binding sites on the octamer surface are exposed [39]. It is possible that similar structures could be generated during the transfer of a histone octamer from one chromatin fibre to another [20^{*},29^{*},40^{**}]. It remains unclear, however, whether octamer transfer and dinucleosome formation can also occur in the absence of DNA ends.

Whereas the human SWI/SNF and yeast RSC complexes appear to be most effective in catalysing a full range of remodelling reactions, other remodelling activities may perform a more limited subset. For example, the ISWI-containing CHRAC and ACF complexes can promote the generation of uniformly spaced nucleosome arrays [41,42]. Thus, it seems likely that these complexes play a more specialised role in nucleosome mobilisation where generation of disrupted intermediates is not favoured [27^{*},28^{*}].

Figure 3

ATP-dependent chromatin remodelling activities may act in concert with other forms of chromatin modification to regulate higher-order chromatin folding. The order in which different forms of remodelling occur would be largely determined by which class of remodelling was recruited to a gene first. For example, in some cases histone acetylation might require prior ATP-dependent remodelling but where a HAT activity was recruited first, the reverse might be true. In other cases only one form of remodelling might be sufficient to either activate or repress transcription resulting in redundancy between different forms of remodelling.



The role of ATP-dependent remodelling during gene regulation

The γ SWI/SNF complex plays an essential role in the activation of ~3% of yeast genes and is involved in the repression of a similar number of genes [43,44]. One of the best characterised examples is the yeast *HO* promoter [45••,46••]. Here, SWI/SNF is initially targeted to the gene through an interaction with the transcription factor Swi5p. SWI/SNF action then results in the recruitment of the histone acetyltransferase activity SAGA, which acetylates chromatin over ~1Kb. Subsequently, additional factors are recruited to the promoter, eventually resulting in transcription. The observation that SWI/SNF-dependent SAGA recruitment is observed most frequently for genes expressed during mitosis suggests a role for SWI/SNF in unfolding condensed chromatin [47••]. Such SWI/SNF-mediated decondensation might expose residues required for the recruitment of SAGA and acetylation of histones mediated by SAGA could stabilise the decondensed state [48•]. In more general terms, a role for ATP-dependent remodelling in concert with other forms of chromatin modification in the assembly and decondensation of chromatin fibres is consistent with a range of observations suggesting links between the function of different modes of chromatin remodelling [49] (see Figure 3).

The disruption of nucleosomes via one of the pathways described above could provide a means to disrupt chromatin

fibres. There is growing evidence, however, to support a role for ATP-dependent remodelling activities in the repression of transcription, possibly at the level of chromatin-fibre formation [50]. One way in which remodelling activities might participate in both the assembly and disassembly of condensed chromatin involves them altering nucleosome spacing. Inter-nucleosome spacing is likely to be a key parameter influencing the ability of chromatin domains to form higher-order structures. Many ATP-dependent remodelling activities can alter nucleosome positioning, and some have been shown to be capable of manipulating nucleosome spacing over large regions of DNA [42,51]. Thus, it is possible that through a role in manipulating nucleosomal spacing ATP-dependent remodelling activities can participate in both the assembly and decondensation of chromatin fibres.

The function of other remodelling activities has not been defined in as much detail as has been possible with the SWI/SNF complex at the yeast *HO* gene. It is becoming clear, however, that although some aspects of the function of other ATP-dependent chromatin remodelling activities may be shared, others will not. For example, the yeast Chd1p like Snf2p has been found to play a role in the activation and repression of a subset of yeast genes [52••]. In higher eukaryotes, however, proteins belonging to the CHD subfamily can also be found in complexes containing histone deacetylase activities [5]. It seems likely that these

complexes will play a more specialised role in the generation of repressive chromatin via a pathway that may also involve targeting to methylated DNA [53]. There is also evidence linking the function of ISWI-containing complexes to histone acetylation and the generation of repressive chromatin [54••]. As some ISWI-containing complexes can participate in the generation of regularly spaced nucleosomes [41,42], it is possible that they may function to manipulate nucleosome spacing over large regions of the genome. The observation that the ISWI protein can play a role in the remodelling of somatic nuclei in *Xenopus* egg extracts indicates that these remodelling reactions may even occur on a genome-wide scale and result in the generation of active as well as inactive chromatin [55••]. There is also some evidence to suggest that the function of ISWI-containing complexes may be linked to DNA replication [42,56]. This illustrates that ATP-dependent remodelling complexes are likely to function in regulating genomic accessibility during DNA repair [57], recombination and DNA replication as well as transcription.

Conclusions

Biochemical studies have shown that ATP-dependent chromatin remodelling activities can alter the positions of nucleosomes along DNA, transfer histone octamer from one DNA fragment to another and generate a range of other remodeled intermediates. Over the past two years, several members of the SF-II superfamily of helicase-like proteins have been shown to be capable of altering the twisting of DNA fragments. Most recently, this has expanded to include certain ATP-dependent chromatin-remodelling activities. This may provide a means by which these complexes are able to generate a range of remodeled intermediates. Despite the rapid progress, our understanding of the function of these complexes *in vitro* cannot fully explain the ways in which ATP-dependent chromatin-remodelling activities are observed to function *in vivo*. This may result in part from the fact that a complex mixture of different species can be generated as a result of remodelling. In addition, recent observations made *in vivo* suggest that ATP-dependent chromatin remodelling may alter higher-order chromatin folding as well as mononucleosome structure. Unfortunately, current biochemical techniques are limited in their suitability for verifying this *in vitro*.

Update

Consistent with the idea that nucleosome remodelling involves alterations to DNA twisting, it has been shown recently that the ability of the yeast SWI/SNF complex to alter nucleosomes is reduced on small circular templates where the ability to alter DNA topology is constrained [63••]. In a separate study, additional evidence has been obtained to support the idea that dinucleosome-like intermediates are generated as the result of the association of two partially unwound mononucleosomes [64••]. Characterization of the changes to chromatin structure that occur during gene regulation has shown that in some cases ATP-dependent chromatin remodelling is required prior to histone acetylation [65•] as in

the case at the yeast HO promoter, whereas in others histone acetylation is a prerequisite for ATP-dependent remodelling [66•,67••]. Thus, although an ordered sequence of remodelling events may be required during the regulation of many genes, the sequence in which different forms of remodelling occur is not fixed. The important role that ATP-dependent remodelling is likely to play in the establishment of developmentally regulated patterns of gene regulation is illustrated by the observation that deletion of both copies of the mouse *BRG1* gene is lethal at a very early stage in development. *BRG1* heterozygous mice are predisposed to exencephaly and epithelial tumors [68•]. Consistent with this there is increasing evidence to suggest that mutations to components of the hSWI/SNF complex are causative for human cancers [69–71].

Acknowledgements

A Flaus is a Human Frontiers Science Programme (HFSP) long-term fellow, T Owen-Hughes is a Wellcome Trust Career Development Fellow. We would like to thank David Norman, Charlie Bond, Neil Perkins and Iestyn Whitehouse for useful comments and assistance and Robert Kingston for communicating results prior to publication.

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