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## The physiological roles of histone deacetylase (HDAC) 1 and 2: complex co-stars with multiple leading parts

**Richard D.W. Kelly and Shaun M. Cowley[1]**
Department of Biochemistry, University of Leicester, Henry Welcome Building, Lancaster Road, Leicester LE1 9HN, U.K.

### Abstract

**HDACs (histone deacetylases) 1 and 2 are ubiquitous long-lived proteins, which are often found together in three major multiprotein co-repressor complexes: Sin3, NuRD (nucleosome remodelling and deacetylation) and CoREST (co-repressor for element-1-silencing transcription factor). Although there is a burgeoning number of non-histone proteins within the acetylome, these complexes contain multiple DNA/chromatin-recognition motifs, which, in combination with transcription factors, target HDAC1/2 to chromatin. Their physiological roles should therefore be viewed within the framework of chromatin manipulation. Classically, HDACs were thought to be recruited predominantly by transcriptional repressors to facilitate local histone deacetylation and transcriptional repression. More recently, genome-wide assays have mapped HDAC1/2 and their associated proteins to transcriptionally active loci and have provided alternative context-specific functions, whereby their repressive functions are subtly exerted to balance transcriptional activation and repression. With a few significant exceptions (early embryogenesis, brain development), HDAC1 and HDAC2 are functionally redundant. In most mouse knockout studies, deletion of both enzymes is required in order to produce a substantial phenotype. HDAC1/2 activity has been implicated in the development of numerous tissue and cell types, including heart, skin, brain, B-cells and T-cells. A common feature in all HDAC1/2-knockout, -knockdown and small-molecule inhibitor studies is a reduction in cell proliferation. A generic role in cell cycle progression could be exploited in cancer cells, by blocking HDAC1/2 activity with small-molecule inhibitors, making them potentially useful drug targets.**

## Introduction: regulation of the ‘acetylome’

The ε-acetylation of lysine residues (Lys-Ac) is an abundant post-translational modification, occurring on thousands of proteins, both nuclear and cytoplasmic, and is likely to play a regulatory role in all cellular processes [1]. However, unlike the complex regulation of the ‘kinome’ (500+ kinases and 100+ phosphatases), the ‘acetylome’ is organized by just 18 acetyltransferase and 18 deacetylase enzymes. Histones were the first acetylated proteins to be described [2], and they remain the best characterized substrates of these enzymes, therefore, despite the hundreds of non-genomic substrates now identified, they are still most often referred to as HATs (histone acetyltransferases) and HDACs (histone deacetylases). Knockout studies in yeast, *Drosophila* and mice have shown that individual HDAC function is highly divergent (summarized in [3–5]), and yet, counterintuitively, there is little substrate specificity between individual enzymes [6]. As a family of enzymes, this is strikingly different from their lysine demethylase counterparts, which display exquisite amino acid specificity [7]. The disconnect between specific function and lack of substrate specificity indicates an important functional role for co-factors.

Following the discovery of the first HDACs [8–10], much of the work that followed was focused on their ability

**Key words:** deacetylase, gene expression, histone deacetylase 1 (HDAC1), histone deacetylase 2 (HDAC2).

**Abbreviations used:** ChIP, chromatin immunoprecipitation; CoREST, co-repressor for element-1-silencing transcription factor; dKO, double knockout; E, embryonic day; ES, embryonic stem; GATA4, GATA-binding protein 4; HAT, histone acetyltransferase; HDAC, histone deacetylase; HID, HDAC-interaction domain; LSD1, lysine-specific histone demethylase 1; Lys-Ac, ε-acetylation of lysine residues; MBD3, methyl-CpG-binding domain protein 3; MTA, metastasis-associated; NF-κB, nuclear factor κB; NuRD, nucleosome remodelling and deacetylation; PNS, peripheral nervous system; SAP, Sin3-associated polypeptide; SDS3, suppressor of defective silencing 3; SMRT, silencing mediator of retinoid and thyroid receptors.

[1]To whom correspondence should be addressed (email smc57@le.ac.uk).


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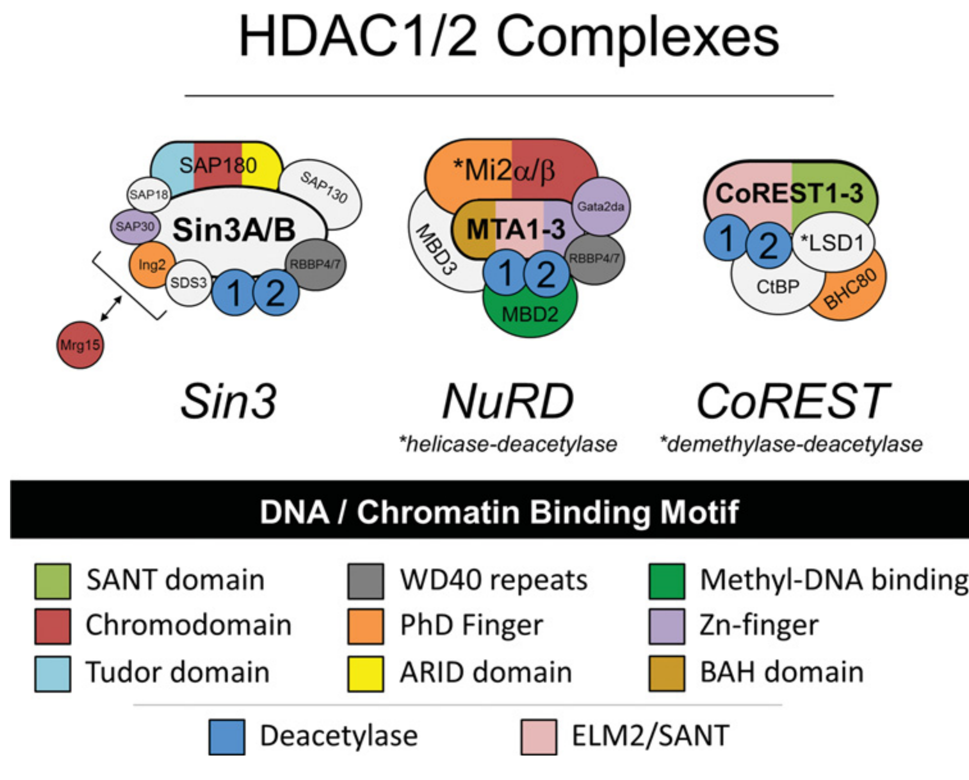
**Figure 1** | **A summary of the three main HDAC1/2-containing complexes: Sin3, NuRD and CoREST**

Each complex contains multiple subunits with DNA/chromatin-recognition motifs indicated by the colour code. In addition, deacetylase and ELM2/SANT domains are also shown. The HDAC1/2-binding subunit within each complex, i.e. Sin3A/B, MTA1/2/3 or CoREST1/2/3, are shown in bold.




to deacetylate histones, because it had been known for some time that histone acetylation correlated with active gene expression [2,11]. The N-terminal tails of the core histones H3 and H4 are rich in lysine residues, which, being positively charged, promote both histone–DNA and histone–histone interactions innately, restricting access to the underlying DNA. Acetylation of key lysine residues in H3 ($Lys^{9}$, $Lys^{14}$, $Lys^{18}$ and $Lys^{23}$) and H4 ($Lys^{5}$, $Lys^{8}$, $Lys^{12}$ and $Lys^{16}$) negates these electrostatic effects and also inhibits the association of histone H1, a linker histone which facilitates nucleosome condensation [12]. Lys-Ac of H3/H4 also provides a docking site for bromodomain-containing proteins, such as P/CAF [p300/CREB (cAMP-response-element-binding protein)-binding protein-associated factor] [13] (itself a HAT), which promotes further a relaxed chromatin structure and active gene transcription. A textbook model thus emerged in which the recruitment of HDACs to target genes by transcriptional repressors facilitates local histone deacetylation and thus transcriptional repression [14].

With a focus on histone deacetylation, it is probably worth pointing out that not all 18 mammalian HDACs are active enzymes, or localized within the nucleus. HDAC6, for instance, is predominantly cytoplasmic [15], and class-2a HDACs (4, 5, 7 and 9) have little or no deacetylase activity owing to the presence of a histidine, rather than a tyrosine, residue within the active site [16]. The subfamily with the most definitive role in regulating gene expression are the class-1 HDACs: 1, 2, 3 and 8. They are ubiquitous long-lived nuclear enzymes which regulate gene expression as the catalytic core of the Sin3, NuRD (nucleosome remodelling and deacetylation), CoREST (co-repressor for element-1-silencing transcription factor) and SMRT (silencing mediator of retinoid and thyroid receptors)/NCoR (nuclear receptor co-repressor) co-repressor complexes. Our own work has focused on the highly related sister proteins HDAC1 and HDAC2 (83 % identical). Simultaneous deletion of *Hdac1* and *Hdac2* in T-cells [17] and ES (embryonic stem) cells causes a 50 % reduction in total HDAC activity, making them the predominant HDACs, at least biochemically, in the mammalian nucleus.

## HDAC1/2-containing complexes

HDAC1/2 are present in the mammalian nucleus as part of stable multiprotein complexes. HDAC1/2 do not bind to DNA directly and are most probably inactive in the absence of an interacting partner [18]. Therefore the complex into which they are incorporated dictates their functional context. The best-characterized HDAC1/2-containing complexes are the Sin3A, NuRD and CoREST complexes (Figure 1). These complexes are recruited to chromatin by transcription factors (e.g. Mad1–Sin3A [19]), and/or the histone-recognition motifs found within complex components [e.g. Sin3A: via the PhD (plant homeodomain) finger of Ing2; summarized

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in Figure 1]. Indeed, the chromatin-recognition properties of the holo-complex may in part explain the lack of specificity among HDAC enzymes. Since each of the three complexes contains at least two histone-binding subunits, HDAC1/2 are aptly titled 'histone' deacetylases and their physiological roles (gene repression, cell cycle, DNA repair, etc.) should be viewed within the framework of chromatin manipulation. The present review is not intended to be a shopping list of complex components and knockout phenotypes, but rather a perspective on individual complexes and the functionality they bring to HDAC1/2 function.

The first and most obvious observation is that there are three major HDAC1/2 complexes (Figure 1). In contrast, HDAC3 (53 % identity with HDAC1) binds exclusively to the co-repressor SMRT. Mouse knockouts of individual complex members, including Sin3A [20], MBD3 (methyl-CpG-binding domain protein 3) [21] and LSD1 (lysine-specific histone demethylase 1) [22], all result in early embryonic lethality, indicating that each has a unique function. This is not entirely unexpected because, other than HDAC1/2 and Rbbp4/7 (retinoblastoma-binding protein 4/7), there are no shared components. Rather, individual complexes are able to mix and match unique, but complementary, combinations of histone-modifying activities: deacetylase/helicase (NuRD), or deacetylase/demethylase (CoREST). The NuRD complex contains HDAC1/2 and Mi2$\beta$, which has an ATP-dependent helicase activity, allowing the ability to reposition and deacetylate nucleosomes simultaneously [23]. The CoREST complex contains both HDAC1/2 and the histone demethylase LSD1 [24]. LSD1 demethylates dimethyl-H3K4 (a signal which potentiates gene expression) which, in combination with deacetylation of H3, synergize to repress active transcription. The canonical Sin3A complex alone appears to contain only deacetylase activity [19,25].

How are HDAC1/2 recruited to such diverse complexes? Both MTA (metastasis-associated) 1 and CoREST1 contain an ELM2 domain, which is sufficient for interaction with HDAC1 [26]. In addition, both proteins contain a SANT domain adjacent to the ELM2 domain. This is significant because the extended SANT-like DAD domain of SMRT recruits HDAC3 in combination with Ins$P_4$ [27]. Residues on the surface of HDAC3 which mediate the interaction with Ins$P_4$ are also conserved in HDAC1/2, suggesting that Ins$P_4$ may also play a role in their interaction with MTA1 and CoREST1. Sin3A binds to HDAC1/2 via its HID (HDAC-interaction domain) [19], which contains no obvious ELM2/SANT-like regions. Instead, it utilizes a third protein, SDS3 (suppressor of defective silencing 3), thus producing a distinct core tertiary complex [25,28]. Sin3A, SDS3 and HDAC1 (Rpd3) are all highly conserved in yeast, whereas obvious orthologues of MTA and CoREST proteins are lacking. Therefore, from an evolutionary point of view, the Sin3A HID may represent the first type of HDAC1/2 interaction, with higher eukaryotes having adopted a second method via adjacent ELM2/SANT domains. The molecular details of how HDAC1/2 are included, but HDAC3 excluded, remain to be resolved.

A third and largely ignored aspect of these multiprotein complexes is the heterogeneity of their composition. Given the multitude of interacting proteins, multiple co-repressor homologues, in addition to HDAC1 and HDAC2, it seems inevitable that several Sin3/NuRD/CoREST species will coexist within the cell. The initial biochemical purification of these complexes, and most of the subsequent follow-up studies, do not distinguish different subtypes. In models, we generally depict HDAC1 and HDAC2 together, but co-immunoprecipitation reveals that approximately 40 % of HDAC1 exists independently of HDAC2 [29]. Composition may even be cell-type-specific, since the Sin3A complex in T-cells contains predominantly HDAC1, with significant HDAC2 recruitment occurring only after *Hdac1* deletion [17]. Assuming that there is more than one HDAC enzyme per complex [30], then this allows for the presence of HDAC1/HDAC1-, HDAC1/HDAC2- or HDAC2/HDAC2-containing complexes. There are a multiple of HDAC1/2-binding subunits within each complex: two Sin3 (Sin3A/B), three MTA (MTA1/2/3) and three CoREST (CoREST1/2/3) which add their own specificity. Sin3A [20] and Sin3B [31] both produce distinct phenotypes in mouse knockouts for example. In addition to multiple core constituents, each of the complexes has numerous additional, possibly substoichiometric, components. The HID domain of Sin3A alone is able to recruit HDAC1, HDAC2, SDS3, MRG15 [MORF4 (mortality factor 4)-related gene on chromosome 15], SAP (Sin3-associated polypeptide) 130 and SAP180 [25]. Whether all of these proteins are able to bind simultaneously is uncertain. In lower organisms, fortunately, the picture is a little clearer. Subfractionation of the Sin3–HDAC1 (Rpd3)-containing complex in *Saccharomyces cerevisiae* identified distinct high-molecular-mass (Sin3A–Sds3–Rpd3–Sap30) and low-molecular-mass (Sin3A–Eaf3–Rpd3) complexes, with the smaller form specifically deacetylating the 3′ end of actively transcribed genes [32]. At present, we lack the molecular details of HDAC1/2 complex isoforms in mammalian cells; many may prove to be redundant. However, as with the example of large and small isoforms of Sin3/HDAC1 in yeast, there are likely to be specific activities associated with some subtypes.

## HDAC1/2: global regulators of gene expression

Since HDAC1/2 are associated with histone deacetylation and co-repressor complexes, it was somewhat surprising that knockout studies in yeast [33] and mice [29,34,35] revealed a significant portion of down-regulated genes, suggesting that HDAC1/2 might also positively regulate transcription. Even so, a view persisted that these might be explained away as indirect effects of *Hdac1/2* deletion, perhaps due to increased expression of transcriptional repressor. However, genome-wide ChIP (chromatin immunoprecipitation) studies of HDAC1/2 and other complex components reveal their enrichment at transcriptionally active loci in human [36],

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mouse [37] and yeast [38] cells, confirming the link between HDAC1/2 and both gene repression and activation.

In human CD4$^{+}$ T-cells [36] and mouse ES cells [37], ChIP-Seq (ChIP combined with high-throughput sequencing) experiments have mapped HDACs (including HDAC1/2) to both transcriptionally active and primed loci. The recruitment of HDACs to active genes is hypothesized to counteract the actions of HATs and RNAP-II (RNA polymerase II), in order to reset the chromatin states between rounds of transcriptional activity. Indeed, gene activation has been shown to be a cyclical process, which requires both activating and repressive epigenetic processes to facilitate the sequential assembly and disassembly of a transcriptionally productive complex [39]. Therefore HDAC recruitment may participate in promoter 'clearance', essential to 'reinitialize' the promoter before a second round of transcriptional initiation can begin [40].

HDAC1/2 have been shown to function within multi-protein repressor complexes and are recruited to DNA via interaction with tissue-specific transcription factors. Recent evidence examining the genetic locations and function of the NuRD complex has provided alternative explanations for the association of deacetylating complexes within transcriptionally active regions. In ES cells, the deletion of *Hdac1* [37] or components of the NuRD complex [41,42] increases pluripotent gene expression, suggesting that histone deacetylation activity may limit the expression level of highly enriched genes in ES cells. Loss of MBD3 disrupts the NuRD complex and increases the expression of a subset of pluripotent genes, preventing lineage commitment. Knockdown of one of these elevated genes, *Klf4* (Krüppel-like factor 4), rescues the defective differentiation phenotype, indicating that NuRD acts to 'fine-tune' the transcription of pluripotent genes. This allows these cells to respond to differentiation signals, by permitting cells to exit self-renewal through the subsequent silencing of pluripotent genes [43].

## A generic role in cell cycle: implications for cancer development and potential therapy?

With the exception of some colon cancer cell types which contain a truncating mutation in *Hdac2* [44], most, if not all, mammalian cells will express both HDAC1 and HDAC2. However, the housekeeping nature of *Hdac1/2* gene expression does not mean that they are entirely unregulated. HDAC1 levels increase 4-fold upon ES cell differentiation, which is consistent with a general tightening of chromatin during lineage commitment [45]. The *Hdac2* gene contains a stress-response element, regulated by the glucocorticoid receptor, which increases HDAC2 expression by approximately 50 % in mouse models of Alzheimer's disease [46]. This ubiquitous expression pattern probably underlines a generic physiological role. A common phenotype in all HDAC1/2-knockout [29,47–49] and knockdown [50] studies, is a reduction in cell proliferation. In both primary and transformed cells, loss of HDAC1/2 is associated with up-regulation of the cyclin-dependent kinase inhibitors, p21$^{WAF1/CIP1}$ [47,49] and p57$^{Kip2}$ [29], which may limit $G_1$–S-phase transition. However, there are additional explanations for this anti-proliferative effect. Mouse embryo fibroblasts lacking HDAC1/2, transformed with large T antigen to bypass $G_1$-phase regulation, display nuclear bridging, nuclear fragmentation and mitotic catastrophe [51].

The anti-proliferative effect of HDAC inhibitors are well known and have been tested in any number of cancer-related settings [52]. However, it is worth noting that the clinically used HDAC inhibitors SAHA (suberoylanilide hydroxamic acid), valproic acid and romidepsin are broad-range inhibitors, blocking the activity of all $Zn^{2+}$-dependent HDACs (HDAC1–11), making them rather blunt pharmacological tools. The data from mouse models and cell lines suggest that inhibition of HDAC1/2 alone will produce the same anti-proliferative effect, and, as a more targeted therapy, with potentially reduced side effects. RNAi (RNA interference) knockdown [50] and small-molecule inhibitors (such as MS-275) which target HDAC1/2 [53] both inhibit the growth of cancer cells with increased levels of apoptosis. Of course, if HDAC1/2 are essential for cell cycle progression, then it is unlikely that tumours will select for inactivating mutations. The COSMIC (Collection Of Somatic Mutations In Cancer) database [54] shows the presence of heterozygous mutations in various cancers (probably bystander mutations), but none that generate homozygous inactivation. In fact, the opposite may be true. There is a growing number of studies which have utilized primary tissue and cells from various cancer types, which show overexpression of HDAC1/2 [55–57].

Although these data satisfy our preconception of HDAC1/2 function, we should view them with some caution. In many examples, HDAC2 alone is overexpressed, and this may simply reflect its stress-response capacity, in reaction to the cellular stress of the tumour (increased DNA damage, hypoxia, etc.). Also, many of the 'HDAC1/2-overexpression' studies treat them as isolated enzymes, when, in reality, their physiological activity is governed by incorporation into multiprotein complexes. Therefore an additional question in these studies ought to be, if HDAC2 is overexpressed, is its binding partner within the complex (Sin3A, MTA1 or CoREST1) also overexpressed to the same extent?

## Mouse models of HDAC1/2 function

Given the degree of primary sequence and biochemical identity of HDAC1/2, it is unsurprising that, to a large degree, they are functionally redundant. Conditional deletion of *Hdac1* or *Hdac2* alone, using tissue-specific transgenic models, produces no obvious deleterious effects on the development of heart, brain, smooth muscle, endothelial cells, neural crest cells [34], oocytes [58], epidermis [59], B-cells [29] and T-cells [17]. Whereas simultaneous deletion of *Hdac1/2* in these same cell types produces a profound phenotype (summarized in Table 1 and discussed below). When one or the other is lost, there is often a degree of compensation,

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**Table 1** | **A list of the mice generated with either a germline or a tissue-specific deletion of *Hdac1* and *Hdac2* and a summary of the phenotype observed.**

MEF, mouse embryonic fibroblast; SV40, simian virus 40.

| Tissue target | Gene target | Genetic model | Phenotype | Reference |
|---|---|---|---|---|
| Embryonic | *Hdac1* | Gene trap; *Hdac1*$^{+/-}$ matings | Embryonic lethality (E10.5) due to severe proliferation defects and retarded development. | [47] |
| | | CAG-Cre; *Hdac1*$^{+/-}$ matings | Embryonic lethality before E9.5 | [34] |
| | | *Hdac1*$^{+/-}$; *p21*$^{-/-}$ matings | Embryonic lethality (∼E9.5) and severely growth retarded. Disruption of the p21 gene does not rescue the lethal phenotype | [49] |
| | *Hdac2* | CAG-Cre; *Hdac2*$^{+/-}$ matings | Knockout mice die perinatally from cardiac defects and display perinatal cardiomyocyte defects | [34] |
| | | Gene trap; *Hdac2*$^{+/-}$ matings | Intrauterine loss and occasional resorbing of fetuses, causing low Mendelian ratios. Approximately 50 % of pups survive and exhibit cardiac hypertrophy | [60] |
| | | Gene trap *Hdac2*$^{+/-}$ matings | Offspring are viable, but exhibit reduced body size and decreased incidence of intestinal tumours | [62] |
| | | EIIa-Cre; *Hdac2*$^{+/-}$ matings | Low Mendelian ratios. Mice are viable but smaller than wild-type littermates. Compromised fertility | [61] |
| ES cell | *Hdac1* | *Hdac1*$^{+/-}$ matings | *Hdac1*-deficient mouse ES cells show reduced cellular proliferation and elevated levels of p21$^{WAF1/CIP1}$ | [47] |
| | | *Hdac1*$^{+/-}$; *p21*$^{-/-}$ matings | Disruption of the p21 gene rescues the proliferation phenotype of *Hdac1*-deficient mouse ES cells | [49] |
| | | *ER*-Cre; *Hdac1*$^{Lox/Lox}$ | *Hdac1*-deficient mouse ES cells display precocious differentiation | [45] |
| | *Hdac2* | *ER*-Cre; *Hdac2*$^{Lox/Lox}$ | *Hdac2*-deficient mouse ES cells are phenotypically similar to controls | [45] |
| Oocyte | *Hdac2* | *Zp3*-Cre; *Hdac2*$^{Lox/Lox}$ | *Hdac2* deficiency in oocytes reduces litter size | [58] |
| | *Hdac1/2* (dKO) | *Zp3*-Cre; *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* dKO are infertile and display developmental arrest of oocytes at the mid-growth stage | |
| T-cell | *Hdac1/2* (dKO) | *Lck*-Cre; *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* dKO lethal at approximately 15 weeks. Mice display reduced thymocyte cellularity, developmental arrest and neoplastic transformation of immature T-cells (thymus) | [17] |
| B-cell | *Hdac1/2* (dKO) | *Mb1*-Cre or *CD23*-Cre; *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* dKO impairs B-cell development, rare pre-B-cells blocked in $G_1$-phase with increased apoptosis. Deletion in mature resting B-cells has no negative impact unless cells are induced to proliferate | [29] |
| Neuron | *Hdac2* | *Nestin*-Cre; *Hdac2*$^{+/-}$ matings | *Hdac2* knockout leads to enhanced learning and memory formation | [61] |
| PNS (peripheral nervous system) | *Hdac1/2* (dKO) | *Dhh*-Cre; *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* dKO mice developed severe tremors, hindlimb paralysis and died postnatal around week 2. Mice exhibited severe myelin deficiency | [64] |
| | *Hdac1/2* (dKO) | *Dhh*-Cre; *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* dKO mice showed tremor and reduced hindlimb mobility, and died at postnatal week 2–3. Mice exhibited severe myelin deficiency and massive Schwann cell loss | [65] |
| CNS (central nervous system) | *Hdac1/2* (dKO) | *Gfap*-Cre; *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* (dKO) in developing neurons results in severe hippocampal abnormalities, disorganization of cortical neurons, and is lethal postnatal by day 7 | [66] |
| Oligodendrocyte | *Hdac1/2* (dKO) | *Olig1*-Cre; *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* (dKO) mice developed severe tremor, reduced oligodendrocyte development and died around postnatal week 2 | [63] |

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**Table 1** | Continued

| Tissue target | Gene target | Genetic model | Phenotype | Reference |
|---|---|---|---|---|
| Heart | *Hdac1/2* (dKO) | αMhc-Cre; *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* (dKO) causes cardiac arrhythmias and dilated cardiomyopathy resulting in neonatal lethality | [34] |
| Skin/epidermis | *Hdac1/2* (dKO) | Krt14-Cre; *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* (dKO) mice died perinatally and exhibit failure of hair follicle specification and epidermal proliferation | [59] |
| Haemopoiesis/liver | *Hdac1/2* (dKO) | *Mx1*-Cre (interferon-inducible); *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* (dKO) mice display no apparent histological abnormalities in liver tissues. However, megakaryocytes undergo massive apoptosis and mice display severe thrombocytopenia | [48] |
| Adipogenesis | *Hdac1/2* (dKO) | Cre-expressing lentiviruses; *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* (dKO) in cultured MEFs blocks adipogenesis | [70] |
| MEF | *Hdac1/2* (dKO) | *ER*-Cre (tamoxifen); *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* (dKO) MEFs fail to proliferate in culture and gradually undergo apoptosis | [29] |
| | *Hdac1/2* (dKO) | *ER*$^{T2}$ – Cre (tamoxifen); *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* (dKO) MEFs results in a dramatic growth arrest and exhibit a cell cycle block in the $G_1$-phase that is associated with up-regulation of p21 and p57 | [48] |
| | *Hdac1/2* (dKO) | *ER*$^{T2}$ – Cre (tamoxifen); *Hdac1/2*$^{Lox/Lox}$ | *Hdac1/2* (dKO) in immortalized MEFs (SV40 T antigen) display nuclear bridging, nuclear fragmentation and mitotic catastrophe. | [51] |

deletion of *Hdac1* causes increased HDAC2 expression for example [35,45,47]. HDAC1, which predominantly occupies the Sin3A complex in T-cells, is replaced by HDAC2 upon deletion [17]. As ever in biology, there a few significant exceptions to the rule and we begin our summary of HDAC1/2 mouse models with these.

## Distinct roles for HDAC1/2 in embryogenesis and heart development

HDAC1 function is essential for development in mouse [34,47,49], with embryos exhibiting growth retardation and severe proliferation defects. Lethality occurs at approximately E (embryonic day) 10.5; however, evidence suggests that HDAC1 function is required at earlier developmental stages. Disruption of the p21 (*Cdkn1a*) gene in *Hdac1*$^{-/-}$ ES cells rescues the proliferative defect; however, the embryonic lethal phenotype is preserved in knockout mice [49]. Although gastrulation appears to be initiated in *Hdac1*-null embryos, it is likely that differentiation is also affected. Indeed, conditional deletion of *Hdac1* (but not *Hdac2*) in ES cells causes precocious differentiation, characterized by increased expression of cardiomyocyte and neural markers in embryoid bodies [45]. These observations suggest a role for HDAC1 in early development and cell cycle regulation. Indeed, ChIP experiments in ES cells confirm that HDAC1 is recruited to the promoters of various cell cycle regulators [37,49], and numerous studies on other cell types have highlighted the role of class I HDACs in cell cycle control and DNA damage response.

In contrast with the essential role of HDAC1 during embryogenesis, HDAC2 appears to be dispensable for differentiation and development (Table 1). Studies examining the consequence of HDAC2 deficiency have observed diverse phenotypes during development and beyond. In one study, *Hdac2*-null (*Hdac2*$^{-/-}$) mice die postnatally from cardiac defects [34], whereas in a second study, approximately half of the *Hdac2*$^{-/-}$ pups died perinatally, with the remaining littermates surviving to adulthood [60]. These surviving mice had smaller hearts with increased myocardium than control littermates, and were unable to exhibit normal hypertrophic responses. Other knockout models suggest that *Hdac2*$^{-/-}$ mice are viable [61,62]. Examples of other non-pathological phenotypes include reduced body size, decreased incidence of intestinal tumours [62] and enhanced memory formation [61]. The explanation for these differing phenotypes may lie in the distinct approaches used to generate loss-of-function *Hdac2* alleles (e.g. knockout compared with genetrap), combined with variability of mouse strains (see Table 1). There are probably additional homologue-specific functions to uncover. However, what is undeniable is that simultaneous loss of both HDAC1 and HDAC2 produces a much stronger phenotype.

## Tissue-specific HDAC1/2 dKO (double knockout)

A variety of tissue-specific *Hdac1*/2 knockouts have been reported in the last 5 years (summarized in Table 1). In the developing nervous system, for instance, deletion

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of both *Hdac1/2* in the oligodendrocyte lineage resulted in stabilization and nuclear translocation of $\beta$-catenin, which negatively regulates oligodendrocyte development by repressing *Olig2* expression [63]. This disruption of oligodendrocyte differentiation results in the development of severe tremors, and mice die within 2 weeks of birth. In the PNS (peripheral nervous system), HDAC1/2 are critical for Schwann cell differentiation [64,65]. Deletion of *Hdac1/2* in developing neurons results in severe hippocampal abnormalities, absence of cerebellar foliation, disorganization of cortical neurons and lethality by postnatal day 7 [66]. These abnormalities in brain formation can be attributed to a failure of neuronal precursors to differentiate into mature neurons and to excessive cell death.

In the developing haemopoietic system, dKO models produce some unexpected phenotypes. HDAC1 and HDAC2 are not essential for liver homoeostasis (*in vivo*), but are critical for erythrocyte–megakaryocyte differentiation [48]. Dual inactivation of *Hdac1* and *Hdac2* results in thrombocytopenia and apoptosis of megakaryocytes. Similar results are observed within B-cell lineages, whereby inactivation of HDAC1/2 in early B-cell progenitors impairs differentiation and is accompanied by the dramatic cell cycle arrest in $G_1$-phase and apoptosis [29]. In an additional study examining T-cell development, *lck*-cre driven HDAC1/2 dKO caused developmental arrest [17]. These animals exhibited reduced thymocyte cellularity, failure to fully activate the CD4 co-receptor and reduced T-cell receptor signalling. This disruption of T-cell development results in lethality after approximately 15 weeks, as a consequence of neoplastic transformation of immature T-cells.

## Evidence for non-histone targets of HDAC1/2 activity in mice

Classically, the biochemical functions of HDACs are generally described in the context of chromatin, as histone deacetylation results in the tightening of nucleosomal arrays. However, HDACs also catalyse the deacetylation of many non-histone proteins such as p53 [59,67], E2F1 [68], GATA4 (GATA-binding protein 4) [69] and NF-$\kappa$B (nuclear factor $\kappa$B) [64]. In some instances, these non-histone targets of HDAC1/2 are deregulated in knockout studies and contribute to phenotypic outcomes.

In the PNS, HDAC1/2 may control Schwann cell differentiation, by co-operating with the NF-$\kappa$B p65 subunit and modifying its acetylation state [64]. It was shown that increased p65 acetylation in conditional knockouts leads to the deregulation of positive regulators of myelination and induces the expression of differentiation inhibitors. Another study, however, demonstrated that, in Schwann cells, HDAC1/2 control the transcriptional programme of myelination and the survival of Schwann cells [65]. More specifically, that study concluded that HDAC2, in co-operation with Sox10, activates the transcriptional programme of myelination, whereas HDAC1 regulates the level of $\beta$-catenin expression to control Schwann cell survival. These independent studies utilized the same *Dhh* (Desert Hedgehog) gene regulatory elements to drive Cre recombinase and induce the conditional knockouts of HDAC1/2. Furthermore, both describe the same phenotypes in knockout mice, suggesting that both histone and non-histone targets of HDACs may simultaneously regulate Schwann cell differentiation.

In epidermal development, HDAC1/2 functions to mediate the repressive activity of p63 and suppress p53 [59]. In this system, conditional dKO pups exhibit undifferentiated epidermis, failed to develop hair follicles, tongue papillae, eyelids and teeth, resulting in perinatal death. Whereas p63-activated basal layer genes were unaffected by *HDAC1/2* deletion, genes suppressed by p63 were markedly deregulated, suggesting that HDAC1/2 regulate the repressive function of p63. Moreover, p53 activity was increased due to hyperacetylation, contributing to proliferative defects in HDAC1/2-deficient epidermis. Therefore, at least in epidermal differentiation, HDAC1/2 function through both histone and non-histone targets.

Simultaneous deletion of *Hdac1/2* in cardiomyocytes results in complete neonatal lethality, accompanied by cardiac arrhythmias and dilated cardiomyopathy [34]. GATA4, the critical regulator of myocyte proliferation, has been identified as a novel non-histone target of HDAC2 [69]. The direct interaction of HDAC2 with GATA4 and a small homeobox protein, HOP, regulate cardiac myocyte proliferation during embryonic development, through the activation of GATA4-dependent cell cycle genes. Taken together, HDAC2 function in cardiac lineages requires further scrutiny to ascertain the role it plays in influencing cardiac differentiation.

## Concluding remarks

There is now a wealth of published papers on the function of HDAC1/2 in the cell cycle, DNA synthesis, DNA repair and the regulation of gene expression. And yet, paradoxically, being an important player in multiple key processes has also limited our analysis. Double deletion of *Hdac1/2* most often results in a fundamental block, early in the development of a system (neuronal, haemopoietic, etc.) due to the simultaneous failure of numerous cellular pathways. Of course, this also makes HDAC inhibitors which block their activity such potent cytotoxic agents and potentially useful anti-cancer agents. To better understand their role in specific pathways, we require more precise tools, e.g. knockin mice with mutant forms of HDAC1/2 which bind only to specific co-repressor complexes, to improve on the informative, but rather blunt, knockout reagents currently in use.

It is becoming increasingly clear that Lys-Ac is an important post-translational modification, which plays a regulatory role in all cellular processes [1]. Lys-Ac is a dynamic modification with a half-life in the order of minutes, rather than hours. It is curious then that, as individual researchers, we tend to study either HATs or HDACs, but rarely both together; despite (presumably) regulating the

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same sites of Lys-Ac as two sides of the same coin. Perhaps, as we begin to understand the substrates of these two enzyme classes better, we will begin to address the balance in their regulation, which, if perturbed, as multiple HAT and HDAC knockouts have demonstrated, can have drastic consequences for the cell.

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