Histone Deacetylases 1 and 2 in Memory Function

HDAC1 and HDAC2 in memory function

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Abstract

Histone deacetylases (HDACs) have been implicated in learning and memory, and their dysregulation has been linked to cognitive impairment in brain aging and neurodegenerative diseases. In this review, we focus on HDAC1 and HDAC2, highlighting recent progress on their roles in regulating brain function through distinct mechanisms, including gene repression and DNA repair pathways. Moreover, we discuss evidence demonstrating how HDAC1 and HDAC2 could be modulated and their potentials as targets to combat memory deficits.

Keywords: Histone acetylation, HDAC1, HDAC2, learning and memory, DNA repair

1. Introduction

Epigenetic mechanisms, including histone modifications, are important processes that change gene expression in response to environmental stimuli[1,2]. Histones are proteins that pack DNA into the structure called nucleosomes, and each nucleosome comprises the core histones H2A, H2B, H3, and H4, together with a linker histone H1[3]. Core histones are enriched with lysine and arginine, and their positive charges facilitate the tight packaging of negatively charged DNA with histone[3]. Post-translational modifications (PTMs) of histones, including histone acetylation, occur on lysine residues within the histone protruding tail and are key players in the regulation of chromatin states (**Figure 1**)[3,4].

The levels of histone acetylation are modulated by the activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs)[4,5]. HATs transfer the acetyl group from acetyl coenzyme A (acetyl CoA) to lysine residues, whereas HDACs remove it. Acetyl-lysine residues on histone protruding tails are recognized and bound by proteins containing the bromodomain (BRD), the plant homeodomain (PHD) finger or the YEATS domains, sometimes referred to as "epigenetic readers"[6–8]. Many epigenetic readers are ATP-dependent chromatin remodelers or transcription factors, which loosen up the tight configuration of chromatin and recruit protein complexes for the initiation of transcription[3–7]. Conversely, deacetylation of histone protruding tails prevents readers from binding, thereby counteracting the activating effects of HATs (**Figure 1**). Moreover, class I HDACs are founds in multiprotein complexes, such as mSin3A, NURD, and CoREST. These HDAC-containing complexes contain distinct components but are generally linked to gene silencing. For instance, CoREST complex is composed of RE1 silencing transcription (REST) factor, HDAC1/HDAC2, BHC80 scaffold protein, and lysine-specific histone demethylase 1A (LSD1)[9]. The CoREST complex is recruited to the RE1 DNA motif recognized by REST, followed by histone H3 deacetylation and histone demethylation (H3K4me2) that facilitate the formation of a repressive chromatin structure and hence gene silencing.

In humans, 18 HDAC enzymes have been identified and categorized into four classes based on their sequence similarities (**Figure 2**). Class I, II, and IV are Zn^{2+}-containing HDACs that use acetyl-CoA as a co-substrate, whereas the class III HDACs use nicotinamide adenosine

dinucleotide (NAD^+). HDACs modulate various biological/cellular processes, and the dysregulation of HDACs leads to numerous pathological states, including neurological symptoms[4,10]. Prior review articles on histone acetylation have provided a comprehensive coverage of their roles in memory function[10–12]. In this review article, we focus on two members of class I HDAC: HDAC1 and HDAC2, with particular emphasis on highlighting their roles in memory function via gene silencing and genomic integrity mechanisms. We also discuss pan-HDAC inhibitors and HDAC1 activators, focusing on their chemical structure and modes of action. Additionally, we summarize the U.S. Food and Drug Administration (FDA)-approved applications for the use of HDAC inhibitors, and we list the completed and on-going clinical trials using HDAC inhibitors for the treatment of brain disorders, including schizophrenia and Alzheimer's disease (AD).

2. Memory formation requires changes in histone acetylation

Changes in histone acetylation are essential for long-term memory formation[13–17]. Contextual fear conditioning is a well-established behavioral paradigm for studying hippocampal-dependent associative memory formation, consolidation, and recall[18,19]. In this paradigm, rodents learn to associate a neutral context with a fear-inducing stimulus (*e.g.,* foot shock) and the fearful experience then transforms into long-term memory, which is process of fear memory formation and consolidation. Recall in fear memory refers to retrieval of memory from the past, causing a freezing behavior as a fear response when placed in the previously neutral context[18,19].

Studies have demonstrated that acetylation of histone on several lysine residues, including H3K9, H3K14, H4K5, and H4K12, increases in mouse hippocampal tissue one hour after fear conditioning[17]. Importantly, intra-hippocampal infusion of the pan-class HDAC inhibitor (trichostatin A/TSA) immediately after fear conditioning increases histone acetylation in mouse brain and enhances fear memory formation[20]. Moreover, pharmacological inhibition of HDAC by TSA also facilitates synaptic plasticity, shown by an increase in the induction of hippocampal long-term potentiation (LTP)[16,20], a molecular mechanism underlying memory formation[21]. Similarly, acute or chronic administration of the pan-class HDAC inhibitor (sodium butyrate, vorinostat/SAHA) prior to fear conditioning increases histone acetylation

and is able to strengthen fear memory formation and augment hippocampal LTP induction[14,22]. Increased histone acetylation leads to chromatin relaxation and gene transcription[4], and pan-class HDAC inhibitor treatment activates the expression of specific genes involved in synaptic plasticity and memory formation, including *Bdnf, Egr1, Nr4a1, Shank3, Snap25, GluR1, NR2A,* and *Synaptotagmin*[23]. Increased histone acetylation (H3K9, H3K14, H4K5, H4K8, and H4K12) is also evident in mice exposed to an enriched environment[14], which also elicits synaptic plasticity and memory consolidation[24], further strengthening the case for a significant contribution of histone acetylation to memory formation.

3. HDAC inhibitor treatment improves memory function mainly via targeting HDAC2

Pharmacological inhibition of HDAC enhances memory function[20,22]. Emerging evidence indicates HDAC2 as the major player responsible for the cognitive enhancement observed following HDAC inhibitor treatment with the particular focus on suberoylanilide hydroxamic acid (vorinostat/SAHA)[22]. SAHA targets predominantly class I HDACs and specifically HDAC6, an HDAC isoform in class IIb[25–27]. Chronic treatment with SAHA reduces histone deacetylation in brain tissue and is accompanied by a robust memory improvement effect in mice[22]. An affinity-based approach followed by proteomic analysis first identified HDAC1 and HDAC2 as the main cellular targets of SAHA[25]. Pharmacological and mouse genetic approaches were utilized in the subsequent studies to further dissect out the contribution of HDAC1 versus HDAC2 to cognitive function. In the study led by Guan *et al.*, the mouse HDAC1 or HDAC2 coding sequence was inserted in frame with the endogenous initiation codon of exon 1 of the *Mapt* (the gene coding Tau protein), thereby overexpressing HDAC1 or HDAC2 predominantly in neurons[22]. Whereas brain-specific conditional knockout (cKO) of HDAC2 was achieved by crossing *Hdac2*$^{f/f}$ mice to those expressing *Nestin-Cre*, resulting in HDAC2 deletion in neurons and astrocytes[22]. Guan *et al.* reported that mice overexpressing HDAC2 in neurons show impairments in synaptic plasticity and memory formation[22], whereas HDAC2 cKO (*Hdac2*$^{f/f}$; *Nestin-Cre*) mice exhibit an increase in dendritic spine density and hippocampal LTP induction accompanied by a more robust fear response in the fear conditioning paradigm[22], which replicates the behavior demonstrated by mice receiving HDAC inhibitor treatment. Similarly, mice with HDAC2 deletion specifically in neurons by

CamKII-Cre line also show improved associated fear memory in the contextual fear conditioning task[28]. Most importantly, SAHA-mediated memory enhancement is abolished in HDAC2 cKO (*Hdac2$^{f/f}$*; *Nestin-Cre*) mice[22]. Chronic treatment with SAHA in HDAC2 cKO (*Hdac2$^{f/f}$*; *Nestin-Cre*) mice did not alter the freezing response in the fear conditioning test, relative to vehicle treatment[22]. Thus, these findings reveal HDAC2 as a specific negative modulator of synaptic plasticity/cognition and as the main target of HDAC inhibitor SAHA for facilitating learning and memory. Genetic manipulation of HDAC1, including neuronal-specific overexpression or neuronal-specific deletion by *CamKII-Cre* line, has no effect on synaptic plasticity and cognitive function in adult mice[22,28]. However, a recent study that we will discuss in the later section reveals HDAC1 modulating memory function in an age-dependent manner[29].

4. HDAC2 represses the expression of synaptic genes through chromatin remodeling

The molecular mechanism by which HDAC2 negatively modulates synaptic plasticity and memory function has been well-characterized[22]. HDAC2 localizes to the promoter region of genes associated with synaptic and cognitive function, where HDAC2 stimulates histone deacetylation and suppresses gene expression by cooperating with the co-repressor CoREST[22]. CoREST is an essential scaffolding protein of a co-repressor complex that suppresses transcription of neuronal-specific genes[30,31]. Studies show that CoREST preferentially complexes with HDAC2 but not HDAC1 in neurons[22]. Evidence suggests that HDAC2 mainly reduces histone acetylation of H4K5 and H4K12 in mouse hippocampal tissue[22]. Furthermore, chromatin immunoprecipitation assays demonstrated that HDAC2 is more enriched than HDAC1 at the promoters of genes regulating synaptic/cognitive function, including *BDNF, Egr1, Fos, Camk2a, Creb1, Nrnx3, GluR1/R2*, and *NR2A/2B,* also known as HDAC2 targets. No such HDAC2 enriched binding to the promoter regions of cell-cycle genes have been found[22]. HDAC1 and HDAC2 show similar abundance at the promoters of *Cdkn1a*, *Atf4*, and *Pgk1*, the genes involved in cell cycle regulation[22]. Increased HDAC2 occupancy is associated with a reduction in histone acetylation at the gene promoters, which subsequently results in chromatin condensation and gene silencing[4]. The expression of HDAC2 target genes decreases in mice overexpressing HDAC2 but increases in mice lacking HDAC2 or in mice receiving HDAC inhibitor treatment conversely[22]. These observations

indicate that HDAC2 is preferentially enriched at the promoter of synaptic/memory-associated genes and represses their expression through epigenetic regulation in concert with CoREST.

5. Increased HDAC2 levels in Alzheimer's disease

Altered histone acetylation have been found in humans and rodents with neurodegenerative diseases, including AD, and are linked to reduced expression of synaptic/memory-associated genes and memory deficits[32,33]. Notably, HDAC2 is believed to play a role in this disease process. Postmortem analysis shows increased HDAC2 expression in the hippocampal CA1 neurons of patients with AD, relative to healthy control individuals[33]. Whereas the levels of other two class I HDAC members, HDAC1 and HDAC3, remain unaltered[33]. Upregulated neuronal expression of HDAC2 but not HDAC1 is also evident in the hippocampal and cortical region of the 5XFAD mouse model of AD that expresses mutated forms of the human *APP* and *PSEN1* genes[33], and in the hippocampal CA1 of the rats injected with amyloid fibril[34]. In the APP/PS1 mice, another mouse model of AD overexpressing mutant *APP* and *PSEN1* genes, animals perform poorly in a contextual fear conditioning paradigm and also display a decline in histone acetylation (H3K9, H3K14, H4K5, H4K8, H4K12, and H4K16) compared to age-matched control group[35]. Chronic administration of HDAC inhibitor sodium butyrate restores histone acetylation (H3K14, H4K5, and H4K12) and enhances fear memory formation in these animals and this effect is paralleled by increased expression of synaptic/memory-associated genes or so-called HDAC2 targets[35]. Similarly, other HDAC inhibitors including TSA, SAHA, and phenylbutyrate have also been demonstrated to reinstate memory function in the APP/PS1 mouse model of AD[23,36,37].

Additional evidence supporting a role for HDAC2 in memory deficits in the context of neurodegenerative diseases was shown in the CK-p25 mice model of AD[33]. CK-p25 is a mouse model of severe neurodegeneration expressing an inducible human p25 under the control of a forebrain-specific *CamKII* promoter[38]. Following p25 induction, HDAC2 levels upregulate in excitatory neurons and are followed by an increase in HDAC2 binding to the promoters of synaptic/memory-associated genes and a reduction in histone acetylation (H2BK5, H3K14, H4K5, and H4K12) in these promoter regions, thereby leading to gene repression and

memory impairment[33]. Reducing HDAC2 levels by small hairpin approach restores histone acetylation in the promoter of synaptic/memory-associated genes and their expression in CK-p25 mice[33]. Accordingly, knockdown of HDAC2 also rescues synaptic plasticity and cognitive deficit in CK-p25 mice[33]. Together, these observations support the potential use of HDAC2 inhibitors as powerful therapeutics to treat memory impairment associated with AD and other neurodegenerative diseases.

6. Regulation of HDAC2 in normal and disease contexts

Given the significant role for HDAC2 in synaptic/memory function, numerous studies have focused on how HDAC2 might be regulated. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that promotes neuronal differentiation, synapse formation, and synaptic plasticity[39]. Importantly, BDNF is a HDAC2 target but it can also regulate HDAC2 function through S-nitrosylation[4]. In rat cultured neurons, BDNF increases nitric oxide (NO) synthesis and promotes the S-nitrosylation of HDAC2[40]. S-nitrosylation of HDAC2 occurs at Cys262 and Cys274 residues, which has no effect on HDAC2 enzymatic activity but induces the release of HDAC2 from chromatin[40](**Figure 3**). In unstimulated neurons, HDAC2 is tightly associated with gene promoters and suppresses transcription by deacetylating histones[40]. Whereas S-nitrosylated HDAC2 unbinds from the chromatin and induces chromatin remodeling, thereby facilitating the expression of HDAC2 target genes that are important for neuronal function such as *Fos* and *Egr1*[40]. S-nitrosylation of HDAC2 is also involved in memory formation. In the fear conditioning paradigm, S-nitrosylation of HDAC2 increases 1 hour after fear conditioning and during recent memory recall[41]. During recent memory recall, upregulated HDAC2 nitrosylation is associated with an increase in histone acetylation and *c-Fos* expression[41]. Mice receiving NO synthase inhibitor L-NAME 1 hour before recent memory recall display reduced HDAC2 S-nitrosylation, and these mice fail to retrieve extinction of recent fear memory[41]. Collectively, these findings describe how HDAC2 modulates neuronal/brain functions by S-nitrosylation under normal circumstances.

HDAC2 accumulates in the brain of AD mouse model and humans with AD[33,34]. Aberrant expression of HDAC2 in AD has been attributed to two molecular mechanisms through gene transcription and post-translational modification, respectively. Glucocorticoid receptor (GR)

is a ligand-inducible transcription factor that belongs to the steroid-responsive nuclear receptor superfamily[42]. GR becomes activated upon the binding of glucocorticoid, a steroid hormone linked to stress response[42]. Activated GR associates with the glucocorticoid responsive elements (GREs) at promoter or enhancer regions of target genes, and is followed by subsequent alteration of gene transcription rates[42]. Active form of GR can act as transcriptional activator or repressor, depending on the recruited protein complex at GREs or on its post-translational modifications[42]. One conserved GRE locates in the proximal promoter region of the *HDAC2* gene[33]. HDAC2 accumulation occurs concomitantly with an increase in phosphorylated GR on serine 211 residue in cultured neurons treated with Aβ42, the predominant amyloid-β peptide founds in the brains of AD patients. Evidence indicates that the cyclin-dependent kinase 5 (Cdk5) mediates the phosphorylation of GR (S211) in pathological contexts. The levels of GR phosphorylation and HDAC2 are increased in mice with aberrant Cdk5 activity and decreased in mice lacking Cdk5 conversely[33]. pGR (S211) is a well-characterized modification that correlates with increased transcriptional activity. Accordingly, pGR (S211) promotes *HDAC2* gene transcription through binding to the GRE in *HDAC2* promoter[33] (**Figure 3**).

HDAC2 accumulation is not restricted to AD but also present in a wide array of disease models associated with stress and synaptic/cognitive impairment, including neuroinflammation induced by the gram-negative bacteria cell wall component lipopolysaccharide (LPS), sleep deprivation, chronic restraint stress procedure, and maternal exposure of high fat diet[43–48]. Thus, aberrant HDAC2 accumulation is likely caused by stress hormone glucocorticoid-GR signaling pathway, and HDAC2 might be one of the factors contributing to defective memory function in these disease models.

Chronic stress has been generally linked to a suppression of synaptic density and glutamate transmission in the hippocampal and cortical regions. However, enhanced synaptic function in the nucleus accumbens (NAc) has been demonstrated in the chronic social defect stress (CSDS) model[49,50], where mice develop a long-lasting aversion to social contact after experiencing repeated aggression. Studies show that NAc medium spiny neurons (MSNs)

have increased spine density and synaptic transmission following social defeat[51]. The expression of HDAC2 known targets, *c-FOS* and *BDNF*, increases in the NAc of mice after repeated social defect. Most importantly, augmented synaptic strength shapes the stress response and correlates with social avoidance in mice[51], and reduction of BDNF in the NAc oppose CSDS-induced social aversion[49]. These findings suggest that weakening synaptic strengthen by HDAC2 in certain brain region/circuit could likely be protective for stress-induced mood and anxiety disorders.

HDAC2 accumulation in AD can also be caused by c-Abl. c-Abl is a tyrosine protein kinase that has been found activated in AD and in many other neurodegenerative diseases[52]. Introducing cultured neurons to Aβ oligos (AβO) results in c-Abl-mediated phosphorylation of HDAC2 at Tyr 222, which is linked to elevated HDAC2 protein stability and its deacetylase activity[53] (**Figure 3**). Pharmacological inhibition of c-Abl by imatinib reduces HDAC2 accumulation in the brain of an AD mouse model[53]. In AβO-treated cultured neurons, imatinib treatment is able to prevent the recruitment of HDAC2 to promoters of genes regulating synaptic/cognitive function, such as *GluR1, NR2A, Synaptophysin,* and *Synaptotagmin*[53]*.* Moreover, c-Abl-induced HDAC2 accumulation is also evident in Niemann-Pick type C disease, a fatal pediatric neurodegenerative lysosomal storage disorder caused by mutations in the *NPC1* or *NPC2* genes. In models of Niemann-Pick type C disease, blocking c-Abl by imatinib attenuates HDAC2 aberrant accumulation and its occupancy to the promoters of synaptic/memory-related genes[54]. Likewise, c-Abl inhibition also rescues HDAC2-dependent gene repression in models of Niemann-Pick type C disease[54]. These findings reveal the participation of c-Abl/HDAC2 signaling pathway in synaptic/memory gene repression in the pathological states.

7. HDAC1 maintains genomic integrity in neurons

Impairment in DNA repair pathway is linked to premature aging and neurodegenerative phenotypes[55–58], and accumulation of DNA damage is found to precede the appearance of neurological symptoms in mouse models of neurodegeneration[59,60]. It is believed that enhancing DNA repair may stave off functional decline associated with brain aging and

neurodegeneration[29,61,62]. HDAC1 appear to be particular important in the aforementioned contexts, with its distinct role in repairing two types of DNA lesion, DNA double-strand break (DSB) and 8-oxoguaine (8-oxoG) oxidative lesion.

Higher level of DSB markers (γH2AX, DNA-PKcs) in neurons correlates with cognitive impairment in humans[63]. Moreover, brain specimens from postmortem AD patients exhibit high levels of DNA DSB concomitant with reduced expression of DSB repair factors and DSB repair capacity. Upon the formation of DNA DSB, HDAC1 is promptly recruited to break sites to catalyze H3K56 and H4K16 deacetylation[60,64,65], which stimulates DSB repair through the non-homologous end joining (NHEJ) pathway, the main DSB repair mechanism utilized in post-mitotic neurons[56]. DNA DSBs are considered to be the most deleterious and potentially lethal types of DNA lesion in neurons[56] (**Figure 4**). Thus, interfering with HDAC1 recruitment to break sites results in defective DSB repair, accumulation of DNA DSB, and neuronal death[60]. Whereas overexpression of HDAC1 prevents neuronal death under neurotoxic conditions that cause DNA DSB, such as brain ischemia[59].

8. HDAC1 ameliorates oxidative DNA damage and protects cognitive function in the aging brain

Brain-specific ablation or overexpression of HDAC1 in adult mouse brain shows no effect on memory function[22,28,29]. However, a recent work suggests that HDAC1 is essential for proper brain function in aged brains. Mice lacking HDAC1 in the neurons and astrocytes (*Hdac1*$^{f/f}$*; Nestin-Cre*, *Hdac1* cKO mice) exhibit marked cognitive deficits as the brain ages, together with other known age-associated phenotypes, including astrogliosis and impaired hippocampal LTP induction[29]. Importantly, aged *Hdac1* cKO mice accumulate 8-oxo-guanine (8-oxoG) DNA lesions in the brain[29]. 8-oxoG DNA lesion is a type of oxidative DNA damage on guanine bases caused by reactive oxygen species (ROS). Increased 8-oxoG lesion in promoter interferes transcription factor binding, and accumulation of 8-oxoG lesion is linked to DNA mutations, altered gene expression, and cognitive impairment in the human brain[66,67]. Compared to DNA DSBs, 8-oxoG lesions have higher incident rate in the brain due to its high energy consumption. In mammals, the base excision repair pathway (BER) is responsible for

the repair of 8-oxoG, and the 8-oxoguanine-DNA glycosylase 1 (OGG1) is the major DNA glycosylase in BER removing 8-oxoG. HDAC1 physically interacts with OGG1 and stimulates its cleavage activity, likely by deacetylating OGG1 on a specific subset of lysine residues[29] (**Figure 4**).

Despite HDAC1 being well-known as a transcriptional repressor, a large proportion of differentially expressed genes (DEGs) are downregulated in aged *Hdac1* cKO mice. Moreover, these downregulated genes are important for brain function and aging process, including solute carrier transporters, protein kinase C isoforms, protein chaperones, and antioxidants[29]. The majority of DEGs have no detectable HDAC1 binding at their promoter, indicating that the loss of HDAC1 alters gene expression likely via non-canonical mechanisms independent of direct promoter binding[29]. Subsequent analysis shows that the promoters of these down-regulated genes are enriched with guanine-rich sequences and are burdened with 8-oxoG lesions[29]. It is known that unrepaired 8-oxoG lesions at gene promoters hinder transcription factor binding and disrupt gene expression[66]. Thus, transcriptional repression of these genes in aged *Hdac1* cKO mice could be linked to aberrant accumulation of oxidative DNA damage at their promoters[29] (**Figure 4**). Together, HDAC1 deficiency in aged brains compromise the activity of OGG1, resulting in cognitive deficits, accumulation of unrepaired 8-oxoG lesions, and aberrant transcriptional repression of genes involved in brain function.

9. Modulations of HDAC1 activity to stimulate DNA repair and improves memory function

HDAC1 activity declines in numerous animal models of neurotoxicity and neurodegeneration[29,59,68], and p25 has emerged to be one of the factors contributing to HDAC1 inhibition. p25 is a proteolytic cleavage product of p35, and is capable of activating Cdk5 kinase in many disease contexts[69]. HDAC1 activity is reduced in mouse model overexpressing p25, and p25 interacts with the catalytic domain of HDAC1[59], yet the mechanism underlying p25-mediated HDAC1 inhibition remains unclear. Nonetheless, p25 aberrant accumulation occurs concomitantly with impaired HDAC1 activity and increased DNA damage in multiple neurodegenerative diseases and disease models[29,59,68].

Given the deleterious effects of DNA damage on brain function, it has been a great focus of the field to identify mechanisms stimulating HDAC1 activity. Studies demonstrate that HDAC1 can be modulated by acetylation. NAD^+-dependent deacetylase SIRT1 removes the acetyl group from Lys 432 of HDAC1, which increases HDAC1 enzymatic activity and stimulates DSB repair via the NHEJ pathway in neurons[60](**Figure 4**). Accordingly, overexpression of SIRT1 attenuates the levels of DNA DSB in neurons upon the challenge of etoposide, a genotoxin that induces DNA DSB by inhibiting topoisomerase II relegation of cleaved DNA. Whereas neurons expressing acetyl-mimetic HDAC1 K432Q mutant show refractory to the effects of SIRT1 overexpression[60]. Moreover, pharmacological activation of SIRT1 (compound #10/SRT3657, resveratrol) reduces neuronal DNA DSB, prevents neuronal death, and improves cognitive function in mouse models of neurodegeneration[60,70,71].

Recent work reveals a small molecule called exifone as a potent HDAC1 activator[72]. Biochemical assays demonstrate that exifone binds to HDAC1 directly and is able to stimulates HDAC1 deacetylase activity on the histone and non-histone substrates (H4K12 and p53K352)[72]. Introducing cultured neurons with exifone promotes deacetylation of histone substrate (H4K12). Exifone-mediated histone deacetylation becomes less effective in neurons with HDAC1 knockdown[29], suggestive of HDAC1 dependence. Moreover, exifone diminishes etoposide-induced DNA DSB in cultured neurons, and administration of exifone reduces neuronal DNA DSB and enhances memory function in mouse model of neurodegeneration[29]. Furthermore, pharmacological activation of HDAC1 by exifone stimulates OGG1 activity and reduces 8-oxoG oxidative lesions in the brain tissues of aged mice[29]. Treatment of another synthetic activator of HDAC1 named 5104434 also reduces neuronal DNA DSB and rescues brain function in rodent model of frontotemporal lobar degeneration and stroke[68]. Thus, HDAC1 activation provides a means of countering DNA damage and its deleterious effects on the brain in the aging and disease contexts.

10. HDAC inhibitor and HDAC1 activator

Numerous synthetic inhibitors of HDAC have been developed, and these inhibitors are structurally categorized into hydroxamic acids, cyclic peptides, short chain fatty acids, and

benzamides (**Figure 5**). HDAC inhibitors are generally equipped with three main pharmacophoric motifs, a zinc-binding group, a cap group, and a linker connecting the above two groups together[73]. Hydroxamic acid, carboxylic acid, thiol, and benzamide groups have zinc-binding property that chelate the zinc ion at the active site, thereby preventing the activation of the Zn^{2+}-dependent HDACs[74]. The cap group is typically a hydrophobic and aromatic group, which serves as a surface recognition unit that binds to the substrate-binding region of the HDACs. It is believed that introducing variations within the cap region might offer the selectivity for targeting different HDAC isoforms, as the substrate-binding domain is less conserved among the HDAC family members[75,76].

With the potent anti-proliferative effects in mitotic cells, HDAC inhibitors show potentials for oncology applications. Many HDAC inhibitors are now in clinical trials testing the efficacy and toxicity as the therapeutic invention for different types of blood and solid tumors. Until now, FDA has approved four HDAC inhibitors for the treatment of T-cell lymphomas (romidepsin, vorinostat/SAHA, belinostat) and myeloma (panobinostat). As the promising efficacy in animal models of AD, vorinostat/SAHA is currently in an open-label, non-randomized phase Ib clinical trial to determine safety and tolerability of vorinostat/SAHA in 44 AD patients with mild symptoms (ClinicalTrials.gov; Identifier: NCT03056495). This phase Ib study is estimated to be completed in March 2022, and the results should pave the way for future clinical studies using vorinostat/SAHA as agent for AD. The short chain fatty acid based HDAC inhibitors, valproate derivatives, are FAD-approved drugs to treat epilepsy, bipolar disorder, and for the prevention of migraine headaches. However, the aforementioned applications are mainly through the action of valproate derivatives on gamma-aminobutyric acid (GABA) turnover. Valproate derivatives have also entered different phases of clinical trials for the treatment of schizophrenia. In a double-blind, randomized, multicenter study led by Casey *et al.*, the results demonstrated that combination of valproate and an antipsychotic agent (olanzapine or risperidone) improves psychotic symptoms in acutely hospitalized patients with schizophrenia[77].

Two HDAC1 activators, exifone and compound 5104434, have been identified both through a high-through put screen[72,78]. Compound 5104434 belongs to the cyclohexanedione class,

whereas exifone contains a benzophenone-based structure (**Figure 5**). Little commonality was shared among their chemical structures, but it is noted that both compounds are composed of two identical or similar ring groups. Studies indicate that exifone and compound 5104434 provide selectivity toward activating HDAC1 over HDAC2[72,78]. It has been demonstrated that exifone activates HDAC1 in a mixed, nonessential manner. Exifone binds to free and substrate-bound HDAC1, and exifone increases the binding affinity of HDAC1 to the acetylated peptide substrate[72]. In the deacetylation assay, preincubation of HDAC1 with exifone reduces the inhibition caused by CI-994, a benzamide-based HDAC inhibitor[72]. However, the mechanism underlying compound 5104434-mediated HDAC1 activation remains elusive. Future characterization on compound 5104434 will surely provide insights into the design for HDAC1 activator.

11. Conclusions

With notable progress through the years, significant insights have revealed the regulations of HDAC1 and HDAC2 in memory function. In particular, HDAC2 appears to be the key player regulating the expression of synaptic/memory-related genes through its direct binding to gene promoter. Upregulation of HDAC2 is linked to cognitive deficits, and HDAC2 inhibition reinstates memory function in the disease models. On the other hand, HDAC1 is essential for maintaining genomic integrity in neurons. HDAC1 protects the brain against conditions that result in the elevation of DNA damage, and pharmacological activation of HDAC1 improves brain function.

The genetic approaches targeting HDAC1 or HDAC2 in mice that we discussed in this review article represent a valuable tool but also exist some limitations. For instance, the crosstalk between HDAC1 and HDAC2 has been reported in several studies, where HDAC1 levels increase in response to HDAC2 knockdown/knockout and vice versa[79,80]. With the recent advances in base editing[81,82], a CRISPR-Cas9-based editing technology, it becomes achievable to manipulate HDAC1 or HDAC2 catalytic activity in mice by introducing dominant negative mutations (*e.g.*, HDAC1 H141A, HDAC2 H140A) without altering their gene expression and having the crosstalk effects[83].

Due to the different modes of action between HDAC1 and HDAC2 and their high protein sequence similarity, the development of isoform-selective small molecules is necessary to achieve better therapeutic efficacy with fewer side effects. A recent work indicates that HDAC2 associates with the transcription factor Sp3 to repress synaptic gene expression[84]. Interfering HDAC2-Sp3 interaction restores synaptic gene expression and ameliorates memory impairment in the mouse model of neurodegeneration[84]. Accordingly, preventing distinct protein interaction with HDAC1 or HDAC2 might be a better strategy to improve the selectivity. Future studies to better understand the mechanisms regulating HDAC1 and HDAC2 will generate novel therapeutic options to combat memory dysfunction.

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Authors' contributions

P.-C.P. and L.-H.T. conceptualized and wrote the manuscript.

Notes

L.-H.T. and P.-C.P. have licensed technology related to HDAC1 activators.

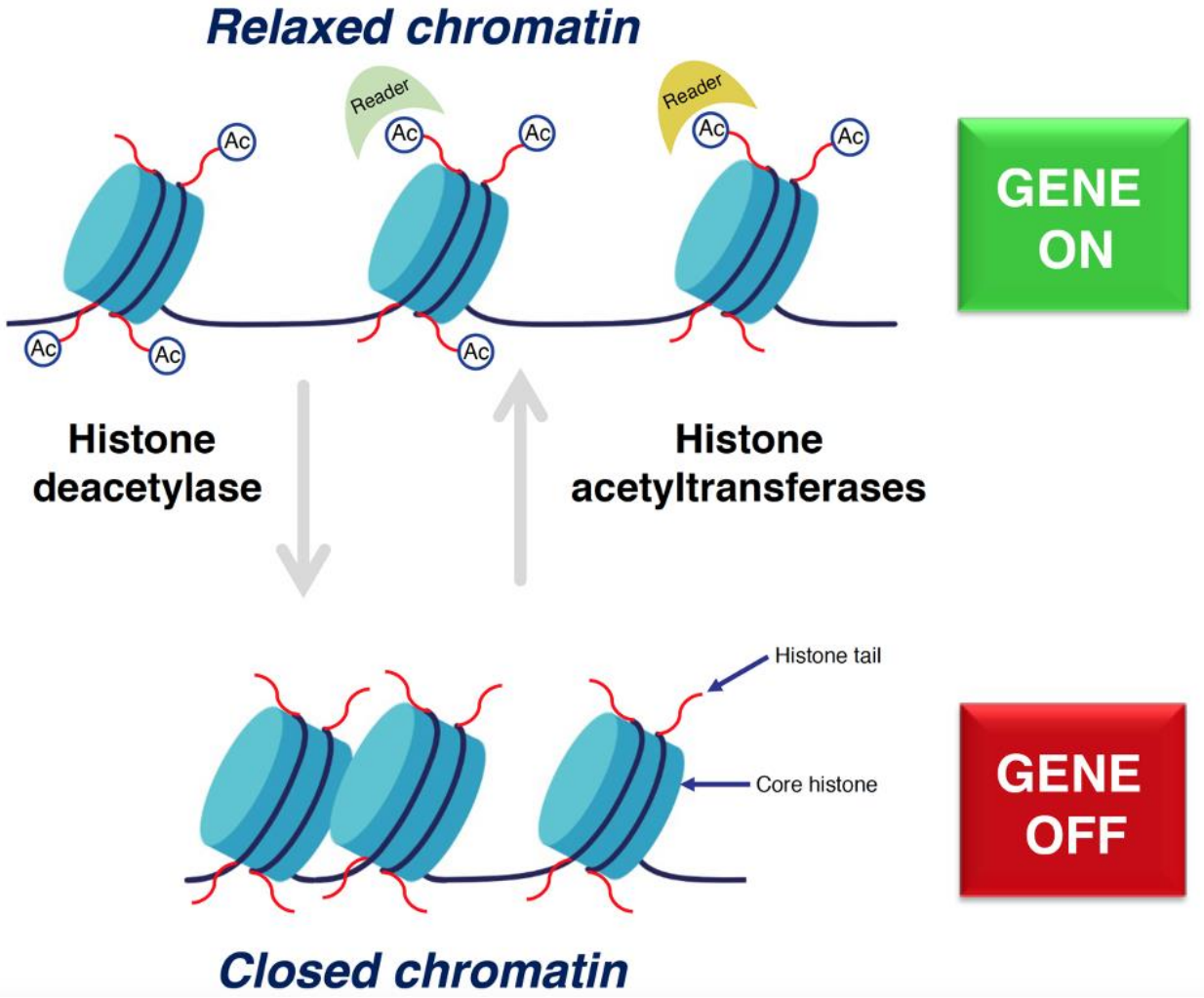

Figure 1. Histone acetylation regulates chromatin remodeling.

Histone acetylation and deacetylation occurs on lysine residues within the histone protruding tail. Acetylation on lysine residues reduces the positive charge of histone and also recruits epigenetic readers, thereby open up the chromatin and facilitates gene expression. The removal of acetyl groups from histone proteins conversely leads to a condensed state of chromatin, which blocks transcription machinery from assessing gene promoter/enhancer and leads to gene repression.

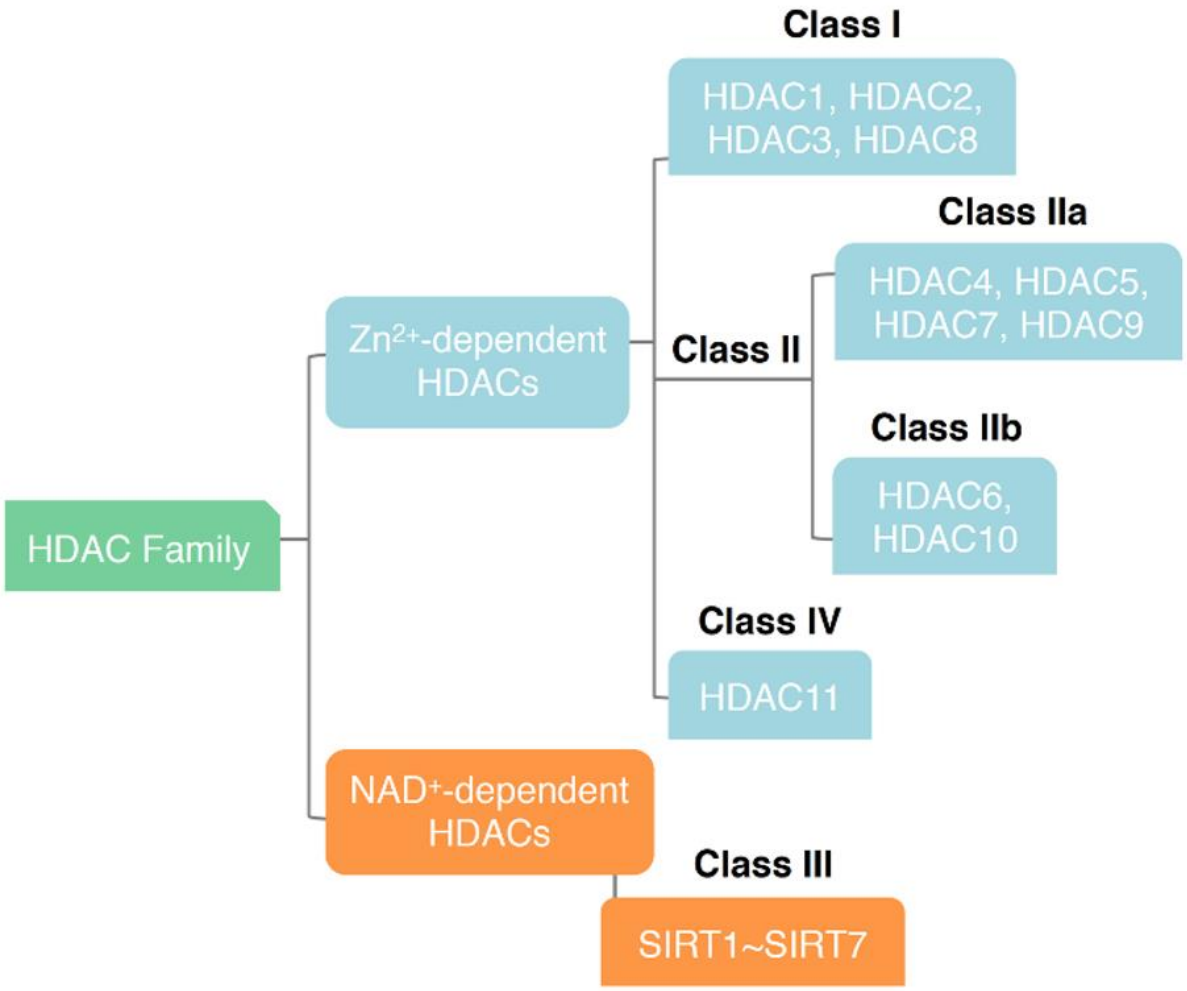

Figure 2. The classification of human HDACs.

HDAC members are first categorized based on the use of co-substrate during deacetylation reaction. Class I, II, and IV are Zn^{2+}-containing HDACs that use acetyl-CoA, and class III members use nicotinamide adenosine dinucleotide (NAD^+). The general structure of HDACs consists of the conserved deacetylase catalytic domain. The class IIa HDACs are additionally characterized by the binding sites for the transcription factor myocyte enhancer factor-2 (MEF2) and for the chaperone protein 14-3-3. In the class IIb, HDAC6 contains a zinc finger at the carboxyl terminus, whereas HDAC10 has a leucine-rich domain near the carboxyl terminus.

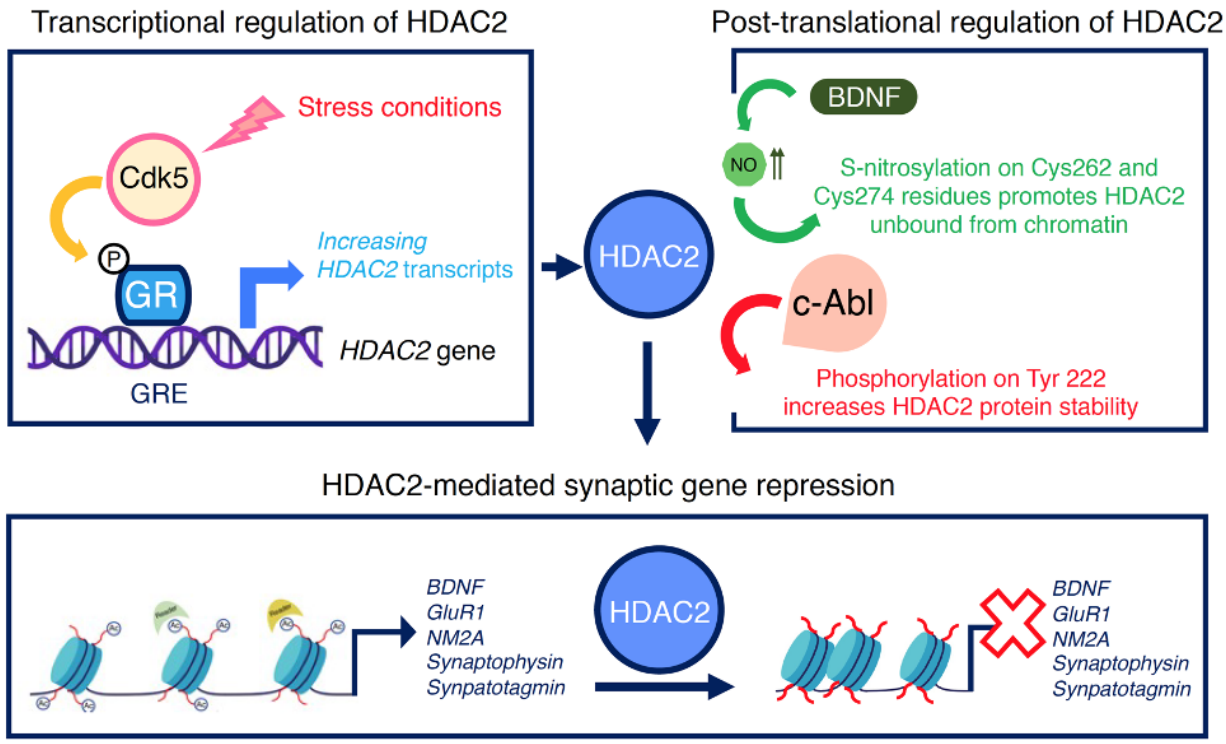

Figure 3. The regulation of HDAC2 expression/function, and the roles of HDA C2 in memory function.

HDAC2 binds to the promoter of synaptic/memory-related genes and represses their expression via chromatin remodeling. The expression of *HDAC2* gene can be stimulated by stress-induced Cdk5-GR signaling cascade, whereas S-nitrosylation controls HDAC2 binding to chromatin and c-Abl-directed phosphorylation increases HDAC2 protein stability.

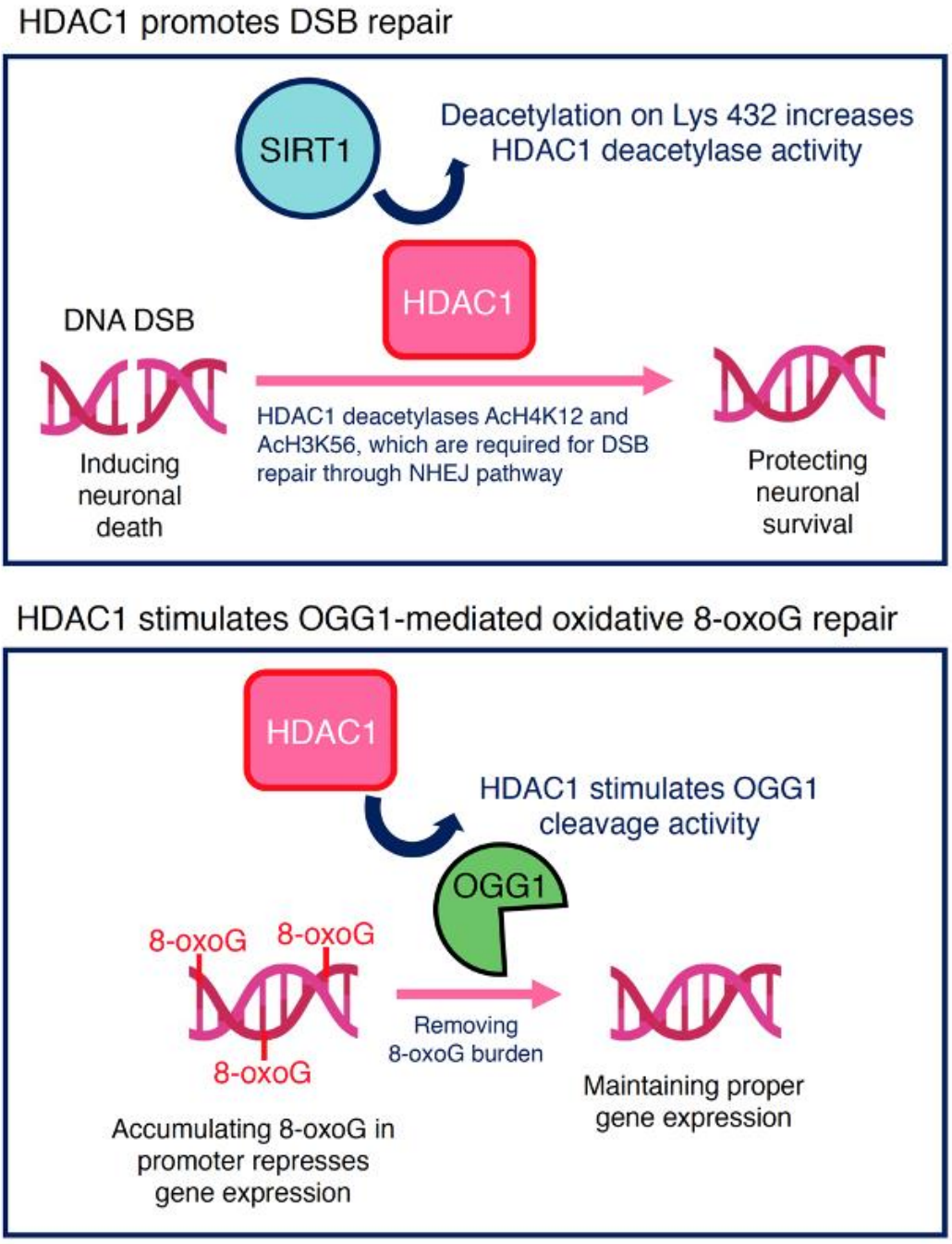

Figure 4. HDAC1 maintains normal brain function via its role in DNA repair pathways. DSB repair requires HDAC1 activity, which can be further strengthened by SIRT1-mediated deacetylation. HDAC1 also positively modulates OGG1 cleavage activity in removing 8-oxoG oxidative lesions.

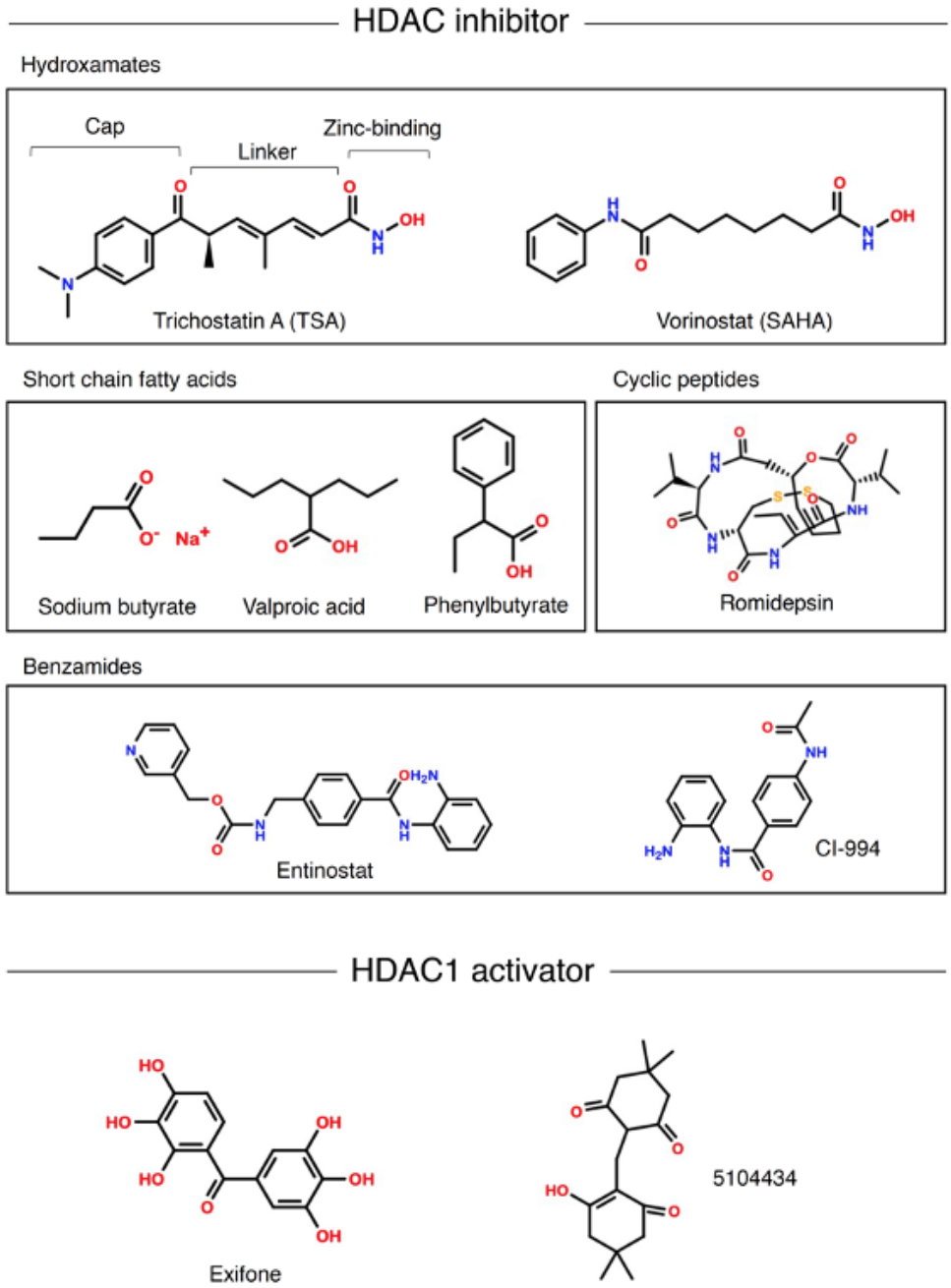

Figure 5. Chemical structures of HDAC inhibitors and HDAC1 activators discussed in this review. HDAC inhibitors can be structurally categorized into at least four classes: hydroxamates, cyclic peptides, short chain fatty acids, cyclic peptides, and benzamides. The reader is referred to several excellent reviews with a more comprehensive list of known HDAC inhibitors[9,85,86]. TSA is an example illustrating the main functional groups of HDAC inhibitors. Exifone and 5104434 are identified as HDAC1 activators.

References

(1) Jaenisch, R.; Bird, A. Epigenetic Regulation of Gene Expression: How the Genome Integrates Intrinsic and Environmental Signals. *Nature Genetics*. 2003. https://doi.org/10.1038/ng1089.

(2) Campbell, R. R.; Wood, M. A. How the Epigenome Integrates Information and Reshapes the Synapse. *Nature Reviews Neuroscience*. 2019. https://doi.org/10.1038/s41583-019-0121-9.

(3) Bannister, A. J.; Kouzarides, T. Regulation of Chromatin by Histone Modifications. *Cell Research*. 2011. https://doi.org/10.1038/cr.2011.22.

(4) Gräff, J.; Tsai, L. H. Histone Acetylation: Molecular Mnemonics on the Chromatin. *Nature Reviews Neuroscience*. 2013. https://doi.org/10.1038/nrn3427.

(5) Seto, E.; Yoshida, M. Erasers of Histone Acetylation: The Histone Deacetylase Enzymes. *Cold Spring Harb. Perspect. Biol.* **2014**. https://doi.org/10.1101/cshperspect.a018713.

(6) Yun, M.; Wu, J.; Workman, J. L.; Li, B. Readers of Histone Modifications. *Cell Research*. 2011. https://doi.org/10.1038/cr.2011.42.

(7) Marmorstein, R.; Zhou, M. M. Writers and Readers of Histone Acetylation: Structure, Mechanism, and Inhibition. *Cold Spring Harb. Perspect. Biol.* **2014**. https://doi.org/10.1101/cshperspect.a018762.

(8) Li, Y.; Wen, H.; Xi, Y.; Tanaka, K.; Wang, H.; Peng, D.; Ren, Y.; Jin, Q.; Dent, S. Y. R.; Li, W.; Li, H.; Shi, X. AF9 YEATS Domain Links Histone Acetylation to DOT1L-Mediated H3K79 Methylation. *Cell* **2014**. https://doi.org/10.1016/j.cell.2014.09.049.

(9) Delcuve, G. P.; Khan, D. H.; Davie, J. R. Roles of Histone Deacetylases in Epigenetic Regulation: Emerging Paradigms from Studies with Inhibitors. *Clinical Epigenetics*. 2012. https://doi.org/10.1186/1868-7083-4-5.

(10) Penney, J.; Tsai, L. H. Histone Deacetylases in Memory and Cognition. *Science Signaling*. 2014. https://doi.org/10.1126/scisignal.aaa0069.

(11) Burns, A. M.; Gräff, J. Cognitive Epigenetic Priming: Leveraging Histone Acetylation for Memory Amelioration. *Current Opinion in Neurobiology*. 2021. https://doi.org/10.1016/j.conb.2020.08.011.

(12) Peixoto, L.; Abel, T. The Role of Histone Acetylation in Memory Formation and Cognitive Impairments. *Neuropsychopharmacology*. 2013.

https://doi.org/10.1038/npp.2012.86.

(13) Alarcón, J. M.; Malleret, G.; Touzani, K.; Vronskaya, S.; Ishii, S.; Kandel, E. R.; Barco, A. Chromatin Acetylation, Memory, and LTP Are Impaired in CBP+/- Mice: A Model for the Cognitive Deficit in Rubinstein-Taybi Syndrome and Its Amelioration. *Neuron* **2004**. https://doi.org/10.1016/j.neuron.2004.05.021.

(14) Fischer, A.; Sananbenesi, F.; Wang, X.; Dobbin, M.; Tsai, L. H. Recovery of Learning and Memory Is Associated with Chromatin Remodelling. *Nature* **2007**. https://doi.org/10.1038/nature05772.

(15) Korzus, E.; Rosenfeld, M. G.; Mayford, M. CBP Histone Acetyltransferase Activity Is a Critical Component of Memory Consolidation. *Neuron* **2004**. https://doi.org/10.1016/j.neuron.2004.06.002.

(16) Levenson, J. M.; O'Riordan, K. J.; Brown, K. D.; Trinh, M. A.; Molfese, D. L.; Sweatt, J. D. Regulation of Histone Acetylation during Memory Formation in the Hippocampus. *J. Biol. Chem.* **2004**. https://doi.org/10.1074/jbc.M402229200.

(17) Peleg, S.; Sananbenesi, F.; Zovoilis, A.; Burkhardt, S.; Bahari-Javan, S.; Agis-Balboa, R. C.; Cota, P.; Wittnam, J. L.; Gogol-Doering, A.; Opitz, L.; Salinas-Riester, G.; Dettenhofer, M.; Kang, H.; Farinelli, L.; Chen, W.; Fischer, A. Altered Histone Acetylation Is Associated with Age-Dependent Memory Impairment in Mice. *Science (80-.).* **2010**. https://doi.org/10.1126/science.1186088.

(18) Curzon, P.; Nr, R.; Ke, B. Chapter 2 Cued and Contextual Fear Conditioning for Rodents 2 . 2 . CONTEXTUAL / CUED FEAR CONDITIONING : OVERVIEW. *Methods Behav. Anal. Neurosci.* **2014**.

(19) Schafe, G. E.; Nader, K.; Blair, H. T.; LeDoux, J. E. Memory Consolidation of Pavlovian Fear Conditioning: A Cellular and Molecular Perspective. *Trends in Neurosciences*. 2001. https://doi.org/10.1016/S0166-2236(00)01969-X.

(20) Vecsey, C. G.; Hawk, J. D.; Lattal, K. M.; Stein, J. M.; Fabian, S. A.; Attner, M. A.; Cabrera, S. M.; McDonough, C. B.; Brindle, P. K.; Abel, T.; Wood, M. A. Histone Deacetylase Inhibitors Enhance Memory and Synaptic Plasticity via CREB: CBP-Dependent Transcriptional Activation. *J. Neurosci.* **2007**. https://doi.org/10.1523/JNEUROSCI.0296-07.2007.

(21) Li, B. S.; Sun, M. K.; Zhang, L.; Takahashi, S.; Ma, W.; Vinade, L.; Kulkarni, A. B.; Brady, R.

O.; Pant, H. C. Regulation of NMDA Receptors by Cyclin-Dependent Kinase-5. *Proc. Natl. Acad. Sci. U. S. A.* **2001**. https://doi.org/10.1073/pnas.211428098.

(22) Guan, J. S.; Haggarty, S. J.; Giacometti, E.; Dannenberg, J. H.; Joseph, N.; Gao, J.; Nieland, T. J. F.; Zhou, Y.; Wang, X.; Mazitschek, R.; Bradner, J. E.; DePinho, R. A.; Jaenisch, R.; Tsai, L. H. HDAC2 Negatively Regulates Memory Formation and Synaptic Plasticity. *Nature* **2009**. https://doi.org/10.1038/nature07925.

(23) Benito, E.; Urbanke, H.; Ramachandran, B.; Barth, J.; Halder, R.; Awasthi, A.; Jain, G.; Capece, V.; Burkhardt, S.; Navarro-Sala, M.; Nagarajan, S.; Schötz, A. L.; Johnsen, S. A.; Bonn, S.; Löhrmann, R.; Dean, C.; Fischer, A. HDAC Inhibitor-Dependent Transcriptome and Memory Reinstatement in Cognitive Decline Models. *J. Clin. Invest.* **2015**. https://doi.org/10.1172/JCI79942.

(24) Nithianantharajah, J.; Hannan, A. J. Enriched Environments, Experience-Dependent Plasticity and Disorders of the Nervous System. *Nature Reviews Neuroscience*. 2006. https://doi.org/10.1038/nrn1970.

(25) Salisbury, C. M.; Cravatt, B. F. Activity-Based Probes for Proteomic Profiling of Histone Deacetylase Complexes. *Proc. Natl. Acad. Sci. U. S. A.* **2007**. https://doi.org/10.1073/pnas.0608659104.

(26) Grant, S.; Easley, C.; Kirkpatrick, P. Vorinostat. *Nature Reviews Drug Discovery*. 2007. https://doi.org/10.1038/nrd2227.

(27) Witter, D. J.; Harrington, P.; Wilson, K. J.; Chenard, M.; Fleming, J. C.; Haines, B.; Kral, A. M.; Secrist, J. P.; Miller, T. A. Optimization of Biaryl Selective HDAC1&2 Inhibitors (SHI-1:2). *Bioorganic Med. Chem. Lett.* **2008**. https://doi.org/10.1016/j.bmcl.2007.11.047.

(28) Morris, M. J.; Mahgoub, M.; Na, E. S.; Pranav, H.; Monteggia, L. M. Loss of Histone Deacetylase 2 Improves Working Memory and Accelerates Extinction Learning. *J. Neurosci.* **2013**. https://doi.org/10.1523/JNEUROSCI.1001-12.2013.

(29) Pao, P. C.; Patnaik, D.; Watson, L. A.; Gao, F.; Pan, L.; Wang, J.; Adaikkan, C.; Penney, J.; Cam, H. P.; Huang, W. C.; Pantano, L.; Lee, A.; Nott, A.; Phan, T. X.; Gjoneska, E.; Elmsaouri, S.; Haggarty, S. J.; Tsai, L. H. HDAC1 Modulates OGG1-Initiated Oxidative DNA Damage Repair in the Aging Brain and Alzheimer's Disease. *Nat. Commun.* **2020**. https://doi.org/10.1038/s41467-020-16361-y.

(30) Lunyak, V. V.; Burgess, R.; Prefontaine, G. G.; Nelson, C.; Sze, S. H.; Chenoweth, J.;

592 Schwartz, P.; Pevzner, P. A.; Glass, C.; Mandel, G.; Rosenfeld, M. G. Corepressor-
593 Dependent Silencing of Chromosomal Regions Encoding Neuronal Genes. *Science*
594 *(80-.).* **2002**. https://doi.org/10.1126/science.1076469.
595 (31) Ballas, N.; Grunseich, C.; Lu, D. D.; Speh, J. C.; Mandel, G. REST and Its Corepressors
596 Mediate Plasticity of Neuronal Gene Chromatin throughout Neurogenesis. *Cell* **2005**.
597 https://doi.org/10.1016/j.cell.2005.03.013.
598 (32) Sheng, M.; Sabatini, B. L.; Südhof, T. C. Synapses and Alzheimer's Disease. *Cold Spring*
599 *Harb. Perspect. Biol.* **2012**. https://doi.org/10.1101/cshperspect.a005777.
600 (33) Gräff, J.; Rei, D.; Guan, J. S.; Wang, W. Y.; Seo, J.; Hennig, K. M.; Nieland, T. J. F.; Fass, D.
601 M.; Kao, P. F.; Kahn, M.; Su, S. C.; Samiei, A.; Joseph, N.; Haggarty, S. J.; Delalle, I.; Tsai, L.
602 H. An Epigenetic Blockade of Cognitive Functions in the Neurodegenerating Brain.
603 *Nature* **2012**. https://doi.org/10.1038/nature10849.
604 (34) Bie, B.; Wu, J.; Yang, H.; Xu, J. J.; Brown, D. L.; Naguib, M. Epigenetic Suppression of
605 Neuroligin 1 Underlies Amyloid-Induced Memory Deficiency. *Nat. Neurosci.* **2014**.
606 https://doi.org/10.1038/nn.3618.
607 (35) Govindarajan, N.; Agis-Balboa, R. C.; Walter, J.; Sananbenesi, F.; Fischer, A. Sodium
608 Butyrate Improves Memory Function in an Alzheimer's Disease Mouse Model When
609 Administered at an Advanced Stage of Disease Progression. *J. Alzheimer's Dis.* **2011**.
610 https://doi.org/10.3233/JAD-2011-110080.
611 (36) Kilgore, M.; Miller, C. A.; Fass, D. M.; Hennig, K. M.; Haggarty, S. J.; Sweatt, J. D.;
612 Rumbaugh, G. Inhibitors of Class 1 Histone Deacetylases Reverse Contextual Memory
613 Deficits in a Mouse Model of Alzheimer's Disease. *Neuropsychopharmacology* **2010**.
614 https://doi.org/10.1038/npp.2009.197.
615 (37) Francis, Y. I.; Fà, M.; Ashraf, H.; Zhang, H.; Staniszewski, A.; Latchman, D. S.; Arancio, O.
616 Dysregulation of Histone Acetylation in the APP/PS1 Mouse Model of Alzheimer's
617 Disease. *J. Alzheimer's Dis.* **2009**. https://doi.org/10.3233/JAD-2009-1134.
618 (38) Cruz, J. C.; Kim, D.; Moy, L. Y.; Dobbin, M. M.; Sun, X.; Bronson, R. T.; Tsai, L. H.
619 P25/Cyclin-Dependent Kinase 5 Induces Production and Intraneuronal Accumulation
620 of Amyloid β in Vivo. *J. Neurosci.* **2006**. https://doi.org/10.1523/JNEUROSCI.3133-
621 06.2006.
622 (39) Miranda, M.; Morici, J. F.; Zanoni, M. B.; Bekinschtein, P. Brain-Derived Neurotrophic

623 Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Frontiers*
624 *in Cellular Neuroscience*. 2019. https://doi.org/10.3389/fncel.2019.00363.
625 (40) Nott, A.; Watson, P. M.; Robinson, J. D.; Crepaldi, L.; Riccio, A. S-Nitrosylation of Histone
626 Deacetylase 2 Induces Chromatin Remodelling in Neurons. *Nature* **2008**.
627 https://doi.org/10.1038/nature07238.
628 (41) Gräff, J.; Joseph, N. F.; Horn, M. E.; Samiei, A.; Meng, J.; Seo, J.; Rei, D.; Bero, A. W.; Phan,
629 T. X.; Wagner, F.; Holson, E.; Xu, J.; Sun, J.; Neve, R. L.; Mach, R. H.; Haggarty, S. J.; Tsai,
630 L. H. Epigenetic Priming of Memory Updating during Reconsolidation to Attenuate
631 Remote Fear Memories. *Cell* **2014**. https://doi.org/10.1016/j.cell.2013.12.020.
632 (42) Oakley, R. H.; Cidlowski, J. A. The Biology of the Glucocorticoid Receptor: New Signaling
633 Mechanisms in Health and Disease. *Journal of Allergy and Clinical Immunology*. 2013.
634 https://doi.org/10.1016/j.jaci.2013.09.007.
635 (43) Rei, D.; Mason, X.; Seo, J.; Gräff, J.; Rudenko, A.; Wang, J.; Rueda, R.; Siegert, S.; Cho, S.;
636 Canter, R. G.; Mungenast, A. E.; Deisseroth, K.; Tsai, L. H. Basolateral Amygdala
637 Bidirectionally Modulates Stress-Induced Hippocampal Learning and Memory Deficits
638 through a P25/Cdk5-Dependent Pathway. *Proc. Natl. Acad. Sci. U. S. A.* **2015**.
639 https://doi.org/10.1073/pnas.1415845112.
640 (44) Wu, J.; Liu, C.; Zhang, L.; He, B.; Shi, W. P.; Shi, H. L.; Qin, C. Chronic Restraint Stress
641 Impairs Cognition via Modulating HDAC2 Expression. *Transl. Neurosci.* **2021**.
642 https://doi.org/10.1515/tnsci-2020-0168.
643 (45) Wu, J.; Liu, C.; Zhang, L.; Qu, C. H.; Sui, X. L.; Zhu, H.; Huang, L.; Xu, Y. F.; Han, Y. L.; Qin,
644 C. Histone Deacetylase-2 Is Involved in Stress-Induced Cognitive Impairment via
645 Histone Deacetylation and PI3K/AKT Signaling Pathway Modification. *Mol. Med. Rep.*
646 **2017**. https://doi.org/10.3892/mmr.2017.6840.
647 (46) Sun, X. Y.; Zheng, T.; Yang, X.; Liu, L.; Gao, S. S.; Xu, H. B.; Song, Y. T.; Tong, K.; Yang, L.;
648 Gao, Y.; Wu, T.; Hao, J. R.; Lu, C.; Ma, T.; Gao, C. HDAC2 Hyperexpression Alters
649 Hippocampal Neuronal Transcription and Microglial Activity in Neuroinflammation-
650 Induced Cognitive Dysfunction. *J. Neuroinflammation* **2019**.
651 https://doi.org/10.1186/s12974-019-1640-z.
652 (47) Duan, R.; Liu, X.; Wang, T.; Wu, L.; Gao, X.; Zhang, Z. Histone Acetylation Regulation in
653 Sleep Deprivation-Induced Spatial Memory Impairment. *Neurochem. Res.* **2016**.

https://doi.org/10.1007/s11064-016-1937-6.

(48) Fusco, S.; Spinelli, M.; Cocco, S.; Ripoli, C.; Mastrodonato, A.; Natale, F.; Rinaudo, M.; Livrizzi, G.; Grassi, C. Maternal Insulin Resistance Multigenerationally Impairs Synaptic Plasticity and Memory via Gametic Mechanisms. *Nat. Commun.* **2019**. https://doi.org/10.1038/s41467-019-12793-3.

(49) Berton, O.; McClung, C. A.; DiLeone, R. J.; Krishnan, V.; Renthal, W.; Russo, S. J.; Graham, D.; Tsankova, N. M.; Bolanos, C. A.; Rios, M.; Monteggia, L. M.; Self, D. W.; Nestler, E. J. Essential Role of BDNF in the Mesolimbic Dopamine Pathway in Social Defeat Stress. *Science (80-.).* **2006**. https://doi.org/10.1126/science.1120972.

(50) Krishnan, V.; Han, M. H.; Graham, D. L.; Berton, O.; Renthal, W.; Russo, S. J.; LaPlant, Q.; Graham, A.; Lutter, M.; Lagace, D. C.; Ghose, S.; Reister, R.; Tannous, P.; Green, T. A.; Neve, R. L.; Chakravarty, S.; Kumar, A.; Eisch, A. J.; Self, D. W.; Lee, F. S.; Tamminga, C. A.; Cooper, D. C.; Gershenfeld, H. K.; Nestler, E. J. Molecular Adaptations Underlying Susceptibility and Resistance to Social Defeat in Brain Reward Regions. *Cell* **2007**. https://doi.org/10.1016/j.cell.2007.09.018.

(51) Christoffel, D. J.; Golden, S. A.; Dumitriu, D.; Robison, A. J.; Janssen, W. G.; Ahn, H. F.; Krishnan, V.; Reyes, C. M.; Han, M. H.; Ables, J. L.; Eisch, A. J.; Dietz, D. M.; Ferguson, D.; Neve, R. L.; Greengard, P.; Kim, Y.; Morrison, J. H.; Russo, S. J. IκB Kinase Regulates Social Defeat Stress-Induced Synaptic and Behavioral Plasticity. *J. Neurosci.* **2011**. https://doi.org/10.1523/JNEUROSCI.4763-10.2011.

(52) Schlatterer, S. D.; Acker, C. M.; Davies, P. C-Abl in Neurodegenerative Disease. In *Journal of Molecular Neuroscience*; 2011. https://doi.org/10.1007/s12031-011-9588-1.

(53) Gonzalez-Zuñiga, M.; Contreras, P. S.; Estrada, L. D.; Chamorro, D.; Villagra, A.; Zanlungo, S.; Seto, E.; Alvarez, A. R. C-Abl Stabilizes HDAC2 Levels by Tyrosine Phosphorylation Repressing Neuronal Gene Expression in Alzheimer's Disease. *Mol. Cell* **2014**. https://doi.org/10.1016/j.molcel.2014.08.013.

(54) Contreras, P. S.; Gonzalez-Zuñiga, M.; González-Hódar, L.; Yáñez, M. J.; Dulcey, A.; Marugan, J.; Seto, E.; Alvarez, A. R.; Zanlungo, S. Neuronal Gene Repression in Niemann-Pick Type C Models Is Mediated by the c-Abl/HDAC2 Signaling Pathway. *Biochim. Biophys. Acta - Gene Regul. Mech.* **2016**. https://doi.org/10.1016/j.bbagrm.2015.11.006.

(55) López-Otín, C.; Blasco, M. A.; Partridge, L.; Serrano, M.; Kroemer, G. The Hallmarks of Aging. *Cell*. 2013. https://doi.org/10.1016/j.cell.2013.05.039.

(56) Madabhushi, R.; Pan, L.; Tsai, L. H. DNA Damage and Its Links to Neurodegeneration. *Neuron*. 2014. https://doi.org/10.1016/j.neuron.2014.06.034.

(57) De Boer, J.; Andressoo, J. O.; De Wit, J.; Huijmans, J.; Beems, R. B.; Van Steeg, H.; Weeda, G.; Van der Horst, G. T. J.; Van Leeuwen, W.; Themmen, A. P. N.; Meradji, M.; Hoeijmakers, J. H. J. Premature Aging in Mice Deficient in DNA Repair and Transcription. *Science (80-.).* **2002**. https://doi.org/10.1126/science.1070174.

(58) Borgesius, N. Z.; de Waard, M. C.; van der Pluijm, I.; Omrani, A.; Zondag, G. C. M.; van der Horst, G. T. J.; Melton, D. W.; Hoeijmakers, J. H. J.; Jaarsma, D.; Elgersma, Y. Accelerated Age-Related Cognitive Decline and Neurodegeneration, Caused by Deficient DNA Repair. *J. Neurosci.* **2011**. https://doi.org/10.1523/JNEUROSCI.1589-11.2011.

(59) Kim, D.; Frank, C. L.; Dobbin, M. M.; Tsunemoto, R. K.; Tu, W.; Peng, P. L.; Guan, J. S.; Lee, B. H.; Moy, L. Y.; Giusti, P.; Broodie, N.; Mazitschek, R.; Delalle, I.; Haggarty, S. J.; Neve, R. L.; Lu, Y. M.; Tsai, L. H. Deregulation of HDAC1 by P25/Cdk5 in Neurotoxicity. *Neuron* **2008**. https://doi.org/10.1016/j.neuron.2008.10.015.

(60) Dobbin, M. M.; Madabhushi, R.; Pan, L.; Chen, Y.; Kim, D.; Gao, J.; Ahanonu, B.; Pao, P. C.; Qiu, Y.; Zhao, Y.; Tsai, L. H. SIRT1 Collaborates with ATM and HDAC1 to Maintain Genomic Stability in Neurons. *Nat. Neurosci.* **2013**. https://doi.org/10.1038/nn.3460.

(61) Hou, Y.; Lautrup, S.; Cordonnier, S.; Wang, Y.; Croteau, D. L.; Zavala, E.; Zhang, Y.; Moritoh, K.; O'Connell, J. F.; Baptiste, B. A.; Stevnsner, T. V.; Mattson, M. P.; Bohr, V. A. NAD+ Supplementation Normalizes Key Alzheimer's Features and DNA Damage Responses in a New AD Mouse Model with Introduced DNA Repair Deficiency. *Proc. Natl. Acad. Sci. U. S. A.* **2018**. https://doi.org/10.1073/pnas.1718819115.

(62) Fang, E. F.; Kassahun, H.; Croteau, D. L.; Scheibye-Knudsen, M.; Marosi, K.; Lu, H.; Shamanna, R. A.; Kalyanasundaram, S.; Bollineni, R. C.; Wilson, M. A.; Iser, W. B.; Wollman, B. N.; Morevati, M.; Li, J.; Kerr, J. S.; Lu, Q.; Waltz, T. B.; Tian, J.; Sinclair, D. A.; Mattson, M. P.; Nilsen, H.; Bohr, V. A. NAD+ Replenishment Improves Lifespan and Healthspan in Ataxia Telangiectasia Models via Mitophagy and DNA Repair. *Cell Metab.* **2016**. https://doi.org/10.1016/j.cmet.2016.09.004.

(63) Simpson, J. E.; Ince, P. G.; Matthews, F. E.; Shaw, P. J.; Heath, P. R.; Brayne, C.; Garwood, C.; Higginbottom, A.; Wharton, S. B. A Neuronal DNA Damage Response Is Detected at the Earliest Stages of Alzheimer's Neuropathology and Correlates with Cognitive Impairment in the Medical Research Council's Cognitive Function and Ageing Study Ageing Brain Cohort. *Neuropathol. Appl. Neurobiol.* **2015**. https://doi.org/10.1111/nan.12202.

(64) Miller, K. M.; Tjeertes, J. V.; Coates, J.; Legube, G.; Polo, S. E.; Britton, S.; Jackson, S. P. Human HDAC1 and HDAC2 Function in the DNA-Damage Response to Promote DNA Nonhomologous End-Joining. *Nat. Struct. Mol. Biol.* **2010**. https://doi.org/10.1038/nsmb.1899.

(65) Wang, W. Y.; Pan, L.; Su, S. C.; Quinn, E. J.; Sasaki, M.; Jimenez, J. C.; MacKenzie, I. R. A.; Huang, E. J.; Tsai, L. H. Interaction of FUS and HDAC1 Regulates DNA Damage Response and Repair in Neurons. *Nat. Neurosci.* **2013**. https://doi.org/10.1038/nn.3514.

(66) Lu, T.; Pan, Y.; Kao, S. Y.; Li, C.; Kohane, I.; Chan, J.; Yankner, B. A. Gene Regulation and DNA Damage in the Ageing Human Brain. *Nature* **2004**. https://doi.org/10.1038/nature02661.

(67) Lodato, M. A.; Rodin, R. E.; Bohrson, C. L.; Coulter, M. E.; Barton, A. R.; Kwon, M.; Sherman, M. A.; Vitzthum, C. M.; Luquette, L. J.; Yandava, C. N.; Yang, P.; Chittenden, T. W.; Hatem, N. E.; Ryu, S. C.; Woodworth, M. B.; Park, P. J.; Walsh, C. A. Aging and Neurodegeneration Are Associated with Increased Mutations in Single Human Neurons. *Science (80-.).* **2018**. https://doi.org/10.1126/science.aao4426.

(68) Wu, C.; Jin, L.; Wang, I.; Wei, W.; Ho, P.; Liu, Y.; Tsai, K. HDAC1 Dysregulation Induces Aberrant Cell Cycle and DNA Damage in Progress of TDP-43 Proteinopathies. *EMBO Mol. Med.* **2020**. https://doi.org/10.15252/emmm.201910622.

(69) Dhavan, R.; Tsai, L. H. A Decade of CDK5. *Nature Reviews Molecular Cell Biology*. 2001. https://doi.org/10.1038/35096019.

(70) Gräff, J.; Kahn, M.; Samiei, A.; Gao, J.; Ota, K. T.; Rei, D.; Tsai, L. H. A Dietary Regimen of Caloric Restriction or Pharmacological Activation of SIRT1 to Delay the Onset of Neurodegeneration. *J. Neurosci.* **2013**. https://doi.org/10.1523/JNEUROSCI.5657-12.2013.

(71) Kim, D.; Nguyen, M. D.; Dobbin, M. M.; Fischer, A.; Sananbenesi, F.; Rodgers, J. T.; Delalle,

I.; Baur, J. A.; Sui, G.; Armour, S. M.; Puigserver, P.; Sinclair, D. A.; Tsai, L. H. SIRT1 Deacetylase Protects against Neurodegeneration in Models for Alzheimer's Disease and Amyotrophic Lateral Sclerosis. *EMBO J.* **2007**. https://doi.org/10.1038/sj.emboj.7601758.

(72) Patnaik, D.; Pao, P. C.; Zhao, W. N.; Silva, M. C.; Hylton, N. K.; Chindavong, P. S.; Pan, L.; Tsai, L. H.; Haggarty, S. J. Exifone Is a Potent HDAC1 Activator with Neuroprotective Activity in Human Neuronal Models of Neurodegeneration. *ACS Chem. Neurosci.* **2021**. https://doi.org/10.1021/acschemneuro.0c00308.

(73) Jung, M.; Hoffmann, K.; Brosch, G.; Loidl, P. Analogues of Trichostatin A and Trapoxin B as Histone Deacetylase Inhibitors. *Bioorganic Med. Chem. Lett.* **1997**. https://doi.org/10.1016/S0960-894X(97)00284-9.

(74) Zhang, L.; Zhang, J.; Jiang, Q.; Zhang, L.; Song, W. Zinc Binding Groups for Histone Deacetylase Inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 2018. https://doi.org/10.1080/14756366.2017.1417274.

(75) Nielsen, T. K.; Hildmann, C.; Dickmanns, A.; Schwienhorst, A.; Ficner, R. Crystal Structure of a Bacterial Class 2 Histone Deacetylase Homologue. *J. Mol. Biol.* **2005**. https://doi.org/10.1016/j.jmb.2005.09.065.

(76) Wang, D. F.; Wiest, O.; Helquist, P.; Lan-Hargest, H. Y.; Wiech, N. L. On the Function of the 14 Å Long Internal Cavity of Histone Deacetylase-like Protein: Implications for the Design of Histone Deacetylase Inhibitors. *J. Med. Chem.* **2004**. https://doi.org/10.1021/jm0498497.

(77) Casey, D. E.; Daniel, D. G.; Wassef, A. A.; Tracy, K. A.; Wozniak, P.; Sommerville, K. W. Effect of Divalproex Combined with Olanzapine or Risperidone in Patients with an Acute Exacerbation Ofschizophrenia. *Neuropsychopharmacology* **2003**. https://doi.org/10.1038/sj.npp.1300023.

(78) Tsai, Li-Huei; Haggarty, Stephen J.; Kim, D. *Activation of Histone Deacetylase 1 (HDAC1) Protects against DNA Damage and Increases Neuronal Survival*; 2009.

(79) Jurkin, J.; Zupkovitz, G.; Lagger, S.; Grausenburger, R.; Hagelkruys, A.; Kenner, L.; Seiser, C. Distinct and Redundant Functions of Histone Deacetylases HDAC1 and HDAC2 in Proliferation and Tumorigenesis. *Cell Cycle*. 2011. https://doi.org/10.4161/cc.10.3.14712.

(80) Hagelkruys, A.; Lagger, S.; Krahmer, J.; Leopoldi, A.; Artaker, M.; Pusch, O.; Zezula, J.; Weissmann, S.; Xie, Y.; Schöfer, C.; Schlederer, M.; Brosch, G.; Matthias, P.; Selfridge, J.; Lassmann, H.; Knoblich, J. A.; Seiser, C. A Single Allele of Hdac2 but Not Hdac1 Is Sufficient for Normal Mouse Brain Development in the Absence of Its Paralog. *Dev.* **2014**. https://doi.org/10.1242/dev.100487.

(81) Koblan, L. W.; Erdos, M. R.; Wilson, C.; Cabral, W. A.; Levy, J. M.; Xiong, Z. M.; Tavarez, U. L.; Davison, L. M.; Gete, Y. G.; Mao, X.; Newby, G. A.; Doherty, S. P.; Narisu, N.; Sheng, Q.; Krilow, C.; Lin, C. Y.; Gordon, L. B.; Cao, K.; Collins, F. S.; Brown, J. D.; Liu, D. R. In Vivo Base Editing Rescues Hutchinson–Gilford Progeria Syndrome in Mice. *Nature* **2021**. https://doi.org/10.1038/s41586-020-03086-7.

(82) Newby, G. A.; Liu, D. R. In Vivo Somatic Cell Base Editing and Prime Editing. *Molecular Therapy*. 2021. https://doi.org/10.1016/j.ymthe.2021.09.002.

(83) Humphrey, G. W.; Wang, Y. H.; Hirai, T.; Padmanabhan, R.; Panchision, D. M.; Newell, L. F.; McKay, R. D. G.; Howard, B. H. Complementary Roles for Histone Deacetylases 1, 2, and 3 in Differentiation of Pluripotent Stem Cells. *Differentiation* **2008**. https://doi.org/10.1111/j.1432-0436.2007.00232.x.

(84) Yamakawa, H.; Cheng, J.; Penney, J.; Gao, F.; Rueda, R.; Wang, J.; Yamakawa, S.; Kritskiy, O.; Gjoneska, E.; Tsai, L. H. The Transcription Factor Sp3 Cooperates with HDAC2 to Regulate Synaptic Function and Plasticity in Neurons. *Cell Rep.* **2017**. https://doi.org/10.1016/j.celrep.2017.07.044.

(85) Hontecillas-Prieto, L.; Flores-Campos, R.; Silver, A.; de Álava, E.; Hajji, N.; García-Domínguez, D. J. Synergistic Enhancement of Cancer Therapy Using HDAC Inhibitors: Opportunity for Clinical Trials. *Frontiers in Genetics*. 2020. https://doi.org/10.3389/fgene.2020.578011.

(86) Eckschlager, T.; Plch, J.; Stiborova, M.; Hrabeta, J. Histone Deacetylase Inhibitors as Anticancer Drugs. *International Journal of Molecular Sciences*. 2017. https://doi.org/10.3390/ijms18071414.