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Histone Deacetylases as Transducers and Targets of Nuclear Signaling

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Abstract Histone deacetylase (HDAC) activity was first discovered about 40 years ago, but it was not until the molecular identification of the first HDACs in 1996 that this family of enzymes gained prominence. In addition to histones, HDACs reverse lysine acetylation of various non-histone proteins located in the nucleus and the cytoplasm. Here, we examine the nuclear roles of these enzymes, with a specific focus on their active crosstalk with different chromatin regulators. J. Cell. Biochem. 104: 1541–1552, 2008. © 2008 Wiley-Liss, Inc.

Key words: lysine deacetylase; Rpd3; Hda1; Sir2; SIRT1; MEF2; HDAC inhibitor

Lysine (Lys) acetylation, the addition of an acetyl group to a Lys residue, has recently emerged as a fundamental mechanism for protein function regulation. Histones were the first proteins found to contain acetyl-Lys residues, so Lys deacetylases are traditionally referred to as histone deacetylases (HDACs). Since identification of the first HDACs 12 years ago [Rundlett et al., 1996; Taunton et al., 1996; Yang et al., 1996], the field has progressed rapidly, owing to three major factors. First, HDACs are directly linked to chromatin modifications, and chromatin research has expanded greatly since 1996. Second, in addition to histones, Lys acetylation occurs in various non-histone proteins and regulates different nuclear and cytoplasmic processes that are key to spatiotemporal control in diverse organisms. Third and finally, since identification of trichostatin A as the first specific HDAC inhibitor [Yoshida et al., 1990], compounds inhibiting or stimulating HDAC activity have become chemo-preventive and therapeutic agents for cancer, neurodegenerative disorders, diabetes, and other major diseases [Marks and Breslow, 2007; Milne et al., 2007; Yang and Seto, 2008].

Known HDACs are grouped into different classes according to phylogenetic analyses and sequence homology to yeast prototypes. Class I members are homologous to yeast Rpd3 and include HDAC1, -2, -3, and -8. Class II HDACs possess catalytic domains with similarity to yeast Hda1 and comprise HDAC4, -5, -6, -7, -9, and -10, which are further divided into two subclasses: IIa (HDAC4, -5, -7, and -9) and IIb (HDAC6 and -10). Sirtuins (sir2-related proteins) form class III. There are seven sirtuins in humans, SIRT1-7. While SIRT1, -2, -3, and -5 possess known deacetylase activity, SIRT4, -6, and -7 are ADP-ribosyltransferases and do not appear to have intrinsic deacetylase activity. HDAC11 is the sole member of class IV and shows comparable similarity to both Rpd3 and Hda1. Members of class I/II/IV form the Rpd3/Hda1 family.

Different HDACs function in various subcellular compartments. With the exception of HDAC3, class I members are primarily nuclear.

This article contains supplementary material, which may be viewed at the Journal of Cellular Biochemistry website at http://www.interscience.wiley.com/jpages/0730-2312/suppmat/index.html.

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Class IIa HDACs are regulated by phosphorylation-dependent nucleocytoplasmic shuttling, whereas HDAC6 is mainly localized to the cytoplasm. SIRT1 is largely nuclear, but other sirtuins have unique subcellular distribution (e.g., SIRT3 is localized to mitochondria). In this Prospect, we focus on nuclear functions of HDACs, especially their roles as transducers and targets of diverse signaling networks. In addition, we discuss three emerging concepts: (i) diversity of nuclear processes that are controlled by HDACs, (ii) active crosstalk of histone deacetylation with other chromatin modifications in nuclear signaling, and (iii) potential link of HDACs to non-coding RNA in gene silencing.

MULTISUBUNIT COMPLEXES OF CLASS I DEACETYLASES

Extensive biochemical purification studies revealed that with the exception of HDAC8, class I members are catalytic subunits of multiprotein complexes (Fig. 1), subjects that are worthy of a detailed discussion here.

Subunit Composition of Class I HDAC Complexes

HDAC1/2 and their orthologues, such as Rpd3 in *S. cerevisiae*, exert the majority of their effects as stable components of distinct multiprotein complexes, the archetypes for which are the yeast Rpd3L (large) complex (Fig. 1A) [Carrozza et al., 2005a,b; Colina and Young, 2005; Keogh et al., 2005] and the mammalian Sin3A complex (Fig. 1B) [Silverstein and Ekwall, 2005]. *S. cerevisiae* also contains a small Sin3 complex, termed Rpd3S (Fig. 1A). Dual Sin3 complexes also exist in the fission yeast *S. pombe* [Nicolas et al., 2007], but so far no complexes homologous to Rpd3S have been identified in metazoans. Other major HDAC1/2 complexes in mammals include the Mi-2/NuRD and CoREST complexes (Fig. 1B). Excitingly, initial studies hint to the existence of a new HDAC1/2 complex containing Atrophin corepressor proteins [Zoltewicz et al., 2004; Wang et al., 2006]. Unlike HDAC1/2, HDAC3 functions as part of a multiprotein complex containing the corepressor proteins N-CoR and SMRT (Fig. 1C) [Karagianni and Wong, 2007]. While Sin3 complexes are present in species from yeast to humans, other complexes are only found in metazoans or plants [Yang and Seto, 2008]. The identification of yeast Rpd3S suggests that more careful analysis of mammalian HDAC complexes may lead to new discoveries.

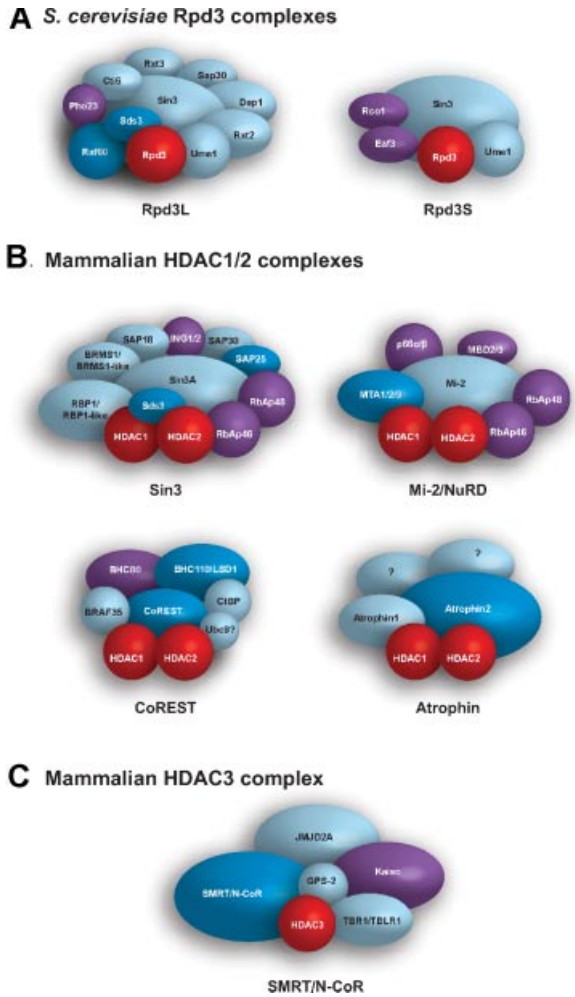

Fig. 1. Class I deacetylase complexes in yeast and mammals. **A**: Cartoons representing the two Rpd3 complexes in the budding yeast *S. cerevisiae*, Rpd3L and Rpd3S. It is interesting to note that there are no RbAp46/48 homologs in these complexes. However, the WD40 domain of Ume1 shows limited similarity to that of RbAp46 (identity/similarity; 20%/48%). **B**: Cartoons showing three HDAC1/2 complexes in mammals, Sin3A, Mi-2/NuRD, and CoREST. Some preparations of the CoREST complex have identified Ubc9 as a subunit [Kuppuswamy et al., 2008]. Also depicted is a putative Atrophin-HDAC1/2 complex, with question marks denoting unknown subunits. **C**: Cartoon illustrating subunit composition of the HDAC3 complex. Deacetylase subunits (i.e., Rpd3, HDAC1/2, and HDAC3) are colored in red, while non-catalytic subunits contributing to deacetylase activity are colored in dark blue, and subunits responsible for genomic targeting are colored in purple. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Targeting Strategies Shared by Class I HDAC Complexes

Class I HDAC complexes are targeted to specific genomic loci through transcription

factor docking, or binding to histones and DNA. The list of transcription factors that bind to these complexes is very long and cannot be covered here, but it is important to discuss the mechanisms through which these complexes bind other chromatin components. Both Sin3A and Mi-2/NuRD complexes contain the histone-binding proteins RbAp46 and RbAp48. Moreover, p66α and p66β from Mi-2/NuRD, as well as N-CoR and SMRT of HDAC3 complexes, have affinity for histones. Furthermore, several subunits of HDAC1/2 complexes contain domains that recognize specific histone modifications. The PHD domain-containing proteins Pho23 and ING2 of the Rpd3L and Sin3A complexes, respectively, preferentially bind to methylated Lys 4 of histone H3 (H3K4me), and the PHD domain of Mi-2α from the Mi-2/NuRD complex can recognize H3K36me3 [Shi et al., 2006]. In the Rpd3S complex, the chromodomain of Eaf3 and the PHD domain of Rco1 cooperate to bind H3K36me3 [Li et al., 2007a]. In contrast, the PHD domain of the CoREST subunit BHC80 selectively associates with non-methylated H3K4 [Lan et al., 2007]. In addition to histones, the Mi-2/NuRD complex can interact with methylated DNA through its MBD2 subunit [Denslow and Wade, 2007]. The wealth of modification-dependent binding modules within HDAC1/2 complexes suggests that specific recruitment of these complexes results from the multifaceted interplay of signaling pathways converging at the level of chromatin modifications.

Regulatory Mechanisms Common to Class I HDACs

Each class I complex has key subunits necessary for deacetylase activation. Deletion analysis demonstrated that Dep1 and Sds3 are essential for Rpd3L complex integrity and deacetylase activity [Carrozza et al., 2005a], while deletion of Raf60 abolished HDAC activity [Colina and Young, 2005]. In the Sin3A complex, Sds3 and SAP25 are crucial for maximal deacetylase activity [Alland et al., 2002; Shiio et al., 2006]. Interestingly, SAP25 is a nucleocytoplasmic shuttling protein, indicating that the Sin3A complex may, at least in part, be regulated through controlled subcellular localization of this subunit [Shiio et al., 2006]. While the SANT domain subunit MTA2 stimulates deacetylase activity of the Mi-2/NuRD complex [Zhang et al., 1999], CoREST, another SANT domain protein, and the histone demethylase BHC110/LSD1 are important for deacetylase activity of the CoREST complex [Lee et al., 2006]. In addition, the SANT domain of Atrophin 2 mediates HDAC1/2 association and affects deacetylase activity (Fig. 1B) [Wang et al., 2006], whereas the SANT domains in N-CoR and SMRT are crucial for HDAC3 activation (Fig. 1C) [Guenther et al., 2001].

Deacetylase activity may also be regulated through post-translational modification. HDAC1 is subject to sumoylation, acetylation, and phosphorylation. CK2-mediated phosphorylation of HDAC3 stimulates deacetylase activity, while dephosphorylation by PP4c/PP4R1 reduces HDAC3 activity [Zhang et al., 2005]. Non-catalytic subunits are also subject to post-translational modification. Sumoylation of p66 subunits affects association with other Mi-2/NuRD subunits [Gong et al., 2006], and Cdk5/p35-mediated phosphorylation of Sds3 enhances its repressive activity [Li et al., 2004b]. Phosphorylation of the N-CoR-interacting protein TAB2 causes nuclear export of an HDAC3 complex [Baek et al., 2002]. Therefore, complex formation provides additional means for deacetylase activity control.

Biological Function of Class I HDAC Complexes in Mammals

Elucidating the precise biological functions of each HDAC1/2 complex is hampered by the presence of common subunits and variation in complex composition. Genetic deletion of HDAC1 in mice is embryonic lethal, while HDAC2 knockout causes perinatal lethality due to cardiac defects [Lagger et al., 2002; Montgomery et al., 2007]. However, it is not yet possible to attribute these HDAC1/2 functions to a particular complex, if any at all. For this, it will be necessary to study the phenotypes of mice lacking HDAC1/2-associating subunits, particularly those unique to a specific complex. However, the results to date, restricted to single gene knockouts of non-catalytic subunits, only serve as a reminder of the difficulty of this task. For example, while mice homozygous for either Sds3 or Sin3A die during early embryogenesis, the underlying defects created by each mutation are distinct [David et al., 2003; Cowley et al., 2005; Dannenberg et al., 2005]. In addition, haploinsufficiency of Sds3, but not Sin3A, accelerates tumor incidence and burden in p53 null mice [David et al., 2006]. These results

suggest that either (i) the major effects of Sds3 are independent of the Sin3/HDAC complex, or (ii) that the presence of Sin3B partially compensates for the loss of Sin3A, thus lessening its phenotypic severity.

Like the Sin3A complex, the biological functions of the NuRD complex can only be inferred from the phenotypes of mice lacking individual NuRD subunits. Yet this is complicated by the heterogeneity of Mi-2/NuRD complexes resulting from various combinations of alternate subunits. Two versions of the Mi-2/NuRD complex are defined by the mutually exclusive presence of either MBD2 or MBD3 [Le Guezennec et al., 2006]. Genetic analysis of these proteins suggests that these two complexes are functionally distinct. MBD2 knockout mice are viable [Hendrich et al., 2001] and resistant to intestinal tumorigenesis [Sansom et al., 2003], while MBD3 knockout mice die in early embryogenesis [Hendrich et al., 2001] due to impaired pleuripotency of $MBD3^{-/-}$ embryonic stem cells [Kaji et al., 2006]. Knockout of a p66 subunit in mice also causes early embryonic lethality [Marino and Nusse, 2007]. Similar to MBD2, it is well established that the MTA proteins are important factors in multiple stages of cancer pathology [Manavathi et al., 2007]. Although it is still not possible to attribute these phenotypes exclusively to the Mi-2/NuRD complex, they hint at the prospect that Mi-2/NuRD has important functions in embryogenesis and carcinogenesis.

The CoREST complex was originally identified based on its ability to prevent the expression of neural genes in non-neural tissues through its association with the RE-1 silencing transcription factor (REST) [Ballas et al., 2001]. It has since been implicated in hematopoietic differentiation [Saleque et al., 2007] and pituitary development [Wang et al., 2007]. Not surprisingly, the effort to ascertain CoREST complex functions is afflicted by the same limitations inherent in precisely identifying the functions of the Sin3A and Mi-2/NuRD complexes. Like these two complexes, subunit composition of the CoREST complex varies depending on the purification technique employed. In fact, it is becoming increasingly evident that these HDAC1/2 complexes are heterogeneous with respect to subunit composition.

Atrophins are evolutionarily conserved transcriptional repressors implicated in various developmental processes [Zhang et al., 2002]. In vertebrates, there are two Atrophin proteins, Atrophin-1 (Atr1) and Atrophin-2 (Atr2, also known as RERE). Atr1 is mutated in the neurodegenerative disease dentatorubral pallidoluysian atrophy (DRPLA), and genetic deletion of Atr2 in mice and zebrafish causes widespread developmental defects [Zoltewicz et al., 2004; Plaster et al., 2007]. The potential involvement of HDAC1/2 in Atr2-mediated gene repression is supported by the finding that pharmacological inhibition of class I/II HDACs phenocopies the physiological perturbations induced by Atr2 gene deletion in zebrafish [Plaster et al., 2007]. Initial experiments suggest that Atr1/2 exist in a complex with HDAC1/2 [Zoltewicz et al., 2004; Wang et al., 2006], but this complex has yet to be subjected to rigorous biochemical purification.

Global deletion of mouse HDAC3 causes embryonic lethality resulting from endothelial and vascular defects [reviewed in Yang and Seto, 2008]. Consistent with the endothelial defects, HDAC3 is required for shear stress- and VEGF-induced stem cell differentiation into endothelial cells [Zeng et al., 2006]. N-CoR deletion results in prenatal lethality [Jepsen et al., 2007]. The mutant embryos show defects in definitive erythropoiesis, as well as in nervous system and thymocyte development. In addition, N-CoR and SMRT promote normal brain development, by preventing precocious differentiation of neural stem cells into astroglia and neurons, respectively [Hermanson et al., 2002; Jepsen et al., 2007]. However, it is not known whether an HDAC3/SMRT/N-CoR complex is responsible for these effects.

Taken together, it is clear that while the functions of yeast Sin3 complexes are well defined [Kurdistani and Grunstein, 2003; Carrozza et al., 2005b; Nicolas et al., 2007], further studies are needed to fully define the composition, function, and regulation of class I complexes in mammals.

CLASS IIa HDACS AS NOVEL SIGNAL TRANSDUCERS

Like Rpd3, Hda1 and the fission yeast counterpart Clr3 form multiprotein complexes. While Hda1 forms a trimeric complex with Hda2 and Hda3 [Kurdistani and Grunstein, 2003], Clr3 forms a distinct complex [Sugiyama et al., 2007]. Both are important for regulating transcription and chromatin organization.

The associated subunits in the complexes are not conserved in metazoans, suggesting that class II HDACs function differently in multicellular organisms. In support of this, a long N-terminal extension and a C-terminal tail of class IIa HDACs (Fig. 2) confer a battery of unique sequence elements important for transducing signals from the cytoplasm to the nucleus.

Class IIa HDACs as Signal-Dependent Transcriptional Corepressors

One of the unique sequence elements is the conserved binding site for MEF2 (Fig. 2A). Class

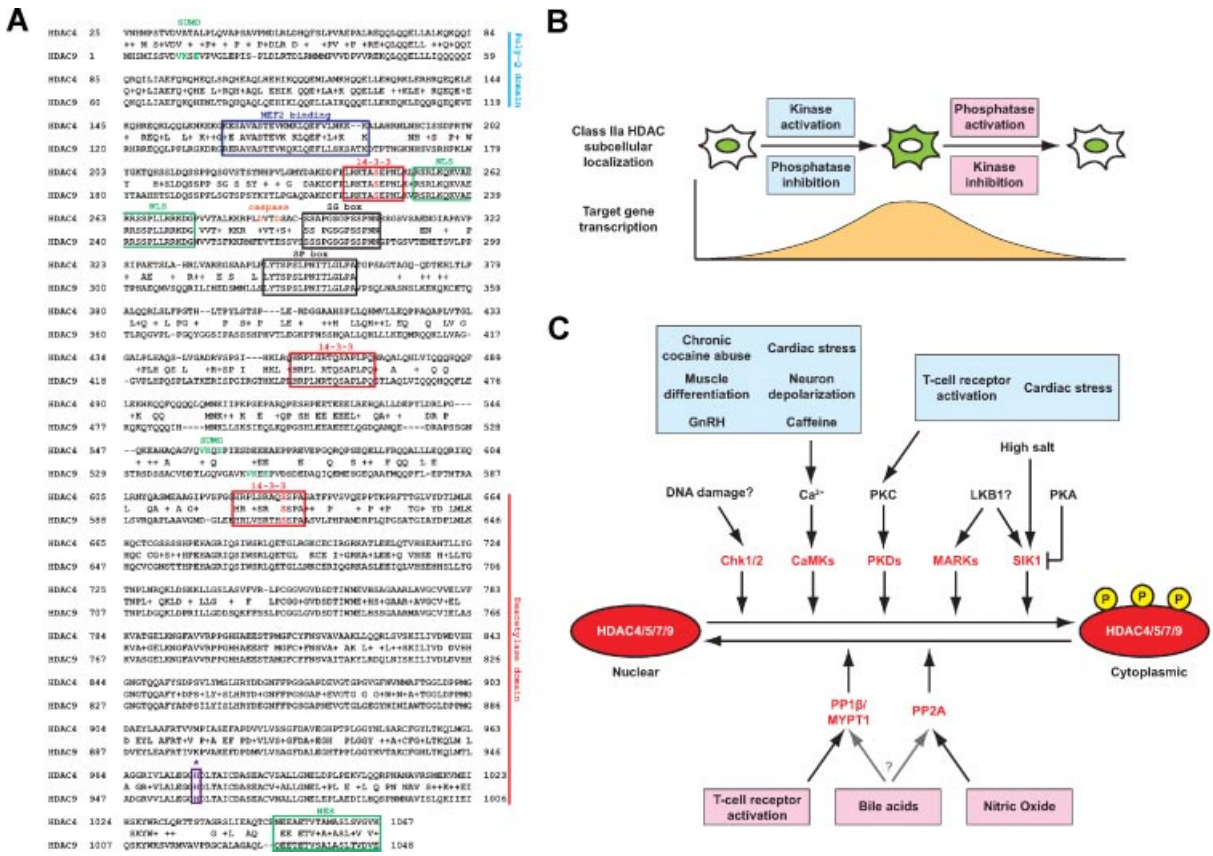

Fig. 2. Regulation of class IIa HDACs by nucleocytoplasmic shuttling. **A**: Sequence alignment of human HDAC4 (GenBank accession number, P56524) and HDAC9 (GenBank accession number, NP_848572). Pairwise comparison with other class IIa HDACs gives similar alignment. The MEF2-binding motif and the 14-3-3 binding sites are boxed in blue and red, respectively, with the conserved serines for 14-3-3 binding denoted with a red ''S.'' The nuclear localization signal (NLS) and nuclear export sequence (NES) are highlighted with green borders. Conserved SG and SP boxes are boxed in black to denote that these two regions remain to be characterized. Of note, S298 of HDAC4, located in the SG box, has been identified as a major site for PP2A-mediated dephosphorylation and nuclear import of HDAC4 [Paroni et al., 2008]. Also indicated are the known and putative sumoylation sites (in green letters), caspase cleavage site (in orange letters), and the His residue that replaces the critical Tyr residue (purple box with asterisk). The 3D structures of the poly-Q domain of HDAC4, the MEF2-binding domain of HDAC5, and the catalytic domain of HDAC7 are known. **B**: Two-step model illustrating the sequence of events involved in regulated nuclear export/import of class IIa HDACs, highlighting the potential importance of reversing the initial change in localization in order to reset the system. Areas of cartoon cells filled in green represent the compartment where a class IIa HDAC is located. **C**: Cartoon depicting the kinases and phosphatases that phosphorylate and dephosphorylate class IIa HDACs, respectively. Also shown are the physiological signals known to act through these kinase/phosphatase pathways. It is noteworthy that some of the kinases and phosphatases, or the signal events, have not been shown for all four class IIa HDACs. Information for specific kinases/phosphatases and their upstream inputs can be found in [Verdin et al., 2003; Yang and Gregoire, 2005; Martin et al., 2007] and references therein, except for the following: bile acids [Mitro et al., 2007], caffeine [Mukwevho et al., 2008], Chk1/2 [Kim et al., 2007], chronic cocaine [Renthal et al., 2007], GnRH [Lim et al., 2007], nitric oxide and PP2A [Illi et al., 2008; Paroni et al., 2008]. CaMK, Ca^{2+}/calmodulin-dependent protein kinase; Chk1/2, checkpoint kinase; GnRH, gonadotropin releasing hormone; LKB1, serine/threonine protein kinase 11, mutated in Peutz-Jeghers syndrome; MARK, microtubule affinity-regulating kinase; PKA, cAMP-dependent protein kinase; PKC, protein kinase C; PKD, protein kinase D; PP1β/MYPT1, protein phosphatase 1β/myosin phosphatase targeting subunit; PP2A, protein phosphatase 2A; SIK1, salt-inducible kinase 1. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

IIa HDACs bind to MEF2 and repress transcription through multiple repression domains. As clearly established from gene inactivation analysis in mice, the MEF2-class IIa HDAC axis plays a key role in diverse tissues [Potthoff and Olson, 2007]. Docking sites for 14-3-3 proteins represent another type of unique sequence element (Fig. 2A). Phosphorylation at these sites stimulates 14-3-3 binding and nuclear export. Conversely, in the non-phosphorylated state, class IIa HDACs do not associate with 14-3-3 proteins and are thus localized to the nucleus, where they bind transcription factors such as MEF2 to repress transcription (Fig. 2B). Multiple kinases targeting these 14-3-3 sites have been identified, and more will undoubtedly be uncovered given the importance and diversity of processes regulated by phosphorylation-dependent nucleocytoplasmic shuttling of class IIa HDACs (Fig. 2C) [Verdin et al., 2003; Yang and Gregoire, 2005; Martin et al., 2007]. In addition, two phosphatases have been shown to dephosphorylate class IIa HDACs and induce nuclear import (Fig. 2B) [Martin et al., 2007; Parra et al., 2007; Illi et al., 2008; Paroni et al., 2008]. Excitingly, bile acids and nitric oxide may act through these phosphatases to induce nuclear localization of HDAC7 [Mitro et al., 2007; Illi et al., 2008]. Therefore, diverse signaling events control reversible phosphorylation of class IIa HDACs to regulate transcription activated by MEF2 and other transcription factors (Fig. 2C).

Ubiquitination and Sumoylation of Class IIa HDACs

In addition to phosphorylation, class IIa HDACs are subject to ubiquitination [Li et al., 2004a; Potthoff et al., 2007] and sumoylation [Kirsh et al., 2002]. Ubiquitination is responsible for the selective degradation of class IIa HDACs in slow-twitch/oxidative skeletal muscle fibers, thus permitting MEF2-dependent transcription of genes that contribute to the slow-twitch phenotype [Potthoff et al., 2007]. Whereas phosphorylation-dependent trafficking of class IIa HDACs allows these proteins to respond to acute signaling events, ubiquitination-induced proteasomal degradation may point to a mechanism for stably activating target genes in situations such as maintenance of cell identity. Sumoylation of HDAC4 and HDAC9 augments transcriptional repression potential. Interestingly, this modification seems to be coupled to HDAC4 nuclear import, and it is inhibited by CaMK-mediated HDAC4 phosphorylation [Kirsh et al., 2002]. This modification is highly efficient, but its biological impact remains to be determined.

Regulation of Class IIa HDAC Deacetylase Activity

Unlike class I HDACs, recombinant proteins of mammalian class IIa HDACs only possess a low level of deacetylase activity. In these class IIa HDACs, a catalytically important Tyr residue is replaced by His [Lahm et al., 2007] (Fig. 2A). This significant discovery raises three intriguing possibilities: (i) mammalian class IIa HDACs are not authentic deacetylases; (ii) their deacetylase activity is regulated, for example, activated by an unknown mechanism; and (iii) they possess deacetylase activity toward acetyllysine-like substrates. Since the orthologs from *C. elegans* and *Drosophila* do not have the Tyr → His substitution and possess high deacetylase activity [Lahm et al., 2007], it is likely that mammalian class IIa HDAC activity is regulated. Addressing this issue is vitally important to our understanding of class IIa HDAC function and regulation.

POTENTIAL ROLES OF CLASS IIb HDACS IN THE NUCLEUS

Most research about the class IIb member HDAC6 has been focused on its roles in the cytoplasm, where it targets tubulin, Hsp90, and cortactin [Boyault et al., 2007a; Yang and Seto, 2008]. Here we briefly discuss its potential roles in the nucleus. HDAC6 can directly repress transcription through its association with several proteins, including the histone acetyltransferase p300, the corepressors L-CoR and ETO-2, and the transcription factors Runx2 and NFκB [Boyault et al., 2007a]. In addition, HDAC6 plays an indirect role in regulating transcription dependent on glucocorticoid receptor [Kovacs et al., 2005]. Related to this, it was recently demonstrated that HDAC6, normally found in a complex with the AAA ATPase p97/VCP, binds the ubiquitinated proteins that accumulate following proteosome impairment [Boyault et al., 2007b]. This leads to the dissociation of the HDAC6-p97/VCP complex, which subsequently frees p97/VCP to act as a segregase and dissociate HSF1 from HSP90 for action in the nucleus. While murine HDAC6 is

actively maintained in the cytoplasm via CRM1-dependent nuclear export, nucleocytoplasmic trafficking of human HDAC6 appears to involve an additional level of control [Boyault et al., 2007a]. Little is known about the function of HDAC10, although it may regulate RNA processing [Shimazu et al., 2007]. Clearly, more studies are warranted to further delineate potential nuclear functions of the class IIb HDACs.

SIRTUINS: LINKING METABOLISM TO GENOME REGULATION

As opposed to zinc-dependent Rpd3/Hda1-like deacetylases, sirtuins require NAD^+ as a cofactor for deacetylation reactions. The central role of NAD^+ in metabolic pathways as a coenzyme with electron-transferring properties links the activity of sirtuins to cell metabolism. In addition, sirtuins have been linked to cell cycle control, apoptosis, differentiation, and the aging process in diverse organisms [Longo and Kennedy, 2006]. Different from other sirtuins, SIRT1 has a tripartite domain organization: a regulatory N-terminal extension for compound binding [Milne et al., 2007], an NAD^+-dependent catalytic domain, and a C-terminal domain of unknown function (Supplementary Fig. S1). The four mammalian sirtuins with known deacetylase activity have distinct biological functions (Fig. 3) and the list of substrates is rapidly growing. On the list are histones H1 and H4, as well as transcription factors and coactivators, including p53, FOXOs, PGC-1α, LXR, and NF-κB [Vaquero et al., 2007]. Interestingly, SIRT1 deacetylation often reverses inhibitory acetylation events and leads to transcriptional activation (e.g., PGC-1α and LXR). In addition, SIRT1 has been implicated in DNA damage response [Yuan et al., 2007].

Cells must be able to response to environmental and internal cues rapidly and efficiently. For this purpose, they utilize sensor/modifier proteins that can both sense external and internal cues and also translate them to proper functional outputs (e.g., post-translational modification of effector proteins). Sirtuins are one group of sensor/modifier proteins that can translate changes in the cellular NAD^+/NADH ratio to protein acetylation status. Recently, the interconnection between SIRT1 and three important sensor/modifier proteins, Akt, AMPK, and PKCβ, has attracted significant attention [Hajnoczky and Hoek, 2007]. This network is integral to aging and age-related phenomena, including cancer, diabetes, and neurodegenerative diseases. Therefore, an emerging issue is to dissect the various links between sirtuin regulation and cellular signaling networks.

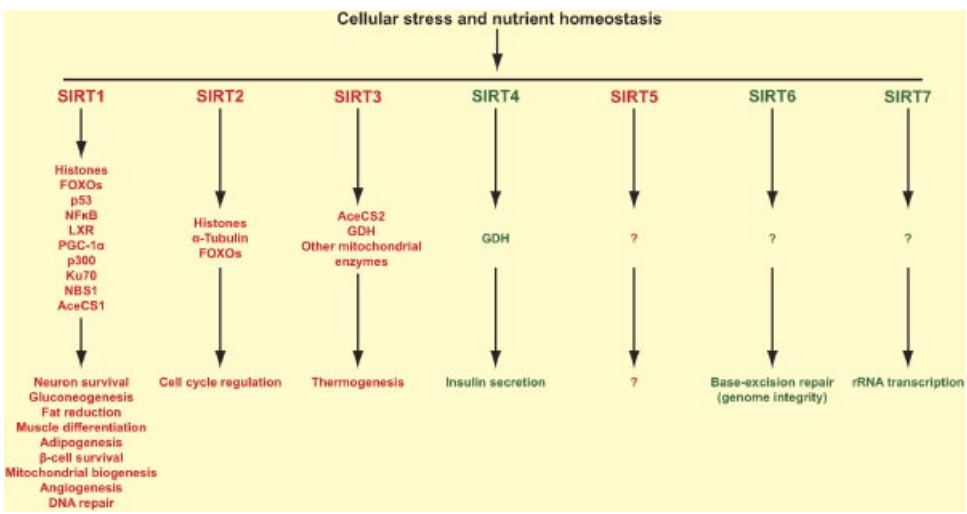

Fig. 3. The human sirtuin family. SIRT1, -2, -3, and -5 are known to possess authentic deacetylase activity. Among them, SIRT5 has a low-level of intrinsic activity, and no in vivo targets of SIRT5 have been identified yet. SIRT4, -6, and -7 do not posses deacetylase activity and instead serve as ADP-ribosyltransferases. Activities of all seven sirtuins are regulated by the cellular NAD^+/NADH ratio. Known substrates for each sirtuin are also shown. Listed below the substrates are the physiological implications of SIRT-mediated deacetylation or ADP-ribosylation. AceCS, acetyl-CoA synthetase; FOXOs, forkhead box O transcription factors; GDH, glutamate dehydrogenase; LXR, liver X receptor; NBS1, Nijmegen Breakage Syndrome 1; NFκB, nuclear factor κB; PGC-1α, peroxisome proliferator-activated receptor γ (PPARγ) coactivator 1α. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

HDACS AS COLLABORATIVE GENOMIC REGULATORS

Although first appreciated as repressors of transcriptional initiation, it is now clear that HDACs regulate multiple genomic processes through interactions with other chromatin regulators. First, there is a clear link between methylation and HDAC activity. The Mi-2/NuRD complex is recruited to DNA regions through a methyl-CpG-binding domain (Fig. 4A) [Denslow and Wade, 2007]. In addition, MeCP proteins interact with HDACs [Klose and Bird, 2006], and plant HDA6 directs histone and DNA methylation [Aufsatz et al., 2007]. Second, since acetylation and methylation on a single Lys residue are mutually exclusive, deacetylation would facilitate methylation. Related to this, *S. pombe* Clr3 stabilizes the heterochromatic mark H3K9me3 and prevents RNA Pol II access to heterochromatic domains [Yamada et al., 2005]. In addition, mouse embryonic fibroblasts (MEFs) lacking Sds3 (of the Sin3A complex) display defects in pericentric heterochromatin formation and Sin3A knockout MEFs exhibit mislocalization of heterochromatin protein 1 [David et al., 2003; Cowley et al., 2005]. Third, mammalian ING1 and ING2 recognize H3K4me3 and target Sin3A complexes to specific genomic locations in a methylation-dependent manner (Fig. 4B) [Shi et al., 2006]. Similarly, yeast Eaf3 binds to H3K36me3 and recruits the Rpd3S complex to coding regions, which is necessary for preventing spurious transcription initiation at cryptic start sites (Fig. 4B) [Carrozza et al., 2005b; Li et al., 2007b].

Fourth, the Lys demethylase activity of LSD1 and the deacetylase activity of HDAC1/2 act cooperatively in the CoREST complex (Fig. 4C) [Lee et al., 2006]. Fifth, a recent study implicated HDACs in silencing of transposable DNA elements [Cam et al., 2008]. In *S. pombe*, the centromeric protein CENP-B binds to and silences *Tf2* retrotransposons in part through the recruitment of class I Clr6 and class II Clr3

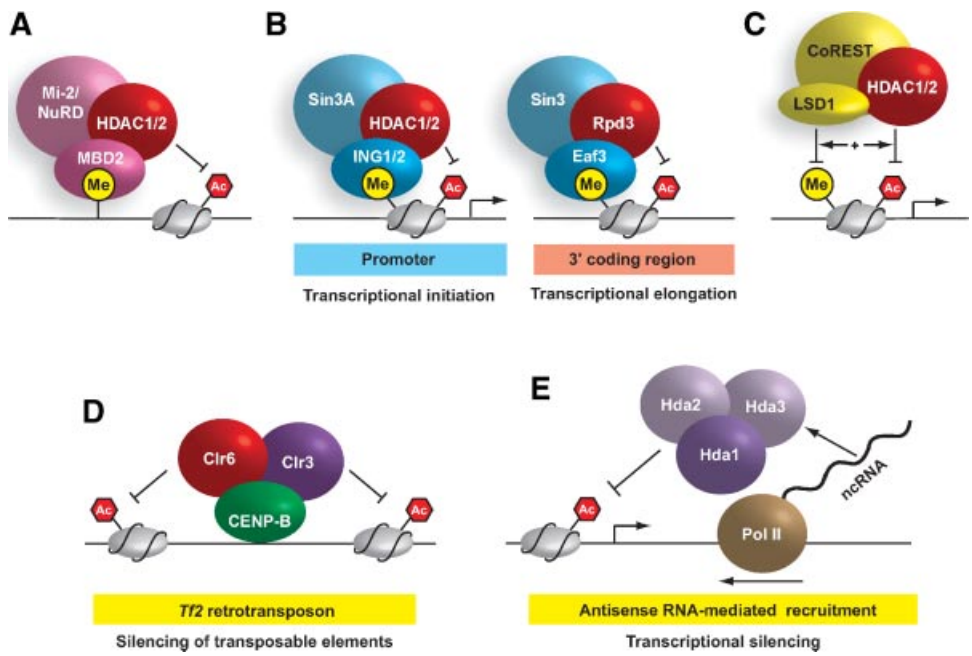

Fig. 4. Interplay of HDACs with different chromatin regulators. **A**: The Mi-2/NuRD complex contains a methyl-CpG-binding subunit to target the complex to methylated DNA for gene silencing. **B**: Two Sin3 complexes contain proteins recognizing specific histone methylation marks. Through their PHD domains, ING1/2 of the Sin3A complex can both bind H3K4me3 for methylation-dependent recruitment to promoters. In comparison, the Rpd3S complex binds H3K36me3 through the chromodomain subunit Eaf3 and the PHD domain subunit Rco1, leading to Rpd3S recruitment to coding regions. **C**: The demethylase activity of BHC110/LSD1 stimulates deacetylase activity of the CoREST complex, while HDAC activity is essential for BHC110/LSD1 activity. **D**: The centromere-binding protein CENP-B associates with *Tf2* retrotransposons and recruits Clr6 and Clr3 to silence *Tf2* retrotransposon expression in *S. pombe*. **E**: The trimeric Hda1 complex is recruited to the Pho84 coding region by antisense RNA transcripts, leading to repression of transcription in *S. cerevisiae*. Ac, acetylation; Me, methylation, ncRNA, non-coding RNA. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

(Fig. 4D). Given the prevalence of transposable elements in the genomes of most eukaryotes, this finding strengthens the role of HDACs in regulating genome integrity and points to their participation in genome evolution. Finally, chronological aging in *S. cerevisiae* (or loss of the exosome protein Rrp6) causes the stabilization of antisense transcripts from the Pho84 coding region (Fig. 4E) [Camblong et al., 2007]. These antisense RNA molecules recruit the class II HDAC Hda1, along with Hda2 and Hda3, to repress transcription of the Pho84 gene, suggesting a role for HDACs in RNA-dependent epigenetic modifications.

CONCLUSIONS AND PROSPECTS

Since the first few HDACs were identified in 1996, the field has grown to considerable maturity. These enzymes are now known to play key roles in numerous physiological processes. However, despite the successes to date in identifying and characterizing HDACs, a wealth of issues remains unexplored. Central among them is the continued elucidation of biological functions of HDACs. To achieve this, conditional knockout mice for all known HDACs, as well as associated subunits (if any), will reveal which HDACs and their complexes (Fig. 1) are important in different tissues at various times. ChIP-on-chip studies of every HDAC in different cell types will shed light on relevant target genes, pointing to new functions for individual HDACs. Moreover, studies using knock-in mutations of non-phosphorylatable class IIa HDACs, and knockout and transgenic mice with altered levels of class IIa HDAC kinases/phosphatases (Fig. 2), will uncover novel physiological processes controlled by this emerging signaling mechanism. It will also be important to extend recent findings from yeast, such as transposable element silencing and cooperation with non-coding RNAs (Fig. 4D,E), to mammalian cells. The processes regulated by sirtuins (Fig. 3) also demand much consideration. The tantalizing prospect of extending human lifespan represents an area of research that will no doubt expand greatly in the coming decades, and sirtuins are likely to be major targets in this endeavor.

HDACs have emerged as exciting drug targets for multiple pathological conditions, as evidenced by the recent FDA approval of the first HDAC inhibitor as an anti-cancer drug [Marks and Breslow, 2007]. A deep reserve of HDAC functions and therapeutic opportunities waits to be mined. Moreover, continued enhancement of our understanding of how HDACs are regulated will directly boost our search for safer and more effective drugs to alter HDAC activity. More careful biochemical purification of class I HDAC complexes and structural analysis of the subunits will help us discover more avenues through which HDAC activity can be manipulated. Furthermore, since histones only comprise a small percentage of the proteins that are deacetylated by HDACs, identification of new non-histone targets will provide valuable information in the search for HDAC functions and "druggable" targets. As we uncover more information about HDAC functions and regulation, it will be imperative to investigate how HDAC signaling pathways connect to the broad nuclear signaling networks that regulate gene expression and other cellular processes.

In addition to drugs for treating various diseases, it is conceivable that resveratrol or other sirtuin activators and possibly inhibitors of classical HDACs will become routinely used as health supplements for disease prevention. Indeed, these types of activities have already been found in red grapes and wine (resveratrol), as well as in garlic and broccoli (classical HDAC inhibitors) [Dashwood and Ho, 2007]. Although considerable progress has been made in the HDAC field over the last decade, it is clear that we remain near the beginning of our journey toward completely understanding the function and regulation of this superfamily of enzymes.

NOTE ADDED IN PROOF

Related to the findings of Lahm et al., 2007, a very recent study provides structural insight into the low deacetylase activity of HDAC7 [Schuetz et al., 2008]. In addition, it was just reported that SIRT7 possesses deacetylase activity [Vakhrusheva et al., 2008].

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REFERENCES

Alland L, David G, Shen-Li H, Potes J, Muhle R, Lee HC, Hou H, Jr., Chen K, DePinho RA. 2002. Identification of mammalian Sds3 as an integral component of the Sin3/histone deacetylase corepressor complex. Mol Cell Biol 22:2743–2750.

Aufsatz W, Stoiber T, Rakic B, Naumann K. 2007. Arabidopsis histone deacetylase 6: A green link to RNA silencing. Oncogene 26:5477–5488.

Baek SH, Ohgi KA, Rose DW, Koo EH, Glass CK, Rosenfeld MG. 2002. Exchange of N-CoR corepressor and Tip60 coactivator complexes links gene expression by NF-kappaB and beta-amyloid precursor protein. Cell 110: 55–67.

Ballas N, Battaglioli E, Atouf F, Andres ME, Chenoweth J, Anderson ME, Burger C, Moniwa M, Davie JR, Bowers WJ, Federoff HJ, Rose DW, Rosenfeld MG, Brehm P, Mandel G. 2001. Regulation of neuronal traits by a novel transcriptional complex. Neuron 31:353–365.

Boyault C, Sadoul K, Pabion M, Khochbin S. 2007a. HDAC6, at the crossroads between cytoskeleton and cell signaling by acetylation and ubiquitination. Oncogene 26:5468–5476.

Boyault C, Zhang Y, Fritah S, Caron C, Gilquin B, Kwon SH, Garrido C, Yao TP, Vourc'h C, Matthias P, Khochbin S. 2007b. HDAC6 controls major cell response pathways to cytotoxic accumulation of protein aggregates. Genes Dev 21:2172–2181.

Cam HP, Noma KI, Ebina H, Levin HL, Grewal SI. 2008. Host genome surveillance for retrotransposons by transposon-derived proteins. Nature 451:431–436.

Camblong J, Iglesias N, Fickentscher C, Dieppois G, Stutz F. 2007. Antisense RNA stabilization induces transcriptional gene silencing via histone deacetylation in *S. cerevisiae*. Cell 131:706–717.

Carrozza MJ, Florens L, Swanson SK, Shia WJ, Anderson S, Yates J, Washburn MP, Workman JL. 2005a. Stable incorporation of sequence specific repressors Ash1 and Ume6 into the Rpd3L complex. Biochim Biophys Acta 1731:77–87; discussion 75–76.

Carrozza MJ, Li B, Florens L, Suganuma T, Swanson SK, Lee KK, Shia WJ, Anderson S, Yates J, Washburn MP, Workman JL. 2005b. Histone H3 methylation by Set2 directs deacetylation of coding regions by Rpd3S to suppress spurious intragenic transcription. Cell 123: 581–592.

Colina AR, Young D. 2005. Raf60, a novel component of the Rpd3 histone deacetylase complex required for Rpd3 activity in *Saccharomyces cerevisiae*. J Biol Chem 280: 42552–42556.

Cowley SM, Iritani BM, Mendrysa SM, Xu T, Cheng PF, Yada J, Liggitt HD, Eisenman RN. 2005. The mSin3A chromatin-modifying complex is essential for embryogenesis and T-cell development. Mol Cell Biol 25:6990–7004.

Dannenberg JH, David G, Zhong S, van der Torre J, Wong WH, Depinho RA. 2005. mSin3A corepressor regulates diverse transcriptional networks governing normal and neoplastic growth and survival. Genes Dev 19:1581–1595.

Dashwood RH, Ho E. 2007. Dietary histone deacetylase inhibitors: From cells to mice to man. Semin Cancer Biol 17:363–369.

David G, Turner GM, Yao Y, Protopopov A, DePinho RA. 2003. mSin3-associated protein, mSds3, is essential for pericentric heterochromatin formation and chromosome segregation in mammalian cells. Genes Dev 17:2396–2405.

David G, Dannenberg JH, Simpson N, Finnerty PM, Miao L, Turner GM, Ding Z, Carrasco R, Depinho RA. 2006. Haploinsufficiency of the mSds3 chromatin regulator promotes chromosomal instability and cancer only upon complete neutralization of p53. Oncogene 25:7354–7360.

Denslow SA, Wade PA. 2007. The human Mi-2/NuRD complex and gene regulation. Oncogene 26:5433–5438.

Gong Z, Brackertz M, Renkawitz R. 2006. SUMO modification enhances p66-mediated transcriptional repression of the Mi-2/NuRD complex. Mol Cell Biol 26:4519–4528.

Guenther MG, Barak O, Lazar MA. 2001. The SMRT and N-CoR corepressors are activating cofactors for histone deacetylase 3. Mol Cell Biol 21:6091–6101.

Hajnoczky G, Hoek JB. 2007. Cell signaling. Mitochondrial longevity pathways. Science 315:607–609.

Hendrich B, Guy J, Ramsahoye B, Wilson VA, Bird A. 2001. Closely related proteins MBD2 and MBD3 play distinctive but interacting roles in mouse development. Genes Dev 15:710–723.

Hermanson O, Jepsen K, Rosenfeld MG. 2002. N-CoR controls differentiation of neural stem cells into astrocytes. Nature 419:934–939.

Illi B, Dello Russo C, Colussi C, Rosati J, Pallaoro M, Spallotta F, Rotili D, Valente S, Ragone G, Martelli F, Biglioli P, Steinkuhler C, Gallinari P, Mai A, Capogrossi MC, Gaetano C. 2008. Nitric oxide modulates chromatin folding in human endothelial cells via protein phosphatase 2A activation and class II histone deacetylases nuclear shuttling. Circ Res 102:51–58.

Jepsen K, Solum D, Zhou T, McEvilly RJ, Kim HJ, Glass CK, Hermanson O, Rosenfeld MG. 2007. SMRT-mediated repression of an H3K27 demethylase in progression from neural stem cell to neuron. Nature 450:415–419.

Kaji K, Caballero IM, MacLeod R, Nichols J, Wilson VA, Hendrich B. 2006. The NuRD component Mbd3 is required for pluripotency of embryonic stem cells. Nat Cell Biol 8:285–292.

Karagianni P, Wong J. 2007. HDA C3: Taking the SMRT-N-CoRrect road to repression. Oncogene 26:5439–5449.

Keogh MC, Kurdistani SK, Morris SA, Ahn SH, Podolny V, Collins SR, Schuldiner M, Chin K, Punna T, Thompson NJ, Boone C, Emili A, Weissman JS, Hughes TR, Strahl BD, Grunstein M, Greenblatt JF, Buratowski S, Krogan NJ. 2005. Cotranscriptional set2 methylation of histone H3 lysine 36 recruits a repressive Rpd3 complex. Cell 123:593–605.

Kim MA, Kim HJ, Brown AL, Lee MY, Bae YS, Park JI, Kwak JY, Chung JH, Yun J. 2007. Identification of novel substrates for human checkpoint kinase Chk1 and Chk2 through genome-wide screening using a consensus Chk phosphorylation motif. Exp Mol Med 39:205–212.

Kirsh O, Seeler JS, Pichler A, Gast A, Muller S, Miska E, Mathieu M, Harel-Bellan A, Kouzarides T, Melchior F, Dejean A. 2002. The SUMO E3 ligase RanBP2 promotes modification of the HDAC4 deacetylase. EMBO J 21: 2682–2691.

Klose RJ, Bird AP. 2006. Genomic DNA methylation: The mark and its mediators. Trends Biochem Sci 31: 89–97.

Kovacs JJ, Murphy PJ, Gaillard S, Zhao X, Wu JT, Nicchitta CV, Yoshida M, Toft DO, Pratt WB, Yao TP. 2005. HDAC6 regulates Hsp90 acetylation and chaperone-dependent activation of glucocorticoid receptor. Mol Cell 18:601–607.

Kuppuswamy M, Vijayalingam S, Zhao LJ, Zhou Y, Subramanian T, Ryerse J, Chinnadurai G. 2008. Role of the PLDLS-binding cleft region of CtBP1 in recruitment of core and auxiliary components of the corepressor complex. Mol Cell Biol 28:269–281.

Kurdistani SK, Grunstein M. 2003. Histone acetylation and deacetylation in yeast. Nat Rev Mol Cell Biol 4:276–284.

Lagger G, O'Carroll D, Rembold M, Khier H, Tischler J, Weitzer G, Schuettengruber B, Hauser C, Brunmeir R, Jenuwein T, Seiser C. 2002. Essential function of histone deacetylase 1 in proliferation control and CDK inhibitor repression. EMBO J 21:2672–2681.

Lahm A, Paolini C, Pallaoro M, Nardi MC, Jones P, Neddermann P, Sambucini S, Bottomley MJ, Lo Surdo P, Carfi A, Koch U, De Francesco R, Steinkuhler C, Gallinari P. 2007. Unraveling the hidden catalytic activity of vertebrate class IIa histone deacetylases. Proc Natl Acad Sci USA 104:17335–17340.

Lan F, Collins RE, De Cegli R, Alpatov R, Horton JR, Shi X, Gozani O, Cheng X, Shi Y. 2007. Recognition of unmethylated histone H3 lysine 4 links BHC80 to LSD1-mediated gene repression. Nature 448:718–722.

Le Guezennec X, Vermeulen M, Brinkman AB, Hoeijmakers WA, Cohen A, Lasonder E, Stunnenberg HG. 2006. MBD2/NuRD and MBD3/NuRD, two distinct complexes with different biochemical and functional properties. Mol Cell Biol 26:843–851.

Lee MG, Wynder C, Bochar DA, Hakimi MA, Cooch N, Shiekhattar R. 2006. Functional interplay between histone demethylase and deacetylase enzymes. Mol Cell Biol 26:6395–6402.

Li X, Song S, Liu Y, Ko SH, Kao HY. 2004a. Phosphorylation of the histone deacetylase 7 modulates its stability and association with 14-3-3 proteins. J Biol Chem 279:34201–34208.

Li Z, David G, Hung KW, DePinho RA, Fu AK, Ip NY. 2004b. Cdk5/p35 phosphorylates mSds3 and regulates mSds3-mediated repression of transcription. J Biol Chem 279:54438–54444.

Li B, Gogol M, Carey M, Lee D, Seidel C, Workman JL. 2007a. Combined action of PHD and chromo domains directs the Rpd3S HDAC to transcribed chromatin. Science 316:1050–1054.

Li B, Gogol M, Carey M, Pattenden SG, Seidel C, Workman JL. 2007b. Infrequently transcribed long genes depend on the Set2/Rpd3S pathway for accurate transcription. Genes Dev 21:1422–1430.

Lim S, Luo M, Koh M, Yang M, bin Abdul Kadir MN, Tan JH, Ye Z, Wang W, Melamed P. 2007. Distinct mechanisms involving diverse histone deacetylases repress expression of the two gonadotropin beta-subunit genes in immature gonadotropes, and their actions are overcome by gonadotropin-releasing hormone. Mol Cell Biol 27: 4105–4120.

Longo VD, Kennedy BK. 2006. Sirtuins in aging and age-related disease. Cell 126:257–268.

Manavathi B, Singh K, Kumar R. 2007. MTA family of coregulators in nuclear receptor biology and pathology. Nucl Recept Signal 5:e010.

Marino S, Nusse R. 2007. Mutants in the mouse NuRD/Mi2 component P66alpha are embryonic lethal. PLoS ONE 2:e519.

Marks PA, Breslow R. 2007. Dimethyl sulfoxide to vorinostat: Development of this histone deacetylase inhibitor as an anticancer drug. Nat Biotechnol 25:84–90.

Martin M, Kettmann R, Dequiedt F. 2007. Class IIa histone deacetylases: Regulating the regulators. Oncogene 26: 5450–5467.

Milne JC, Lambert PD, Schenk S, Carney DP, Smith JJ, Gagne DJ, Jin L, Boss O, Perni RB, Vu CB, Bemis JE, Xie R, Disch JS, Ng PY, Nunes JJ, Lynch AV, Yang H, Galonek H, Israelian K, Choy W, Iffland A, Lavu S, Medvedik O, Sinclair DA, Olefsky JM, Jirousek MR, Elliott PJ, Westphal CH. 2007. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. Nature 450:712–716.

Mitro N, Godio C, De Fabiani E, Scotti E, Galmozzi A, Gilardi F, Caruso D, Vigil Chacon AB, Crestani M. 2007. Insights in the regulation of cholesterol 7alpha-hydroxylase gene reveal a target for modulating bile acid synthesis. Hepatology 46:885–897.

Montgomery RL, Davis CA, Potthoff MJ, Haberland M, Fielitz J, Qi X, Hill JA, Richardson JA, Olson EN. 2007. Histone deacetylases 1 and 2 redundantly regulate cardiac morphogenesis, growth, and contractility. Genes Dev 21:1790–1802.

Mukwevho E, Kohn TA, Lang DM, Nyatia E, Smith JA, Ojuka EO. 2008. Caffeine induces hyperacetylation of histones at the Mef2 Site on the Glut4 promoter and increases Mef2a binding to the site via a Camk-dependent mechanism. Am J Physiol Endocrinol Metab (in press). DOI: 10.1152/ajpendo.00312.2007.

Nicolas E, Yamada T, Cam HP, Fitzgerald PC, Kobayashi R, Grewal SI. 2007. Distinct roles of HDAC complexes in promoter silencing, antisense suppression and DNA damage protection. Nat Struct Mol Biol 14:372–380.

Paroni G, Cernotta N, Russo CD, Gallinari P, Pallaoro M, Foti C, Talamo F, Orsatti L, Steinkuhler C, Brancolini C. 2008. PP2A regulates HDAC4 nuclear import. Mol Biol Cell 19:655–657.

Parra M, Mahmoudi T, Verdin E. 2007. Myosin phosphatase dephosphorylates HDAC7, controls its nucleocytoplasmic shuttling, and inhibits apoptosis in thymocytes. Genes Dev 21:638–643.

Plaster N, Sonntag C, Schilling TF, Hammerschmidt M. 2007. REREa/Atrophin-2 interacts with histone deacetylase and Fgf8 signaling to regulate multiple processes of zebrafish development. Dev Dyn 236:1891–1904.

Potthoff MJ, Olson EN. 2007. ME F2: A central regulator of diverse developmental programs. Development 134:4131–4140.

Potthoff MJ, Wu H, Arnold MA, Shelton JM, Backs J, McAnally J, Richardson JA, Bassel-Duby R, Olson EN. 2007. Histone deacetylase degradation and MEF2 activation promote the formation of slow-twitch myofibers. J Clin Invest 117:2459–2467.

Renthal W, Maze I, Krishnan V, Covington HE III, Xiao G, Kumar A, Russo SJ, Graham A, Tsankova N, Kippin TE, Kerstetter KA, Neve RL, Haggarty SJ, McKinsey TA, Bassel-Duby R, Olson EN, Nestler EJ. 2007. Histone deacetylase 5 epigenetically controls behavioral adaptations to chronic emotional stimuli. Neuron 56:517–529.

Rundlett SE, Carmen AA, Kobayashi R, Bavykin S, Turner BM, Grunstein M. 1996. HDA1 and RPD3 are members of distinct yeast histone deacetylase complexes that regulate silencing and transcription. Proc Natl Acad Sci USA 93:14503–14508.

Saleque S, Kim J, Rooke HM, Orkin SH. 2007. Epigenetic regulation of hematopoietic differentiation by Gfi-1 and Gfi-1b is mediated by the cofactors CoREST and L SD1. Mol Cell 27:562–572.

Sansom OJ, Berger J, Bishop SM, Hendrich B, Bird A, Clarke AR. 2003. Deficiency of Mbd2 suppresses intestinal tumorigenesis. Nat Genet 34:145–147.

Schuetz A, Min J, Allali-Hassani A, Schapira M, Shuen M, Loppnau P, Mazitschek R, Kwiatkowski NP, Lewis TA, Maglathin RL, McLean TH, Bochkarev A, Plotnikov AN, Vedadi M, Arrowsmith CH. 2008. Human HDAC7 harbors a class IIa HDAC-specific zinc binding motif and cryptic deacetylase activity. J Biol Chem DOI: 10.1074/jbc.M707362200.

Shi X, Hong T, Walter KL, Ewalt M, Michishita E, Hung T, Carney D, Pena P, Lan F, Kaadige MR, Lacoste N, Cayrou C, Davrazou F, Saha A, Cairns BR, Ayer DE, Kutateladze TG, Shi Y, Cote J, Chua KF, Gozani O. 2006. ING2 PHD domain links histone H3 lysine 4 methylation to active gene repression. Nature 442:96–99.

Shiio Y, Rose DW, Aur R, Donohoe S, Aebersold R, Eisenman RN. 2006. Identification and characterization of SAP25, a novel component of the mSin3 corepressor complex. Mol Cell Biol 26:1386–1397.

Shimazu T, Horinouchi S, Yoshida M. 2007. Multiple histone deacetylases and the CREB-binding protein regulate pre-mRNA 3′-end processing. J Biol Chem 282:4470–4478.

Silverstein RA, Ekwall K. 2005. Sin3: A flexible regulator of global gene expression and genome stability. Curr Genet 47:1–17.

Sugiyama T, Cam HP, Sugiyama R, Noma K, Zofall M, Kobayashi R, Grewal SI. 2007. SHREC, an effector complex for heterochromatic transcriptional silencing. Cell 128:491–504.

Taunton J, Hassig CA, Schreiber SL. 1996. A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p. Science 272:408–411.

Vakhrusheva O, Smolka C, Gajawada P, Kostin S, Boettger T, Kubin T, Braun T, Bober E. 2008. Sirt7 increases stress resistance of cardiomyocytes and prevents apoptosis and inflammatory cardiomyopathy in mice. Circ Res DOI: 10.1161/CIRCRESAHA.107.164558.

Vaquero A, Sternglanz R, Reinberg D. 2007. NAD+-dependent deacetylation of H4 lysine 16 by class III HDACs. Oncogene 26:5505–5520.

Verdin E, Dequiedt F, Kasler HG. 2003. Class II histone deacetylases: Versatile regulators. Trends Genet 19:286–293.

Wang L, Rajan H, Pitman JL, McKeown M, Tsai CC. 2006. Histone deacetylase-associating Atrophin proteins are nuclear receptor corepressors. Genes Dev 20:525–530.

Wang J, Scully K, Zhu X, Cai L, Zhang J, Prefontaine GG, Krones A, Ohgi KA, Zhu P, Garcia-Bassets I, Liu F, Taylor H, Lozach J, Jayes FL, Korach KS, Glass CK, Fu XD, Rosenfeld MG. 2007. Opposing LSD1 complexes function in developmental gene activation and repression programmes. Nature 446:882–887.

Yamada T, Fischle W, Sugiyama T, Allis CD, Grewal SI. 2005. The nucleation and maintenance of heterochromatin by a histone deacetylase in fission yeast. Mol Cell 20:173–185.

Yang XJ, Gregoire S. 2005. Class II histone deacetylases: From sequence to function, regulation, and clinical implication. Mol Cell Biol 25:2873–2884.

Yang XJ, Seto E. 2008. The Rpd3/Hda1 family of lysine deacetylases: From bacteria and yeast to mice and men. Nat Rev Mol Cell Biol 9:206–218.

Yang WM, Inouye C, Zeng Y, Bearss D, Seto E. 1996. Transcriptional repression by YY1 is mediated by interaction with a mammalian homolog of the yeast global regulator R PD3. Proc Natl Acad Sci USA 93:12845–12850.

Yoshida M, Kijima M, Akita M, Beppu T. 1990. Potent and specific inhibition of mammalian histone deacetylase both in vivo and in vitro by trichostatin A. J Biol Chem 265:17174–17179.

Yuan Z, Zhang X, Sengupta N, Lane WS, Seto E. 2007. SIRT1 regulates the function of the Nijmegen breakage syndrome protein. Mol Cell 27:149–162.

Zeng L, Xiao Q, Margariti A, Zhang Z, Zampetaki A, Patel S, Capogrossi MC, Hu Y, Xu Q. 2006. HDAC3 is crucial in shear- and VEGF-induced stem cell differentiation toward endothelial cells. J Cell Biol 174:1059–1069.

Zhang Y, Ng HH, Erdjument-Bromage H, Tempst P, Bird A, Reinberg D. 1999. Analysis of the NuRD subunits reveals a histone deacetylase core complex and a connection with DNA methylation. Genes Dev 13:1924–1935.

Zhang S, Xu L, Lee J, Xu T. 2002. Drosophila atrophin homolog functions as a transcriptional corepressor in multiple developmental processes. Cell 108:45–56.

Zhang X, Ozawa Y, Lee H, Wen YD, Tan TH, Wadzinski BE, Seto E. 2005. Histone deacetylase 3 (HDAC3) activity is regulated by interaction with protein serine/threonine phosphatase 4. Genes Dev 19:827–839.

Zoltewicz JS, Stewart NJ, Leung R, Peterson AS. 2004. Atrophin 2 recruits histone deacetylase and is required for the function of multiple signaling centers during mouse embryogenesis. Development 131:3–14.