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Minireview

Dynamic chromatin: concerted nucleosome remodelling and acetylation

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Abstract

The flexibility of chromatin that enables translation of environmental cues into changes in genome utilisation, relies on a battery of enzymes able to modulate chromatin structure in a highly targeted and regulated manner. The most dynamic structural changes are brought about by two kinds of enzymes with different functional principles. Changes in the acetylation status of histones modulate the folding of the nucleosomal fibre. The histone-DNA interactions that define the nucleosome itself can be disrupted by ATP-dependent remodelling factors. This review focuses on recent developments that illustrate various strategies for integrating these disparate activities into complex regulatory schemes. Synergies may be brought about by consecutive or parallel action during the stepwise process of chromatin opening or closing. Tight co-ordination may be achieved by direct interaction of (de-)acetylation enzymes and remodelling ATPases or even permanent residence within the same multi-enzyme complex. The fact that remodelling ATPases can be acetylated by histone acetyltransferases themselves suggests exciting possibilities for the co-ordinate modulation of chromatin structure and remodelling enzymes.

Keywords: ATPase; HAT; histone modification; repair; transcription.

Introduction

The chromatin organisation of eukaryotic genomes serves to store the genetic information within the confines of the eukaryotic nucleus, to protect it from damage and to orchestrate its use. Information management in the nucleus involves tuning of gene expression in response to the demands of a changing environment. The dynamic nature of chromatin that allows genes to be switched on or off within minutes after an inducing signal are best illustrated by two of the most rapid reversible transitions of chromatin structure. The folding of the nucleosomal fibre is strongly affected by acetylation of histones at their conserved N-terminal domains. Domain-wide acetylation levels and local enrichment of particular acetylated histone isoforms are negotiated by families of antagonising enzymes, the histone acetyltransferases (HATs) and histone deacetylases (HDACs); for more detailed summaries of these enzymes and their subunit composition, see Eberharter and Becker (2002), Vaquero et al. (2003), and Yang (2004a). In general, histone acetylation correlates with open, active chromosomal domains; repressed chromatin is usually hypoacetylated. The histone N-termini are required for folding of the nucleosomal array into 30-nm fibres, the next level of chromatin organisation, which is prevented by high levels of acetylation (Eberharter and Becker, 2002). Acetylated lysines may also help define binding sites for downstream regulators.

By contrast, ATP-dependent nucleosome remodelling factors act at the level of the nucleosome, the basic structure that chromatin is built on [for a comprehensive listing of nucleosome remodelling factors, their subunit composition and functions, see Eberharter and Becker (2004)]. A nucleosome is made up of 147 base pairs of DNA wound around an octamer consisting of four 'core' histones. The DNA is held in place by a multitude of weak interactions that collectively render the nucleosome a rather stable structure. Remodelling factors interact with the DNA and histone moieties of canonical nucleosomes. ATP binding and subsequent hydrolysis is thought to trigger a series of conformational changes within the enzyme that lead to partial detachment of DNA from the histone surface. Depending on the precise nature of this disruption and on the involvement of cofactors, such as histone or DNA chaperones, the remodelling action may lead to partial or complete disassembly of the histone octamer, or to the relocation of intact nucleosomes on DNA (Eberharter and Becker, 2004). In the absence of cofactors that trap the 'remodelled' state, reversion to the canonical structure is rapid. Chromatin that is subject to ATP-dependent remodelling can thus be considered 'vibrant' or 'fluid'. Remodelling may render nucleosomal DNA accessible but this does not necessarily correlate with activation of the underlying gene, as both activators and repressors may profit from transient accessibility. Furthermore, nucleosome relocation ('sliding') may serve to clear an area of DNA, but may also be used to 'iron out' inhomogeneity in the nucleosomal array, thereby promoting its folding into states that are more compact.

A breakthrough in our ability to identify primary targets of regulators of chromatin structure has been the widespread application of chromatin immunoprecipitation (X-ChIP) methodology to monitor the interaction of

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HAT/HDACs and remodelling enzymes with regulatory elements *in vivo* at high resolution. It now appears clear that histone acetylation and nucleosome remodelling systems are involved in the control of most, if not all, gene activity. The rules that apply to regulation of transcription may be generalised to include all other nuclear functions with chromatin substrate, be it the replication of the genome (Zhou et al., 2005), meiotic recombination (Yamada et al., 2004), the repair of damaged DNA (for a review see Peterson and Cote, 2004) or chromosome metabolism throughout the cell cycle and meiosis (De La Fuente et al., 2004). These processes are all governed by protein factors that recognise DNA features, such as a particular sequence, a break or a distortion of DNA that arises from a damaging insult. Interestingly, while some enzymes appear clearly dedicated to one particular process, such as the Mi2 ATPase that resides with histone deacetylases in NuRD complexes that appear dedicated to transcriptional repression (Feng and Zhang, 2003; Bowen et al., 2004), other remodelling enzymes, such as the SWI/SNF (BAF) complexes, contribute to regulation of different processes, such as gene activation and repression, replication and immunoglobulin gene recombination (Eberharter and Becker, 2004). Given the widespread activities of both classes of enzymes, it is not surprising to find that deregulation of their activity may lead to disease (Cho et al., 2004).

Histone acetylation and ATP-dependent nucleosome remodelling activities are frequently integrated into common regulatory pathways and the first ones to be discovered have been described in excellent reviews (Narlikar et al., 2002; Neely and Workman, 2002; Vaquero et al., 2003). This mini-review aims to discuss some of the more recent experimental observations that corroborate earlier concepts but also add novel twists. The action of HATs/HDACs and nucleosome remodelling enzymes may be orchestrated by different strategies. Each complex may be independently recruited to target sites through interactions with bound proteins or other chromatin marks (Figure 1A). The action of one enzyme may lead to tuning in the other type of complex (Figure 1C). The two types of activities may become transiently associated through physical contact between subunits of their respective complexes, but stable complexes containing both acetylation and ATPase subunits are also possible (Figure 1B). Finally, one activity may directly modulate the activity of another enzyme, notably in the acetylation of nucleosome remodelling ATPases (Figure 1D).

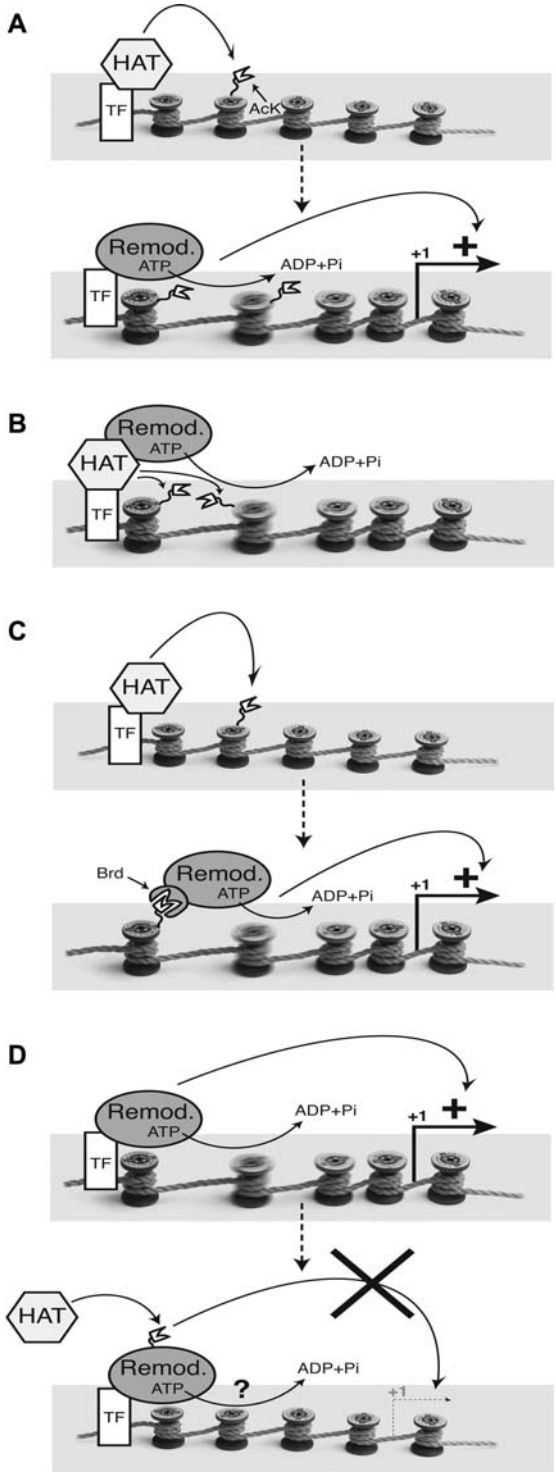

Figure 1 Models for the interplay between ATP-dependent remodelling complexes (Remod.) and histone acetyltransferase complexes (HAT).
(A) Recruitment of a HAT complex by a transcription factor, and histone acetylation (AcK), precedes the targeting of a nucleosome remodelling complex and leads to transcriptional activation. The opposite situation (Remod. precedes HAT) may also occur.
(B) The two kinds of activities are present within the same complex and work in synergy.
(C) The acetylation mark, set by a HAT complex, is recognised by the remodelling complex via a bromodomain-containing subunit (Brd) and stabilises the binding of the remodeller to chromatin.
(D) Direct regulation of the nucleosome remodelling complex by site-specific acetylation.

Counter-point and Fugue: pathways to gene activation

Gene activation in chromatin is a multi-step process, which may involve dazzling numbers of regulatory activities (Metivier et al., 2003). Although promoters may share binding sites for transcription factors, their combination and arrangement renders each promoter an individual and, accordingly, the precise circumstances that lead to its activation may vary. Requirement for chromatin modifiers may also depend much on the concentrations of sequence-specific activators and thus their occupancy at promoters: nucleosome remodelling by SWI/SNF com-

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plexes becomes more important if the sequence-specific activators are present at low concentrations (Dhasarathy and Kladde, 2005).

Sometimes it is difficult to pinpoint clear-cut effects of either nucleosome remodelling ATPases or enzymes that affect the nucleosomal histone acetylation status, because they are involved in parallel, redundant pathways towards the same goal. For example, a number of yeast loci appear to be repressed by the ISW2 remodelling ATPase as well as the HDA1 histone deacetylase. Deleting either protein alone leads to only mild de-repression, whereas combined deletion of both regulators leads to full de-repression (Zhang and Reese, 2004). Often however, nucleosome remodelling and histone acetylation contribute within one pathway. In fortunate cases where gene activation is sufficiently slow and synchronous population of cells can be obtained, it is possible to resolve the timing of interaction of various activities. Earlier studies of this kind, reviewed in Narlikar et al. (2002) and Neely and Workman (2002), and more recent work aimed at understanding whether recruitment was ordered and hierarchical, concluded that generalisations were not appropriate. A prominent case where ATP-dependent nucleosome remodelling precedes the action of histone modifiers is the silencing of rDNA promoters transcribed by RNA polymerase I (Grummt and Pikaard, 2003). Silencing is initiated by targeting the SNF2h-containing Nucleolar Remodelling Complex (NoRC) to the rDNA promoter through interaction with promoter-bound TTF-1. NoRC is a multi-functional entity that catalyses the precise positioning of a nucleosome at the promoter but also recruits HDAC and DNA methylase complexes, which establish silent chromatin (Santoro and Grummt, 2005).

An example where acetylation precedes the remodelling reaction (Figure 1A) is provided by the case of the yeast *PHO5* promoter. Here, Gcn5-dependent hyperacetylation speeds up subsequent nucleosome displacement by an ATP-dependent nucleosome remodelling machinery, most likely the SWI/SNF complex (Reinke and Horz, 2003; Dhasarathy and Kladde, 2005). However, O'Shea and colleagues have shown that the Ino80 complex is also targeted to the *PHO5* promoter and is required for full induction (Steger et al., 2003). SWI/SNF and Ino80 complexes are very different when it comes to their subunit composition and the structures of their ATPase subunits (Eberharter and Becker, 2004). The data either point to redundant functions of rather dissimilar remodelling factors, or to subtle, non-overlapping contributions of each factor to promoter opening that we do not yet understand. Trying to pinpoint the HAT involved in inducing the *PHO5* gene also has recently revealed unexpected complexity. While it was long known that *PHO5* activation involved histone acetylation by Gcn5 within the SAGA (Spt-Ada-Gcn5 acetyltransferase) complex, Cote and colleagues described an additional involvement of the NuA4 complex, which harbours the histone H4-specific HAT Esa1. Interestingly, NuA4 was required to establish a specific promoter conformation that was inactive, yet pre-set to respond to induction (Nourani et al., 2004).

Co-operation between the acetylation enzymes and remodelling ATPases are equally well documented when it comes to shutting off genes, as many transcriptional repressors and co-repressors are able to interact with these activities. For example, the human SWI/SNF complex contributes to repression of cell cycle genes, including the Plk1 gene, through interaction with the promoter-bound retinoblastoma-E2F complex. Interestingly, the hypoacetylation characteristic of the inactive Plk1 promoter and concomitant repression was no longer observable in the absence of SWI/SNF although the retinoblastoma-E2F repression complex was still bound to the promoter (Gunawardena et al., 2004). This may suggest a role of the SWI/SNF complex in facilitating the action of a histone deacetylase, however it remains to be explored whether this effect is direct. Other ATP-dependent remodelling enzymes that synergise with deacetylases include Mi2 (Wang, 2003) and the yeast Isw2 enzyme. Repression in yeast often involves parallel recruitment of the nucleosome remodelling ATPase Isw2 and HDAC complexes to target genes. Examples for repressors that function via these disparate co-repressor complexes include the repressor of meiotic genes, Ume6 and the Ssn6-Tup1 repressor system (for reviews, see Mellor and Morrillon, 2004; Zhang and Reese, 2004).

The question of a timed order of promoter interactions of multi-subunit regulatory complexes may lead to rather convoluted answers if two recent observations reflect the rule rather than the exception. First, Gannon and colleagues described cyclical recruitment of dozens of regulators to the estrogen-regulated pS2 promoter (Metivier et al., 2003). Time-resolved chromatin immunoprecipitations suggest that various histone modification systems, including either one of the acetyltransferases Tip60, P/CAF, CBP or GCN5 co-operating with an SWI/SNF complex containing either the ATPase BRM or BRG1, contribute to setting up an active promoter. Although activation domains are able to interact with the many different components involved (e.g., see Memedula and Belmont, 2003, and references therein), directing a dynamic series of large protein assemblies presumably does not rely solely on binary interactions between DNA-bound transcription factors and remodelling machineries, but involves a network of protein-protein interactions including co-factors and RNA polymerase itself (Huang et al., 2003; Lemieux and Gaudreau, 2004). Intriguingly, after only a short time of transcription the entire structure was rapidly dismantled again. The presence of SWI/SNF, deacetylases and the NuRD complex (containing the CHD-type ATPase Mi2) during the disassembly of the active promoter may suggest their involvement in this process (Metivier et al., 2003). Repeated Sisyphean cycles of chromatin reorganisation and initiation complex formation followed by rapid reversal of all processes generates waves of transcription, which may be better suited for fine regulation than more stable states of activity (Metivier et al., 2003). Interestingly, nucleosome remodelling ATPases may once again be crucial for the observed dynamic interplay of factors, since the human SWI/SNF complex is not only able to reorganise nucleosome structure, but also to displace the glucocorticoid receptor from its binding site within the MMTV promoter in an ATP-dependent reaction (Nagaich et al., 2004). Since histone acetyltransferases commonly are able to

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modify transcription factors, sometimes with profound consequences for their DNA binding properties, regulation of DNA interactions of non-histone proteins defines a further area of potential synergy between ATPases and acetyltransferases.

The second complication, if one tries to resolve the individual steps that lead to chromatin opening, stems from the recent observation of Memendula and Belmont (2003) that challenges the generality of the concept of pre-assembled chromatin remodelling complexes that are recruited as entities to their sites of action. They show that the VP16 activator is able to recruit individual HAT complex subunits, like the TRRAP protein, to *in vivo* target sites significantly before the corresponding HATs themselves, like GCN5, P/CAF or CBP/p300. Likewise, the nucleosome remodelling BAF complex ATPases BRG1 and BRM were recruited before the regulatory subunits BAF155 and BAF170. The experiment involved targeting a condensed area of chromatin, which may restrict the access of large (1–2 MDa complexes), pre-assembled complexes. One alternative pathway to 'invade' such a rigid structure may thus involve assembly of complexes on site. Since frequently the activity of the enzyme subunit is strongly dependent on the appropriate molecular environment provided by associated subunits, one cannot conclude from the presence of an enzyme at a given site that the enzyme is fully functional. Indeed, a significant delay of histone acetylation after HAT binding has been observed (Soutoglou and Talianidis, 2002).

Towards perfection in synchrony

Synchronisation of histone acetylation and nucleosome remodelling may sometimes be crucial, notably when timely action is required as is the case when DNA damage requires urgent repair. Targeting chromatin modifiers via interaction to sequence-specific DNA binding proteins is not possible in this case, since damage usually occurs in anonymous areas of chromatin. Double-strand breaks in DNA are recognised by complex processes and marked by phosphorylation of the C-terminal tails of H2A (in yeast) or the variant H2AX in higher eukaryotes (Peterson and Cote, 2004). These phosphorylation marks serve to conduct the concerted entry of the nucleosome remodelling and histone acetylation systems involved in repair. Recently, Cote and colleagues suggested that co-ordination of action of the NuA4 HAT complex, and the Ino80 or Swr1 remodelling complexes is achieved by interaction of the shared Arp4 subunit with the phosphorylated H2A epitope (Downs and Jackson, 2004). In this study, interaction of the HAT complex appeared before that of the remodellers, and acetylation of histone H4 at lysine 8 (H4K8ac) facilitated the action of the remodelling complex (Figure 1A). Recognition of an epigenetic mark through a dedicated subunit shared by diverse complexes involved in repair certainly provides an attractive strategy for conducting the entry of diverse activities. However, a conflict with a parallel study by Morrison et al. (2004), who concluded that the Nhp10 subunit of the Ino80 complex was primarily involved in binding the phosphorylated H2A, still needs to be resolved.

Even tighter integration of the HAT and ATPase complexes involved in DNA double-strand break repair have recently been documented in the *Drosophila* model by the Workman lab, who isolated a complex combining both activities (Kusch et al., 2004). This large complex contains the HAT dTip60 (the homologue of yeast Esa1) and the domino ATPase (the homologue of yeast Ino80) (Figure 1B). It catalyses the exchange of the phosphorylated histone variant H2Av [phospho-H2Av (the fly homologue of H2AX)] that marks the site of damage, with the unmodified H2Av. Recognition of the nucleosomal phospho-H2Av leads to its acetylation at lysine 5 by dTip60. In a second step, the ATPase subunit domino catalyses the exchange of the acetylated phospho-H2Av with an unmodified version of the H2Av histone molecule (Kusch et al., 2004). Biochemically speaking, two separate complexes in yeast are found combined into one super-complex in *Drosophila*. However, since biochemical analysis inevitably leads to disruption of structures, the enzyme assemblies may not look so different after all in live yeast and fly cells. Consistent with this, several novel factors turn out to be shared subunits of NuA4 and SWR complexes in yeast (Krogan et al., 2003).

Other examples of multi-enzyme complexes combining HAT or HDAC and remodelling activities in one biochemical entity have been described (Feng and Zhang, 2003; Bowen et al., 2004; Sif, 2004). A most recent example of particular interest involves the yeast Gcn5-containing HAT complexes SAGA and SLIK (SAGA-like), two highly homologous entities able to acetylate the histones H3 and H2B and to de-ubiquitinylate histone H2B in nucleosomes. Through affinity purification, Grant and colleagues reported the association of Chd1 with SAGA and SLIK (Pray-Grant et al., 2005). Yeast Chd1 belongs to the CHD (chromo-helicase-DNA binding domain) family of remodelling ATPases (Eberharter and Becker, 2004) and its activity is connected to gene expression and transcription elongation (Simic et al., 2003). While it is not yet clear whether Chd1 in SAGA/SLIK also possesses ATPase and/or chromatin remodelling activity, and hence contributes to transcriptional regulation, its role in the targeting of the complex is highly interesting. One of the two chromodomains of Chd1 specifically recognises a histone H3 N-terminus methylated at lysine 4, which effectively tethers SAGA/SLIK to this mark for transcriptional competent chromatin (Pray-Grant et al., 2005).

Strategies for successful relay teams

Ordered pathways towards a specific chromatin structure may be defined by direct interactions between chromatin modifiers, where the first one is recruited to a site through interaction with a DNA-bound regulator and then provides a platform for additional factors to work in relay. Such a scenario begins to take shape for the silencing of rDNA, where recruitment of the remodelling complex NoRC not only leads to an initial nucleosome movement, but also attracts histone deacetylase and DNA methylase activities that contribute to establishing the silent state (Santoro et al., 2002; Grummt and Pikaard, 2003; Santoro and Grummt, 2005). An alternative strategy does not involve direct contact of the second factor with the preceding one, but recognition of the product of the first factor's action. Histone modifications, like the H2A phosphorylation and H3 methylation mentioned above, are

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examples of such function. In the context of the current discussion, the acetylation marks delivered by HATs may also serve as binding sites for subsequent regulators (Figure 1C). Alone or in combination with other modifications, they may constitute a modification 'code' to be interpreted by combinations of recognition domains of chromatin regulators (Turner, 2005). Acetylated lysines are recognised by so-called bromodomains (Zeng and Zhou, 2002; Yang, 2004b), which are present in a large number of HATs, such as Gcn5, p300, P/CAF and $TAF_{II}250$ subunits of nucleosome remodelling factors (e.g., ATPases of the SWI2/SNF2 type, and proteins of the WAL/BAZ family of ISWI-associated proteins) and in the less characterised group of BET (bromodomain and ET domain) proteins (de la Cruz et al., 2005). Depending on specifics and context, bromodomains may bind distinct subsets of acetylated lysines *in vitro* and *in vivo* (Ladurner et al., 2003; Matangkasombut and Buratowski, 2003; Kanno et al., 2004). For example, the BET family protein Brd2 preferentially interacts with acetylated lysine 12 of histone H4 (H4K12ac), whereas the double-bromodomain-containing HAT $TAF_{II}250$ associates with H3K14ac and H4 acetylated at lysines 8, 12 and 16 [Kanno et al., 2004; for a nomenclature of histone modifications, see Turner (2005)].

Bromodomains in HATs and nucleosome remodelling complexes may thus help orchestrate the succession of chromatin regulators at a target site. Acetylation marks on histones set by the SAGA or NuA4 complexes may be bound by the bromodomains of Gcn5 or the nucleosome remodelling ATPase Swi2/Snf2 *in vitro*, and thus contribute to stabilising the interactions of these regulators with a target promoter (Hassan et al., 2002).

The yeast proteome contains 15 bromodomains and, most remarkably, eight of them are contained in the SWI/SNF-related remodelling complex RSC (remodels the structure of chromatin). Recently, functional roles for the two bromodomains in the Rsc4 subunit were described (Kasten et al., 2004). The tandem bromodomains were required for integrity of the complex, cell viability and for the activation of target genes. Biochemical and genetic evidence suggests that the Rsc4 bromodomains interact with the transcription-related H3K14ac signal (Kasten et al., 2004).

Although not equally well documented, certain histone modification marks may prevent binding or action of subsequent remodelling factors. The CHD-type NuRD complex, whose binding to the H3 N-terminus was occluded by lysine 4 methylation (Zegerman et al., 2002), provides one example. Interestingly, both complexes, the deacetylase-containing NuRD complex that fails to bind to H3K4me and the SLIK acetyltransferase complex that is attracted by this methylation mark (Pray-Grant et al., 2005), contain remodelling ATPases of the chromodomain-containing CHD type, highlighting the complexity of recognition of histone marks. Acetylation of histone H4 at lysine 16 may render nucleosomes carrying this tag less susceptible to nucleosome remodelling by the ISWI ATPase and may thus reduce the effect of ISWI-containing nucleosome remodelling complexes on H4K16ac substrates (Clapier et al., 2002; Corona et al., 2002). In *Drosophila*, H4K16 acetylation is a hallmark of the hyperactive male X chromosome. It has therefore been hypothesised that H4K16 acetylation leads to a twofold increased transcription of X-linked genes through counteracting an ISWI-dependent repressive chromatin compaction (Corona et al., 2002).

Direct regulatory crosstalk

In these examples the effect of one regulator on the activity of a successor has been indirect, mediated through the common nucleosome substrate. However, recent findings suggest that these HATs and remodelling ATPases may regulate each other's activity more directly. Most histone acetyltransferases are also able to acetylate non-histone proteins, and these modifications can have profound effects on the structure and function (Roth et al., 2001). For example, the effects of acetylation on the tumour suppressor protein p53 have been greatly studied (Brooks and Gu, 2003). In an interesting extension of this principle, Muchardt and colleagues observed that the effect of the BRM ATPase on cell proliferation can be regulated by acetylation (Figure 1D). The data suggest that site-specific acetylation of the ATPase by, for example P/CAF, may adversely affect its function, possibly by interfering with targeting interactions (Bourachot et al., 2003). Furthermore, we recently found that the *Drosophila* ISWI ATPase was subject to site-specific acetylation by GCN5 *in vitro* and *in vivo*. This acetylation marks a novel developmental isoform of the remodelling ATPase which, unlike bulk ISWI, is highly concentrated on condensed metaphase chromosomes (R. Ferreira, M. Chioda, A. Eberharter and P.B. Becker, in preparation).

Could ATP-dependent nucleosome remodelling enzymes also affect the function of HATs more directly? A mechanism of nucleosome remodelling involving anchored DNA translocation (Längst and Becker, 2004) may be easily utilised to disrupt protein-DNA interactions in more direct ways. That the action of nucleosome remodelling machines may not be restricted to destabilising histone-DNA interactions, but may also be used to disrupt the DNA interactions of non-histone regulators, is illustrated impressively by the eviction of the glucocorticoid receptor from DNA through the ATP-dependent action of the SWI/SNF complex (Nagaich et al., 2004). Eviction of critical transcription factors may deprive HATs of their recruiting partners.

In conclusion, dynamic transitions of chromatin structure involve concerted actions of nucleosome remodelling activities and the histone acetylation system. We are just beginning to realise how co-ordination and fine-tuning of these activities endow eukaryotic chromatin with plasticity and regulatory potential.

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