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ATP-dependent chromatin remodeling activities

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Abstract. Genetic and biochemical approaches have indicated that the packaging of DNA into chromatin can be repressive to transcription [1]. ATP-dependent chromatin remodelling activities can facilitate transcription from chromatin templates [2]. Consistent with this, biochemical assays have shown that the action of ATP-dependent chromatin remodelling activities increase the accessibility of DNA within chromatin templates [3]. However more recent functional studies suggest that many ATP-dependent chromatin remodelling activities can also function as repressors of transcription. Here we review recent advances to our understanding of the biological function of these complexes. We then consider some of the mechanisms by which ATP-dependent chromatin remodelling activities together with other forms of chromatin remodelling or modifying enzymes may act to regulate genomic accessibility either positively or negatively.

Key words. ATP-dependent chromatin remodeling; SWI/SNF; gene regulation.

Introduction

All Snf2-related ATP-dependent chromatin-remodelling activities contain a region of homology that is shared by an extended family of proteins that include some known DNA and RNA helicases [4]. The chromatin-remodelling activities that share this homology can be further classified based upon similarity extending beyond the helicase-like regions into subfamilies that are most similar to Snf2, ISWI and CHD1. Recent advances to our understanding of the biological function of each of these subclasses are given briefly below.

The Snf2-like subfamily

The yeast SWI/SNF complex was first identified through screens for genes involved in the regulation of the HO endonuclease and SUC2 genes [5]. The catalytic subunit of the SWI/SNF complex, Snf2/Swi2 has been found to have homologs in a wide range of species from *Saccharomyces cerevisae* to human. These proteins all contain a DNA-dependent ATPase domain as well as a C-terminal bromodomain and are found in multiprotein complexes (see table 1).

Whole genome analysis has shown that SWI/SNF mutations affect the expression of approximately 6% of yeast genes. However, it is possible that chromatin remodelling is far more widely involved in transcriptional regulation than these figures suggest. Functional redundancy between different ATP-dependent chromatin-remodelling complexes [6, 7] and between ATP-dependent chromatin remodelling activities and histone acetyltransferases [8, 9] may mean that ATP-dependent chromatin remodelling plays a more global role in transcription than is suggested by the gene-chip experiments that have been performed to date. However, it is clear that dependence on ATP-dependent remodelling varies between different genes and at different stages in the cell cycle. Whereas ATP-dependent chromatin remodelling by the SWI/SNF complex can represent a temporally distinct and essential step in the regulation of genes such as the HO endonuclease promoter during mitosis [10–12], this is not generally true at all genes and at other stages in the cell cycle [12]. Whole genome analysis has also revealed that Snf2 functions as a repressor at about half of the genes that show altered expression in a *Snf2* Δ strain [13, 14]. Hopefully it will soon be possible to use similar approaches to dissect the biological function of the more abundant RSC (remodels the

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Table 1

Complex	Snf2p-like subunit/	Other subunits	Biochemical properties	Biological functions
The Snf 2-like subfamily				
SWI/SNF	Swi2/Snf2 *S.cerevisiae*	Swi1, Snf5, Snf6, Snf11, Swi3, Swp29/Taf_{II}30/ TFG-3, Swp82, Swp 59/Arp9, Swp61/ Arp7, Swp73/ Snf12	DNA-stimulated ATPase activity [61]. Capable of disrupting the nuclease digestion pattern of nucleosomes in a way that stimulates transcription factor binding [61]. Can cause nucleosomes to be displaced in cis or trans [50]. Association with DNA or chromatin creates loops.	Nonessential, but affects either the activation or repression of around 6% of yeast genes [13, 14]. Can be recruited through interactions with transcription factor activation domains [26]. Functions together with HAT activities to activate transcription of several genes during mitosis [10–12].
RSC	Sth1/Nsp1 *S. cerevisiae*	Sfh1, Rsc8/Swh8, Rsc6, Rsc11/ Arp7, Rsc12/ Arp9, Rsc1, Rsc2, Rsc3-5,-7,-9,-10, Rsc13-15	DNA-stimulated ATPase activity disrupts the nuclease digestion pattern of nucleosomes 15]. Can displace histone octamer in trans and generate dinucleosome-like intermediates [2].	STH1 and several other genes encoding RSC components are essential for viability in yeast [15, 62]. RSC is present in 10 × times the amount of SWI/SNF in the cell [15]. RSC may function in the activation and repression of transcription [16, 17]
INO80.com	Ino80 *S. cerevisiae*	Arp8, p100, p90, Arp5, Arp4, Rvb1, Rvb2, Act1, p32, p28, p26 1-1.5 MDa	DNA-stimulated ATPase activity. Contains Rvb1 and Rvb2, which are both present as hexamers and share homology to the bacterial holiday junction helicase RuvB. Rvb1 and Rvb2 function in strand displacement assays for 3′ to 5′ helicase activity [63].	INO80 deletions cause reductions in the levels of INO1, PHO5 and Ty1 gene expression and have DNA repair phenotypes [63, 64].
Brahma	BRM *Drosophila*	MOR, Bap111, Bap60, Bap55, Bap47, Bap45, OSA, p170, p26	BRM displays weak nucleosome spacing ability in comparison to ISWI, but is an essential cofactor for Zeste mediated transcription from chromatin templates [65].	The brm gene was isolated as a dominant supressor of Pc mutations suggesting that it plays a role in the activation of homeotic genes [66].
E-RC1	hBRG1, human	Baf170, Baf 155, Baf 47, Baf 57.	ATP-dependent mono-nucleosome disruption activity.	E-RC1 acts as a coactivator for tissue specific transciptional regulation of the chromatin assembled erythroid (-globin gene by EKLF in vitro [67].
hBRG1	hBRG1 human	BAF250,BAF170, BAF 155, BAF 60, BAF57, BAF 53, (β-actin, BAF 47, INI1, Snf5, BRAC1 [68]. Note that composition varies [69].	ATPase is DNA dependent. hBRG1 is capable of remodelling nucleosomal arrays in an ATP dependent manner, with a higher specific activity then hBRM. Capable of octamer transfer as well as interconverting nucleosomes between a base and remodelled state [2].	BRG1 is involved in the activation of transcription from the MMTV promoter via GR and is recruited to estrogen-responsive promoters during hormone induction [23]. Signalling pathways can regulate the association of BRG 1 with the chromatin matrix [70]. However, BRG1 also participates in the repression of trancription, e. g. that mediated by Rb [71] and c-fos [21].
hBRM	hBRM human	Similar to BRG1	Similar to BRG-1, though slightly lower specific activity.	Similar to BRG-1
ISWI-like subfamiliy				
ISW1	ISW1p *S. cerevisiae*	P110, p105, p74	ATPase is nucleosome dependent. Can generate regularly spaced nucleosomes from a disordered array.	Partial redundancy with CHD1 and ISWI2 [6].
ISW2	ISW2p *S. cerevisiae*	P140	ATPase is nucleosome dependent. Can generate regularly spaced nucleosomes from a disordered array.	Partial redundancy with CHD1 and ISWI2 [6].
NURF	ISWI *Drosophila*	Nurf-55, p125, Nurf-38- inorganic pyrophosphate	Nucleosome stimulation of ATPase activity requires one or more of the H3/H4 histone tails [72]. Facilitates transcription – factor – mediated disruption of physiologically spaced arrays in complex with histone chaperones	ISWI is essential for *Drosophila* development. It does not co-localise with RNA polymerase. ISWI appears to play a role in maintaining chromosome structure [30].

Table 1 (continued)

ACF	ISWI *Drosophila*	Acf1 [73]	ATPase is nucleosome dependent. ACF promotes the assembly of chromatin and the subsequent spacing into chromatin consisting of regularly spaced arrays. It also mediates the remodelling of arrays by Gal4-VP16 [73].	ISWI is essential for *Drosophila* development. It does not co-localise with RNA polymerase. ISWI appears to play a role in maintaining chromosome structure [30].
dCHRAC	ISWI *Drosophila*	Topoisomerase II, p175, p20, p18, CHRAC-14, CHRAC-16 [74]	ATPase requires a nucleosome template and intact histone tails [75]. dCHRAC can increase chromatin accessibility or regularly space nucleosomal arrays. ISWI only binds to nuclesomes if they contain over 147 bp of DNA [75].	ISWI is essential for *Drosophila* development. It does not co-localise with RNA polymerase. ISWI appears to play a role in maintaining chromosome structure [30]. Likely to play a specialised role in chromatin remodelling in early embryos [74].
ISWI-D	ISWI-D *Xenopus*	xISWI, p195	Nucleosome stimulated ATPase, participates in the remodelling of somatic nuclei in vitro [31].	Not known
RSF	HSnf2h human	P325	ATPase is nucleosome dependent. RSF functions in nucleosome spacing assays and can direct VP16-mediated transcription from chromatin templates [76].	Not known
hACF	hISWI (hSnf2h/ hSnf2l) human	hACF1 (WCRF180) 300–400 kDa	Nucleosome-stimulated ATPase activity. Has nucleosome spacing and remodelling activity [77]. This complex may be closely related to hCHRAC and WCRF.	Mouse homolog of hACF1 localizes to heterochromatin [78], suggesting a role for this complex in repression.
hCHRAC/ hACF	hISWI (hSnf2h/ hSnf2l) human	HuCHRAC-15, HuCHRAC-17, hACF (WCRF180) 800 kDa	ATPase is DNA dependent, although it is stimulated >3-fold more when DNA is packaged into nucleosomes. hCHRAC can increase chromatin accessibility or regularly space nucleosomal arrays [79]. This complex may be closely related to hACF and WCRF.	Mouse homolog of hACF1 localizes to heterochromatin [78], suggesting a role for this complex in repression. hACF1 is closely related to WSTF a gene deleted in Williams syndrome.
WCRF	hISWI (hSnf2h/ hSnf2l) human	WCRF180 (hACF1)	DNA-dependent ATPase-stimulated 2-fold further in the presence of nucleosomes. Functions in mononucleosome disruption assays [80]. This complex may be closely related to hACF and hCHRAC.	Mouse homolog of hACF1 localises to heterochromatin [78], suggesting a role for this complex in repression. WCRF180 is closely related to WSTF a gene deleted in Williams syndrome.
The CHD subfamily				
Chd1p	CHD1/ *S. cerevisiae*	Not known	Has nucleosome disruption activity that is distinct from SWI/SNF [7].	In yeast involved in the regulation of 2–4% of yeast genes. Approximately 1000 molecules/cell. Chd1p is partially redundant with SWI/SNF complex, ISWI1 and ISWI2 [6, 7].
HRP1	HRP1 *S. pombe*	Not known	DNA-stimulated ATPase activity. DNA binding domain binds AT-rich stretches [81].	Hrp1 plays a role in chromosome separation in mitosis [37].
Mi-2	CHD4 *Drosophila*	dRPD3, likely to contain other subunits, native MW 1 MDa	ATPase activity is stimulated by nucleosomes, but does nor require intact histone tails. Able to relocate nucleosomes along DNA in cis. dMI-2 will bind 146 bp mononucleosomes [75].	Interactions with *Drosophila* Hunchback protein. Functions in both Hunchback- and Polycomb-mediated repression in vivo [42].
CHD1	CHD1/ *Drosopila*/ mouse	Not known	Both chromodomain and helicase-like domains are essential for association with chromatin. DNA binding domain binds AT-rich stretches. [82] Not known if CHD1 can disrupt chromatin.	Associated with actively transcribed chromatin [36].

Table 1 (continued)

Complex	Snf2p-like subunit/	Other subunits	Biochemical properties	Biological functions
The CHD subfamily				
Mi-2	CHD4 *Xenopus*	RPD3 (HDAC1/2), RbAp 48 MBD3, MTA1 like, p66	ATPase activity is stimulated by nucleosomes, but does not require intact histone tails. Able to relocate nucleosomes along DNA in cis. ATPase activity stimulates HDAC activity in certain contexts [52].	May be associated with methylation-induced gene silencing [83].
Mi-2	CHD4 but also CHD3 mouse	HDAC1/2, RbAP48, Icaros1, 2, 7, Aiolos	ATPase activity stimulated by nucleosomes. Capable of altering DNA topology in a manner similar to SWI/SNF. [44]	Involved in T cell development. Icaros proteins target NuRD to heterochromatic regions [44].
NuRD oor NURD	CHD3 and/ or CHD4 human	HDAC 1 and 2 RbAp46 and 48 MBD3, MTA2 there are likely to be more as yet uncharacterized subunits	ATPase is stimulated to progressively greater extent by DNA mononucleosomes and oligonucleosomes, respectively [40]. Has nucleosome disruption activity that is distinct from SWI/SNF [39]. ATPase activity stimulates HDAC on mononucleosomes but not nucleosome arrays [38, 39]. Recruited to methylated DNA by MBD2 [84].	Initially characterized as an autoantigen in a human connective tissue disease. May be associated with methylation-induced gene silencing and heterochromatin [84]. Interacts with a component of DNA repair machinery [46]. May play a role in E7 transformation [85, 86].
ATRX	ATRX	Not known	The ATRX complex has not been biochemically characterized however it contains PHD zinc fingers and an ATP-dependent helicase domain that are required for its function [87–89].	Mutations in the gene that code hATRX cause severe syndromal mental retardation associated with α-thalassemia. ATRX is localised to heterochromatin including rDNA repeats, where it plays a role in conferring patterns of DNA methylation [89].

structure of chromatin) complex [15]. Genetic analysis of the function of this complex has been hindered by the fact that it is essential for viability in yeast. However, there is evidence to suggest that this complex can function in both the activation and repression of transcription [16, 17].

Although it has not yet been possible to perform global analysis of the expression of mammalian members of the Snf2 subfamily, a similar picture is emerging in which these complexes may also function in both the activation and repression of transcription. hBRG1 and Rb cooperate to repress the activity of E2F1 [18]. hBRG1 is capable of binding E2F1 directly [18, 19]. Recently, it was found that BRG1 is required for Rb to functions, cell lines lacking endogenous BRG1 are resistant the antiproliferative action of Rb [20]. Similarly, BRG1 has been found to function in the repression of expression from the c-*fos* protooncogene [21]. c33A cells which lack both functional Rb and BRG1 were used to demonstrate that although c-*fos* was marginally inhibited by either Rb or BRG-1 on their own, transcription was greatly decreased in the presence of Rb and BRG-1. Thus, in this case BRG-1 and Rb are once again partners in the department of repression.

BRG1 and Brm can also function as transcriptional coactivators. In humans, hSWI/SNF complexes function as coactivators of GR, ER, *hsp70* and C/EBP-β-regulated gene expression [22–24]. In *Drosophila* the Brhama complex appears to function to counter polycomb-mediated repression [25]. Recently, it has become clear that the activation domains of a number of transcription factors interact directly with the SWI/SNF complex [26]. This provides a mechanism by which SWI/SNF complexes can be targeted to active genes, providing an explanation for the localisation of some hSWI/SNF components to active chromatin [27]. There may be other means by which SWI/SNF complexes can be targeted to specific regions of the genome. The bromodomain is a structural motif which is present in all members of the SWI/SNF family of chromatin remodellers. This 110-amino acid motif was first discovered in *Drosophila* Brahma [25]. Subsequently, two bromodomains have been shown to interact directly with acetylated histone tails [28, 29]. Therefore, the acetylation of histones provides another means by which chromatin-remodelling activities may be targeted.

The ISWI-like subfamily

Members of the ISWI (Imitation Switch) subfamily contain an ATPase with homology to the *Drosophilia* ISWI protein and contain a SANT (swi3, ada2, N-CoR and TFIIIB B) domain. It appears likely that all eukaryotes contain several multiprotein complexes that contain members of this family of proteins (see table 1). Several of these complexes have been purified using biochemical assays for chromatin remodelling. Currently, a major challenge is to define the biological roles of this family of complexes. Genetic analysis of the function of ISWI family members in yeast has been complicated by the fact there are two ISWI family members in *S. cerevisiae* that display signs of functional redundancy [6]. Furthermore, there are genetic links between the yeast ISWI proteins and yCHD1 [6] and between yCHD1 and SWI/SNF [7] that provide an additional levels of redundancy.

In *Drosophila* disruption of the genes encoding ISWI causes individuals to die as late larvae or early pupae [30]. Examination of the structure of salivary gland polytene chromosomes from these mutant larvae revealed abnormalities in the structure of the male X chromosome, suggesting ISWI plays a role in maintaining chromosome structure. The subcellular localisation of dISWI shows it to be associated with a number of euchromatic and heterochromatic sites in mitotic and polytene chromosomes. ISWI does not colocalise with RNA polymerase, but instead appears to be primarily associated with non-transcribing regions of chromosomes [30]. ISWI proteins have been isolated in a number of different complexes that can function in biochemical assays for nucleosome spacing, and the activation of transcription from chromatin templates (see table 1). Most recently, it has been reported that ISWI participates in the remodelling of somatic nuclei in *Xenopus* egg cytoplasm [31]. Thus, ISWI complexes may participate in the remodelling of chromatin at a genome-wide level.

The CHD subfamily

In addition to helicase-like motifs, the CHD subfamily of proteins contain chromo (chromatin organization modifier) domains and DNA binding domains [32]. Chromodomains are found in a variety of proteins many of which have the ability to interact with heterochromatin such as HP1, Polycomb and Su(var)3-9. Although the means by which chromodomains are targeted to heterochromatin has not been fully characterised, this may involve binding to methylated H3 [T. Kouzarides personal communication] or RNA molecules [33]. In addition, chromodomain-containing peptides are able to self-associate, providing chromodomain-containing proteins the ability to form complexes with each other in addition to other heterochromatin components [34]. The DNA-binding motifs present in many CHD proteins are related to motifs present in H1, HMGI/Y and preferentially interact with AT-rich DNA sequences via minor-groove interactions [35].

In *S. cerevisiae* there is one CHD member, Chd1, which is present at approximately 100 copies per cell in a 340-kDa complex [7]. In both *S. cerevisiae* and *S. pombe*,

CHD1 deletions are viable, but have detectable phenotypes such as 6-AzU sensitivity [36] and chromosome instability [37]. Genome-wide analysis has since shown that 2–4% of the *S. cerevisiae* genes are affected by CHD1 deletion more than two-fold and that CHD1 functions to both activate and repress transcription [7]. Although CHD1 affects transcription of a specific subset of yeast genes, chromatin imunoprecipitation (CHIP) analysis has shown that CHD1, unlike the yeast SWI/SNF complex, is not specifically recruited to genes that are affected by CHD1 mutations [7]. Nonetheless, a degree of functional redundancy between the SWI/SNF and CHD1 complexes is suggested by the finding that CHD1 mutations are synthetically lethal with mutations to components of the SWI/SNF complex [7].

Over the last few years a series of studies have resulted in the identification of CHD protein containing complexes associated with histone deacetylases and methylated DNA-binding proteins (see table 1). These include the NuRD or Mi-2 chromatin-remodelling complexes, the catalytic subunits of which contain two chromodomains and two PHD zinc fingers. Initial investigations demonstrated that CHD4 was able to form stable interactions with components of the of the previously characterised corepressor complex sin3 [38–41]. Biochemical evidence suggests that the PHD zinc fingers of CHD4 are required to form an interaction with HDAC proteins [40], and it is notable that other members of the SNF2 family that do not contain such motifs do not associate with histone deacetylases [39]. A functional interaction between these two activities is suggested by the finding that NuRD-mediated repression of the thyroid hormone receptor relies on both chromatin-remodelling and histone deacetylation [39]. That NuRD is involved in repression is further evidenced by a study which demonstrates that the *Drosophila* dMi2 protein is involved in polycomb repression of HOX genes [42]. dMi-2 (a relative of human CHD3 and CHD4) interacts with the D-Box repression domain of hunchback, a protein required for repression of homeotic genes. This ability to repress homeotic genes is abrogated by point mutations to the ATPase domains of Mi-2, demonstrating the importance of ATP-dependent remodelling in the repression process.

The Icaros family of nuclear receptors are sequence-specific DNA-binding proteins [43]. Yeast two-hybrid analysis demonstrated that Icaros is a constituent of the mouse NuRD complex [44]. Furthermore, imunofluorescence studies indicate that NuRD colocalises with Icaros to heterochromatic regions. This Icaros-NuRD complex possesses both chromatin remodelling and histone deacetylase activities, which raises the possibility that Icaros's repressive function is mediated by a chromatin-remodelling event. Differential subnuclear localisation is an interesting feature of the CHD proteins, and provides evidence regarding their biological function. Whereas dCHD1 has been localised to puffs in interband regions of polytene chromosomes, suggesting a role in gene activation, CHD3 and -4-containing complexes have been found associated with heterochromatic and inactive regions [36, 44, 45]. Thus there may be major functional differences between CHD1- and CHD3/4-containing complexes.

Recently, human NuRD has been reported to interact with the phosphatidylinositol kinase (PIK)-related kinase ATR, suggesting a role in the maintenance of DNA integrity [46]. This ATR-NuRD complex displayed DNA-damage-stimulated histone deacetylase activity. This provides one of a growing number of associations between proteins involved in DNA repair and ATP-dependent chromatin remodelling. However, in this case the importance of ATP-dependent chromatin remodelling to the function of the complex is not certain, as no nucleosome disruption activity has been detected.

Mechanisms for ATP-dependent chromatin remodelling

The ability of ATP-dependent chromatin-remodelling activities to disrupt chromatin structure has been studied using a variety of biochemical assays over the last 6 years [47]. Most of these assays detect the ability of ATP-dependent chromatin-remodelling activities to increase the accessibility of DNA within chromatin, which would be consistent with the ability of chromatin-remodelling activities to function during the activation of transcription. By increasing the accessibility of DNA within chromatin, remodellers would improve the probability that regulatory protein will be able to bind their cognate sites within a chromatin environment. However, given the functional data presented above, there is also a need to determine mechanisms by which ATP-dependent chromatin-remodelling activities may act to repress transcription. Some of these are described briefly below:

Alteration of nucleosome posotitioning

Recently, it has become apparent that many ATP-dependent chromatin-remodelling activities can alter the positions of nucleosomes along DNA [48–52]. In theory, this could provide a means by which nucleosomes could either be moved so as to expose or occlude gene regulatory elements. However, it is likely that this reaction will be biased in favour of the exposure of regulatory sequences. Random movement of nucleosomes will result in the transient exposure of sequences between nucleosomes, which will provide an opportunity for regulatory proteins to gain access. Once bound, these factors may prevent the movement of nucleosomes into positions that once again impede binding [53].

Alteration of global nucleosome spacing

The ability to alter the position of nucleosomes along DNA provides a means by which the average spacing between nucleosomes could be altered within entire domains of chromatin. One ATP-dependent chromatin-remodelling activity, CHRAC, has been shown to be capable of catalysing such global changes to nucleosome positioning [54]. Several studies suggest that nucleosomes become more closely spaced within active chromatin domains [55–57]. Changes to nucleosomal spacing are likely to alter the ability of nucleosomal arrays to adopt more highly condensed structures. Thus, by altering global nucleosome spacing ATP-dependent chromatin-remodelling activities may favour the condensation or decondensation of repressive higher-order chromatin structures and so favour activation or repression of transcription.

Direct effects on higher-order chromatin folding

The biophysical techniques currently available for the study-higher-order chromatin folding all suffer from limitations. This means that to date it has been impossible to test whether ATP-dependent chromatin-remodelling activities can directly participate in the assembly of higher-order chromatin structures. Recent evidence such as the important role the ySWI/SNF complex plays in the regulation of genes during mitosis where genes have to be expressed from condensed chromatin make this an attractive possibility. It will, however, be fascinating to determine whether human forms of the SWI/SNF complex function similarly. Human forms of the SWI/SNF complex are excluded from mitotic chromatin [58, 59], thus, they are most likely to function during the later stages of mitosis as the complexes reassociate with chromatin.

The mechanisms described above provide pathways by which ATP-dependent chromatin-remodelling activities may directly participate in repression. In addition, these pathways are also reversible, and so could provide a means by which ATP-dependent chromatin-remodelling activities could function in the activation of transcription through the decondensation of repressive chromatin. However, there is accumulating evidence to suggest that different forms of chromatin-remodelling activity cooperate to manipulate chromatin structure. These include posttranslational modification of histones by acetylation, methylation and phosphorylation, and DNA methylation.

How, then, might all these different activities cooperate during repression of transciption? One possibility is that all these activities could influence chromatin structure at the level of higher-order folding. The role of histone tails in chromatin folding is well established [60]. If ATP-dependent activities also participate in this process, it is easier to understand the close relationship between these different classes of chromatin remodelling activity.

In summary, it is clear that although ATP-dependent chromatin-remodelling activities all share a conserved motif, they can function in diverse aspects of gene regulation. Historically, much effort has been devoted to studies of the biochemical mechanisms by which ATP-dependent remodelling activities increase chromatin accessibility. However, the evidence emerging from in vivo studies suggests that at least a subset of ATP-dependent chromatin-remodelling activities reduces chromatin accessibility. This makes the idea that a proportion of these complexes function at the level of higher-order chromatin folding attractive.

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