

Histone deacetylases: transcriptional repression with SINers and NuRDs

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The nucleosome consists of 146 base pairs of DNA wrapped twice around an octamer that comprises two copies of each of the four core histone proteins – H2A, H2B, H3 and H4. Nucleosomes are assembled onto DNA in repeating arrays to yield the familiar beads-on-string structure of chromatin. The assembly of DNA into nucleosomes or higher-order chromatin structures renders the underlying DNA template transcriptionally inactive by blocking access to regulatory proteins and the transcriptional machinery. Elaborate mechanisms exist both to circumvent and to establish these repressive chromatin structures (Fig. 1). One mechanism that has received a great deal of attention recently is the reversible acetylation of the N-terminal tails of the core histones. In general, regions of chromatin that are hyperacetylated are transcriptionally active, whereas regions that are hypoacetylated are inactive. Recently, our understanding of this regulatory mechanism has been enhanced by the identification, cloning and characterization of several enzymes that catalyse either the forward (histone acetyltransferases – HATs) or the reverse (histone deacetylases – HDACs) acetylation reaction.

The correlation between the hyperacetylation of histones and the activation of gene expression was first observed over 30 years ago. Since then, a wealth of biochemical, genetic and cytogenetic data has, in general, supported this correlation; however, the precise mechanism by which histone hyperacetylation facilitates transcriptional activation has remained elusive^{1,2}. The N-terminal tails of the core histones extend unstructured from the octamer core³. Each core histone has several lysines, conserved across species, in their N-terminal tails that can be reversibly acetylated on their ϵ -amino groups. Acetylation of these lysines results in neutralization of positive charge on the histone tails, which weakens the electrostatic interaction between the histone and the DNA backbone. In the most simple model of acetylation-mediated activation, the weakening of the interaction between the histones and the DNA results in a 'loosened' nucleosome that is generally more accessible to transcriptional activators and the basal transcription machinery². Several other possibilities have been presented to explain why hyperacetylated chromatin is more transcriptionally active; for example, the histone tails themselves might participate directly in the binding of certain transcriptional activators^{4,5} or chromatin-remodelling complexes⁶. Deacetylation of the histone N-terminal tails might simply reflect a reversal of these processes, or, because the hypoacetylated histone tails apparently mediate contacts between adjacent nucleosomes in the recently solved crystal structure, deacetylation might help establish higher-order repressive nucleosomal structures³. There is an extensive literature on the structure and function of the N-terminals of the core histones that is the subject of several recent reviews^{7,8}.

HDACs

The identification and characterization of HATs and HDACs have provided biochemical support for

The DNA in eukaryotic cells is packaged into chromatin, which functions as a boundary to the transcriptional activation process.

The nucleosome is the basic repeating unit of chromatin. The purification and characterization of several chromatin-remodelling complexes and the demonstration that histone acetyltransferases and histone deacetylases are regulatory components of coactivator and corepressor complexes, respectively, demonstrates that the nucleosome is not simply a static architectural feature of chromatin but, rather, plays a dynamic and integral role in the regulation of gene expression.

This review focuses primarily on histone deacetylases and deacetylase-containing complexes and their role in mediating transcriptional repression.

the correlation between histone hyperacetylation and transcriptional activation. Several transcriptional coactivators are histone acetyltransferases (e.g. GCN5, CBP, p300, PCAF, ACTR and TAF_{II}250)¹, and histone deacetylases are active components of transcriptional corepressor complexes. Another key feature to emerge from these studies is that histone acetylation and deacetylation activities are targeted to specific regions of chromatin by interacting with sequence-specific DNA-binding transcriptional activators and repressors, respectively.

The first histone deacetylase, HDAC1, was purified and subsequently cloned using an affinity matrix based on the deacetylase inhibitor trapoxin⁹. HDAC1 is ~60% identical to the *Saccharomyces cerevisiae* global transcriptional repressor Rpd3p, suggesting that the previously characterized repression function of RPD3¹⁰ was mediated by histone deacetylation. There are four *S. cerevisiae* genes that encode proteins similar to Rpd3p: *HDA1*, *HOS1*, *HOS2* and *HOS3*. Initially, it was shown that

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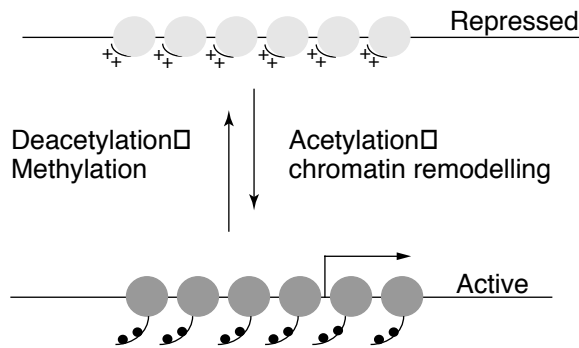


FIGURE 1

Access to DNA sequences in chromatin is highly regulated. Promoter regions that are assembled into chromatin are generally inaccessible and therefore the genes that they regulate are inactive. The repressed state shown is depicted to be generated by histone deacetylation and/or methylation. Originally thought to be independent processes, methylation and deacetylation could be functionally linked (see text for details). Higher-order chromatin structures are also possible and appear to repress transcription as well. Several mechanisms exist to overcome chromatin-mediated repression, among them are acetylation and chromatin remodelling. Initially, chromatin remodelling was thought to play a role only in activation; however, the discovery of a complex with both deacetylase and remodelling activity, the NuRD complex (nucleosome remodelling histone deacetylase; see text for details), challenges that paradigm. The N-termini of the histones are depicted as being tightly associated, deacetylated (+ signs) protruding from repressive (pale shade) nucleosomes and as loosely associated, acetylated (black circles) protruding from activated (dark shade) nucleosomes.

null mutations in either *RPD3* or *HDA1* result in hyperacetylation of the N-terminal tails of the bulk of H3 and H4, suggesting that they encode histone deacetylases and that at least one of their *in vivo* substrates is histones¹¹. It is likely that the HOS proteins possess intrinsic deacetylase activity; however, this has not been demonstrated formally. A similar paralogous family of deacetylases, comprising HDAC1, HDAC2 and HDAC3, has been identified in higher eukaryotes¹²⁻¹⁵. Several residues within the central regions of the yeast and mammalian proteins are highly conserved and are required for catalysis and folding the HDACs into a functional conformation^{16,17}. Searches of the EST databases led to the cloning and characterization of HDACs 4, 5 and 6 (C. M. Grozinger, C. A. Hassig and S. L. Schreiber, pers. commun.). HDACs 4 and 5 share the catalytic core with the other deacetylases but have unique N-terminal extensions, whereas HDAC6 appears to contain two discrete catalytic core domains. These new HDACs and the identification of a nucleolar HDAC from maize that lacks homology with the characterized deacetylase catalytic core¹⁸ suggests the existence of at least three structural classes of HDACs. HDAC1, HDAC2 and HDAC3 are all capable of deacetylating both purified core histones and histones incorporated into nucleosomal templates *in vitro*; however, HDAC1 is unable to deacetylate SV40 minichromosomes under similar conditions, suggesting that HDACs require additional cofactors to access more complex chromatin structures (see below)^{13,16,19}.

HDAC complexes

Histone deacetylases are enzymatically active components of multiprotein complexes. In yeast, HDA1 and RPD3 are components of the HDA and HDB complexes, respectively¹¹. In mammalian cells, HDAC1 and HDAC2 are found in two complexes: the mSinA complex and the NuRD (for: 'nucleosome-remodelling histone deacetylase') complex. mSin3A was identified originally as the corepressor that is utilized by the DNA-binding heterodimeric transcriptional repressor Mad-Max^{20,21}. mSin3A and its paralogue mSin3B are both ~50% similar over their entire open reading frames to the *S. cerevisiae* global transcription repressor SIN3²⁰. SIN3 had been shown to function in the same genetic pathway as the histone deacetylase RPD3, suggesting a biochemical mechanism for SIN3-dependent repression^{10,22,23}. Several groups have shown that HDAC1 and HDAC2 associate stably with mSin3A *in vivo* and that the enzymatic activity of the mSin3A-associated HDACs is required for full repression by Mad-Max²⁴⁻²⁶. Furthermore, association between Rpd3p and Sin3p can be detected in extracts from yeast cells, and both proteins are required for repression by the meiotic transcriptional repressor UME6, suggesting that this mechanism of repression has been conserved^{27,28}. These findings have led to the 'targeted repression' model in which the SIN3-HDAC complex is tethered to the promoter by the transcriptional repressor (e.g. Mad-Max or UME6)²⁹. Targeting of enzymatically active HDACs to promoter sequences via heterologous DNA-binding domains drives transcription repression, providing support for this model^{12,16,27}.

In addition to HDACs 1 and 2, several other components of the mSin3A complex have been identified: RbAp46/48^{24,26}, SAP18²⁶ and SAP30. RbAp46/48 functions in a number of complexes that modify chromatin and appears to target the histone-modifying enzymes in these complexes to the N-terminal tails of histones, particularly H4³⁰. RbAp48 copurifies and associates tightly with HDAC1⁹, suggesting that it enters the mSin3A complex bound to an HDAC. The functional roles of SAP30 and SAP18 are less clear. SAP30 appears to be necessary to target the mSin3A-HDAC complex to a subset of repressors that utilize the nuclear hormone corepressor N-CoR (see below), and its orthologue is required for maximal repression at some yeast promoters^{19,31}. Although the molecular connectivity of the proteins in the mSin3A complex has not been established, it seems most likely that mSin3A itself functions as the scaffold upon which its partners assemble to form the biochemically identifiable 'core repressor complex' (Fig. 2). Neither the protein components of the mSin3A-HDAC complex nor the associated deacetylase activity of the complex change during the cell cycle or during differentiation, suggesting that it is available continuously to the repressors with which it interacts (T. M. Fleischer and D. E. Ayer, unpublished).

In addition to being tethered to DNA by Mad proteins and a growing list of other transcriptional repressors, the mSin3-HDAC complex also interacts

with the corepressors N-CoR and SMRT. N-CoR and SMRT were identified originally as corepressors for unliganded nuclear hormone receptors^{32,33}. A variety of *in vitro* and *in vivo* experiments demonstrate that the interaction between these corepressors and mSin3A and HDAC1 is physiological. Furthermore, transcriptional repression by unliganded nuclear hormone receptors is blocked by the deacetylase inhibitor trichostatin A, demonstrating that the repression by this class of molecules requires deacetylase activity^{34–36}. Several additional transcription repressors that also utilize N-CoR/SMRT also require HDAC activity for their function (Fig. 3). This finding suggests that the dependence of N-CoR/SMRT-mediated repression on HDAC activity is somewhat general. It is currently unknown whether N-CoR and SMRT interact with the 'core mSin3A–HDAC complex' or with a different subpopulation of the cellular mSin3A and/or HDACs.

An excellent example of the biological importance of the interaction between HDACs and N-CoR/SMRT is the regulation of myeloid leukaemia-associated fusion proteins PML–RAR α and PLZF–RAR α . Cell lines expressing PML–RAR α can be induced to differentiate with retinoic acid, whereas cell lines expressing PLZF–RAR α are refractory to retinoic acid treatment. Both fusion proteins bind to HDAC and require HDAC activity to function as transcription repressors. Retinoic acid treatment results in the removal of HDAC from PML–RAR α but does not disrupt the PLZF–RAR α –HDAC complex, suggesting that a crucial feature controlling differentiation of PML–RAR α -expressing cells is the inactivation of the repression function of the fusion protein. In support of this hypothesis, it was shown that cell lines expressing PLZF–RAR α fusion could be induced to differentiate when treated with both retinoic acid and deacetylase inhibitors^{37–39}.

As well as being components of the mSin3A–HDAC complex, HDAC1/HDAC2 are components of a distinct complex, the NuRD complex (Fig. 4)^{40–43}. In addition to HDACs 1 and 2, the NuRD complex contains RbAp46/48 and proteins with apparent molecular masses of 32, 70 and 240 kDa but appears not to contain mSin3A or other components of the mSin3A–HDAC complex. p32 is a novel protein, whereas p70 comprises multiple, closely migrating protein species, including MTA1 and MTA2. The function of the MTA proteins is unknown, but MTA1 overexpression correlates with the metastatic potential of certain tumour cells⁴⁴. Peptide microsequencing and western blotting data indicate that p240 corresponds to two closely related proteins, CHD3 and CHD4, which were identified originally as autoantigens in patients with dermatomyositis.

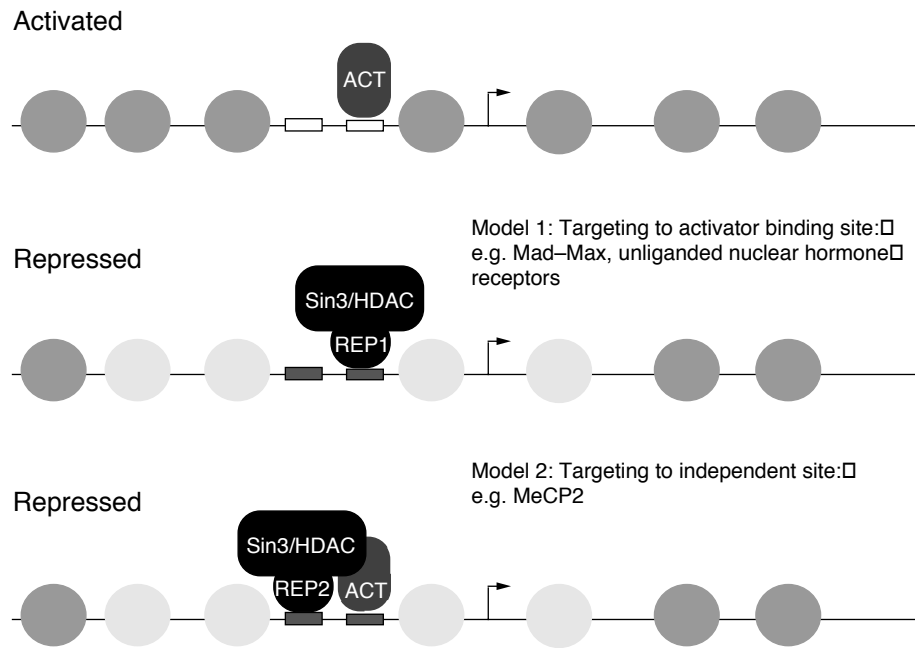


FIGURE 2

'Targeted transcriptional repression'. A schematic of a hypothetical promoter that can be both activated (ACT; top panel) and repressed (REP; bottom panels). In the activated state, the promoter is bound by a single transcriptional activator, and the N-terminal tails of the histones that make up the promoter-proximal nucleosomes are hyperacetylated (dark circles), possibly via an activator-bound histone acetyltransferase (HAT) complex. Two models are presented for targeted repression. In model 1, the repressor–Sin3–HDAC (histone deacetylase) complex competes for the same sequences that bind to the activator, as is the case with Mad–Max heterodimers competing for Myc–Max sites. In model 2, the repressor–Sin3–HDAC complex binds to an element that is distinct from that bound by the activator. In both models, the targeting of the HDAC complex results in localized deacetylation of the N-terminal tails of the histones that make up the promoter-proximal nucleosomes (pale circles).

Surprisingly, CHD3/CHD4 are similar to the Swi/Snf family of DNA-dependent ATPases whose members are the enzymatically active components of all known chromatin-remodelling complexes. Accordingly, the NuRD complex contains both HDAC activity and chromatin-remodelling activity. The nucleosomal HDAC activity of the NuRD complex is stimulated by ATP, suggesting a mechanism by which HDACs might gain access to the histone tails embedded in complex chromatin structures. There are proteins in the mSin3A–HDAC complex with molecular mass similar to that of CHD3/CHD4, but it apparently lacks chromatin-remodelling activity⁴². It is hypothesized that the NuRD complex establishes or maintains a hypoacetylated chromatin domain; however, it is unclear what functional role the NuRD complex plays *in vivo*. By analogy to the mSin3A–HDAC complex, one proposal is that the NuRD complex functions in transcriptional repression; however, additional roles for the NuRD complex in other chromatin-dependent processes – such as recombination, replication and DNA repair – cannot be ruled out. The transcriptional repressor YY1¹² apparently binds to HDACs independently of mSin3A, raising the possibility that it targets the NuRD complex to DNA. A *Drosophila* homologue of CHD3 and CHD4 interacts physically and genetically with hunchback, a repressor of HOX gene expression, suggesting another mechanism for targeting CHD-containing complexes to DNA⁴⁵.

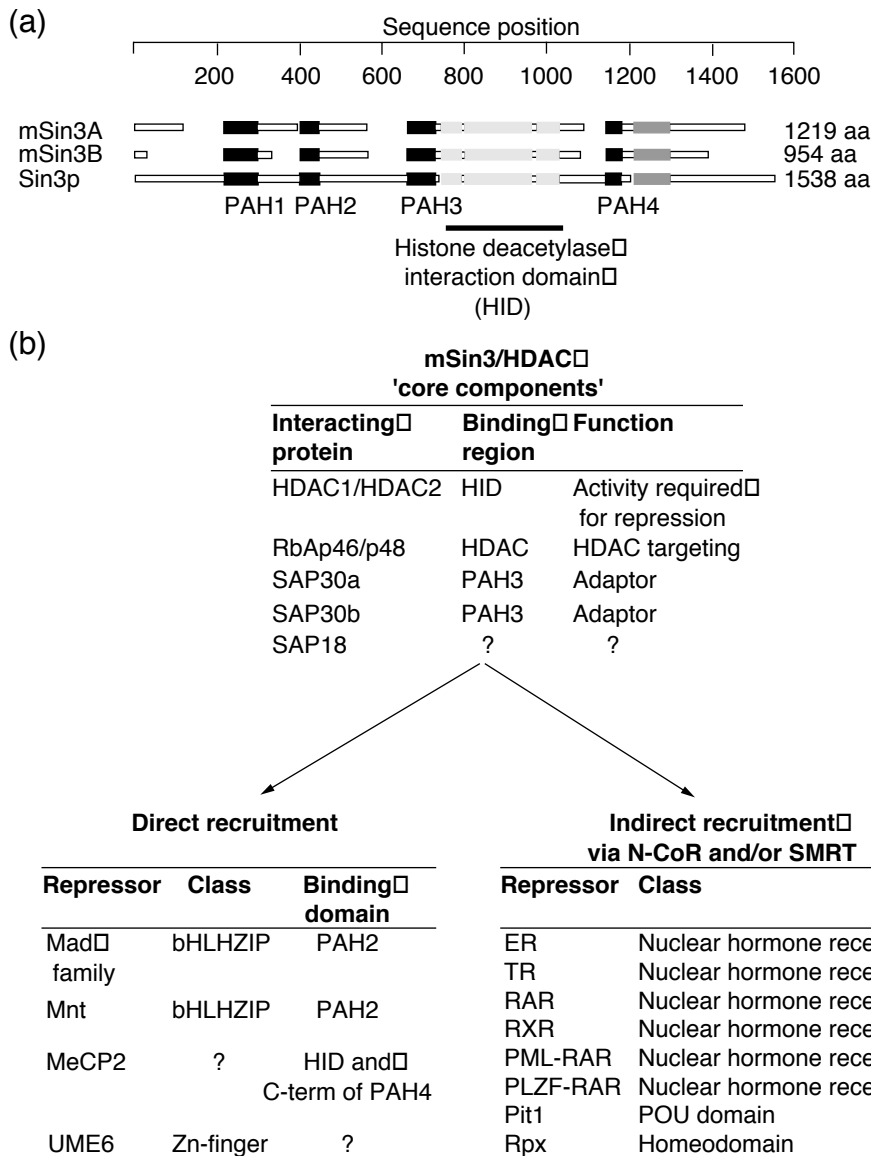


FIGURE 3

Repression by the mSin3A–HDAC (histone deacetylase) complex. (a) Schematics of the SIN3 proteins from mammalian cells, mSin3A and mSin3B, and *Saccharomyces cerevisiae*, Sin3p, are shown. Each protein has four paired amphipathic α -helix domains (PAH) that function as surfaces for protein–protein interactions. The region between PAH3 and PAH4 is highly conserved and binds to histone deacetylases (HDACs); it has thus been termed the histone deacetylase interaction domain (HID).

The function of the conserved domain located just after PAH4 is unknown.

(b) mSin3A has been purified by immunoaffinity chromatography and the tightly associated proteins identified by a variety of methods. It appears that these proteins associate in near-stoichiometric amounts with mSin3A and comprise a biochemically identifiable ‘core’ complex. This ‘core’ complex can be recruited to DNA by at least two mechanisms: directly by proteins such as members of the Mad family, or indirectly by nuclear hormone receptors and other transcriptional repressors through the corepressors N-CoR and SMRT. The list of repressors that utilize mSin3A–HDAC in both classes is growing rapidly. Furthermore, it seems likely that other N-CoR/SMRT-like corepressors that interact with mSin3A will be identified in the future. Several lines of evidence suggest that, while Sin3p-bound HDAC is required for Sin3p repression, it is not sufficient for maximal repression by Sin3p. For example, deacetylase inhibitors do not fully derepress mSin3-dependent repression, and mSin3 molecules that lack the binding domain for the HDACs still drive transcription when tethered to DNA through a heterologous DNA-binding domain^{17,24,25}. Recently, an interaction between mSin3A and the general transcription factor TFIIB has been reported, suggesting that Sin3 proteins might also repress transcription by targeting the preinitiation complex⁶⁶.

Abbreviations: bHLH, basic helix–loop–helix; C-term, C-terminus.

HDACs regulate transcription

Findings from deacetylase inhibitors and null mutations suggest that deacetylase activity is required to mediate repression; however, neither of these methods demonstrates definitively that the enzymatic activity of the HDAC is required for repression. A series of single-amino-acid substitutions in highly conserved residues in the presumptive catalytic core of both RPD3 and HDAC1 have been reported to reduce enzymatic activity^{16,17}. In each case, there was a strict correlation between enzymatic activity and the ability of the HDAC to facilitate repression, implying that it is the actual enzymatic modification of the chromatin template that mediates transcriptional repression.

Several nonhistone transcription regulators are acetylated *in vitro* by recombinant HATs, suggesting additional roles for HATs and HDACs in controlling gene expression. Among these substrates are the general transcription factors TF_{II}E β and TF_{II}F⁴⁶, the tumour-suppressor p53⁴⁷, the erythroid transcription factors GATA1⁴⁸ and EKLF⁴⁹, the interferon beta (IFN β) gene enhanceosome architectural component HMG I(Y)⁵⁰ and the Y-box-binding transcription factor NF-Y⁵¹. Mutation of potential acetylation site lysines, determined by *in vitro* mapping, has both positive and negative effects on the *in vivo* function on individual nonhistone substrates. At present, only p53 is

known to be acetylated *in vivo* on the sites determined by *in vitro* mapping⁵². It is not known whether these nonhistone substrates can serve as substrates for HDACs as well; however, if so, the outcome of targeted deacetylation will not always be inhibition of transcription. Therefore, it is likely that the level of transcription from some promoters will be determined by acetylation/deacetylation of both histone and nonhistone substrates.

Recombinant HATs and the purified GCN5-containing HAT complexes ADA and SAGA have specific substrate specificities^{1,53}. For example, recombinant GCN5 acetylates preferentially lysine 14 of histone H3 and can also acetylate lysines 8 and 16 of H4⁵⁴. By contrast, immunopurified HDACs 1, 2 and 3 can deacetylate all four core histones, demonstrating that the HDACs have little substrate specificity *in vitro*^{13,16,19}. To understand better the *in vivo* consequences of promoter-targeted HDACs on histone acetylation status, several groups have utilized chromatin immunoprecipitation. These experiments show that targeted HDACs result in local regions of promoter-proximal histone hypoacetylation that extend one or two nucleosomes from the site of targeting^{55,56}. Furthermore,

disruption of RPD3 results in transcriptional depression at several UME6-dependent promoters. This derepression is accompanied by hyperacetylation of lysine 5 on histone H4 at the promoter, suggesting that acetylation of a single lysine plays a role in the transcriptional activation⁵⁵. Because deletion of the gene encoding Rpd3p results in an increase in bulk acetylation of both histones H3 and H4, it is likely that deacetylase substrate specificity is tightly controlled *in vivo* in a promoter- and/or (co)repressor-specific fashion. It is difficult to envisage how a single modification on one of the core histones could facilitate derepression and activation; however, several studies point to the functional redundancy of the N-terminal histone H3 and H4 tails², suggesting that acetylation of either H3 or H4 is sufficient to lead to alterations in gene expression.

Methylation recruits HDACs

In addition to being hypoacetylated, transcriptionally silenced regions are often methylated. For example, the inactive X chromosome in mammals is both hypermethylated and hypoacetylated^{57,58}. Furthermore, methylated DNA is transcriptionally repressed, but only under conditions in which the methylated template is assembled into nucleosomal structures^{59,60}. These findings suggest a functional connection between chromatin structure, methylation status and transcriptional silencing. Several recent papers shed light on the mechanism of methylation-dependent and chromatin-mediated repression. MeCP2 binds specifically to methylated CpG dinucleotides and functions as a potent transcriptional repressor. Structure–function analysis of MeCP2 revealed that its transcription-repression domain is separable from its DNA-binding domain, which is reminiscent of the targeted repression described for the Mad family⁶¹. Similarly, *Xenopus* MeCP2 associates with *Xenopus* Sin3A and HDAC in extracts prepared from oocytes and in several *in vitro* interaction assays using the mammalian proteins. Most importantly, the interaction between MeCP2 and mSin3A maps to the previously defined transcription-repression domain of MeCP2, and MeCP2-dependent repression requires both a methylated nucleosomal template and HDAC activity. Together, these findings strongly suggest that methylation-dependent transcriptional repression is mediated by the Sin3A–HDAC complex^{62,63}. Depending on the report, as much as 80% of the cellular MeCP2 associates with the Sin3–HDAC complex, suggesting that the majority of methylation-dependent repression occurs by this mechanism. Again, as with the targeting of the Sin3–HDAC complex by site-specific transcriptional repressors, the mechanism by which hypoacetylation of methylated regions leads to silencing is unclear. The connection between methylation and hypoacetylation has been further strengthened by the direct demonstration that methylated templates are underacetylated and that methylation-silenced transgenes can be reactivated by inhibitors of HDAC or DNA methylation^{64,65}. Interestingly, insulator sequences, which protect

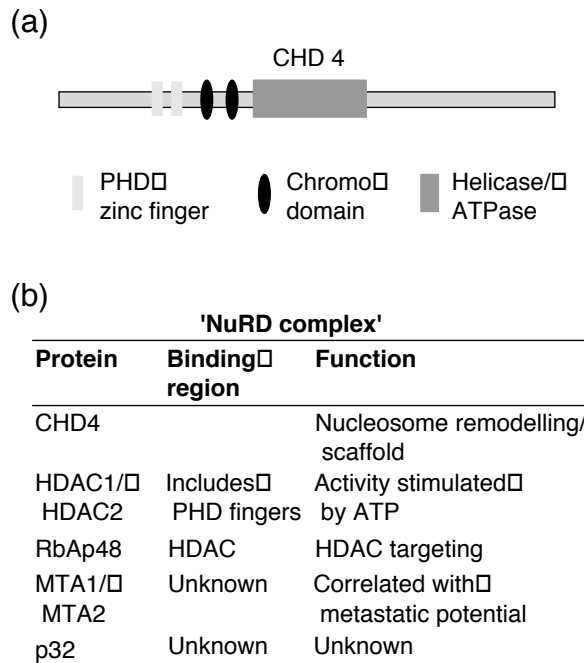


FIGURE 4

The NuRD (nucleosome-remodelling histone deacetylase) complex. (a) A schematic of CHD4 (chromo domain, helicase, DNA binding) is shown. The CHD3 and CHD4 proteins were described originally as autoantigens present in patients with dermatomyositis. CHD4 has two plant homeodomain (PHD) zinc fingers, two chromo domains and a SWI/SNF-like ATPase. PHD fingers are found in proteins that appear to function in transcriptional regulation and are proposed to act as domains for protein–protein interaction. Chromo domains are also found in a number of proteins – e.g. HP1 and polycomb – and appear to target these proteins to heterochromatin and to be involved in the establishment of transcriptionally silenced chromatin regions. SWI/SNF ATPase domains are the enzymatically active components of chromatin-remodelling complexes and are also found in proteins involved in DNA repair and recombination. The NuRD complex was isolated using antibodies specific for histone deacetylases (HDACs) and CHD4. The proteins isolated from these purifications are shown in (b). The functions of the MTA proteins and the novel p32 protein are completely unknown. The role that the NuRD complex plays in the regulation of gene expression is not known. However, at least one transcriptional repressor, YY1, interacts with HDACs independently of mSin3A, suggesting that it recruits the NuRD complex to DNA to facilitate repression. Interestingly, the binding domain on the CHD proteins for HDAC1 maps to close to the PHD fingers and is not similar to the histone deacetylase interaction domain (HID) of the SIN proteins, suggesting that there are alternative modes of binding or intermediary docking proteins.

transgenes from silencing, apparently function, at least in part, by blocking deacetylation of the transgene without altering the underlying methylation pattern. This experiment suggests that insulators restrict access of the deacetylase complex or MeCP2 to the template or somehow recruit HATs that maintain the transgene in a hyperacetylated state⁶⁴.

Future perspectives

The discovery that coactivators possess HAT activity and that HDACs are components of co-repressor complexes provides a mechanistic basis

for the correlation between histone acetylation and transcriptional activation. Although acetylation and deacetylation appear to play pivotal roles in controlling access to the underlying DNA template by transcriptional activators and the basal transcription machinery, the localized and/or higher-order structural alterations in chromatin driven by (de)acetylation remain largely unknown. Furthermore, how chromatin remodelling is coordinated with HATs to facilitate activation and with HDACs to facilitate repression remains an open question. With the purification of chromatin-remodelling complexes, HAT and HDAC complexes and the development of chromatin-based *in vitro* transcription systems, the tools are now available to address these issues. HDAC1/HDAC2 are components of at least two distinct multiprotein complexes; however, it is not known whether the mSin3A or the NuRD complexes purified to date represent unique complexes or collections of sub-complexes. Furthermore, it is unknown whether HDAC1/HDAC2 or HDACs 3, 4, 5 and 6 exist in other biochemically and functionally distinct complexes. Purification and further characterization of the known and yet-to-be-discovered HAT and HDAC complexes will provide a starting point for understanding their regulation and function in specific cellular and developmental contexts. Finally, alterations, through changes in expression, mistargeting or inactivation, in several chromatin-modifying enzymes have been associated with human disease. It is not clear how these changes lead to the diverse cellular phenotypes that have been observed, but it seems most likely that these alterations stem from altered expression of specific genes rather than from gross genome-wide alterations in gene expression. The ability to ascertain gene-expression profiles on a near-genome-wide scale using microarray technology should allow identification of the relevant downstream targets and provide an avenue for understanding the mechanisms underlying these diseases.

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