Autophagy regulation by acetylation—implications for neurodegenerative diseases

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Abstract
Posttranslational modifications of proteins, such as acetylation, are essential for the regulation of diverse physiological processes, including metabolism, development and aging. Autophagy is an evolutionarily conserved catabolic process that involves the highly regulated sequestration of intracytoplasmic contents in double-membrane vesicles called autophagosomes, which are subsequently degraded after fusing with lysosomes. The roles and mechanisms of acetylation in autophagy control have emerged only in the last few years. In this review, we describe key molecular mechanisms by which previously identified acetyltransferases and deacetylases regulate autophagy. We highlight how p300 acetyltransferase controls mTORC1 activity to regulate autophagy under starvation and refeeding conditions in many cell types. Finally, we discuss how altered acetylation may impact various neurodegenerative diseases in which many of the causative proteins are autophagy substrates. These studies highlight some of the complexities that may need to be considered by anyone aiming to perturb acetylation under these conditions.

Introduction
Macroautophagy (hereafter autophagy) is a process mediating the delivery of cytoplasmic components to the lysosome for degradation via double-membrane vesicles called autophagosomes. In mammalian cells, autophagosomes are formed from cup-shaped precursor structures called phagophores, which include a complex of autophagy proteins, including ATG5, ATG12 and ATG16L1. The membranes of phagophores expand and form enclosed autophagosomes, and completed autophagosomes subsequently fuse with lysosomes. Lysosomal digestion of autophagic cargoes protects cells against starvation and related stresses by releasing recycled building blocks from autophagic substrates.

Acetylation is a major posttranslational modification (PTM) and affects diverse aspects of protein function by altering properties such as stability, hydrophobicity, enzymatic activity, subcellular localization and interactions with other substrates and cofactors in the cell. In acetylation, the acetyl group of an acetyl-coenzyme (AcCoA) can be co- or posttranslationally transferred to either the α-amino group of the N-terminus of a protein (Nt-acetylation) or to the ε-amino group of a lysine residue (K-acetylation). Nt-acetylation is catalyzed by highly conserved Nt-acetyltransferases (NATs) and is considered irreversible. On the other hand, K-acetylation is a reversible modification mediated by lysine acetyltransferases (KATs) at the ε-amino group of lysine residues. The tight regulation of acetylation by these enzymes plays fundamental regulatory roles in development and diverse human diseases, including diabetes and neurodegenerative conditions.

In this review, we describe how autophagy is regulated by acetylation, particularly K-acetylation, by previously identified KATs and deacetylases (KDACs). We also summarize the therapeutic targeting of acetylation, which may potentially lead to effective strategies to treat neurodegenerative diseases.
Introduction to autophagy

Under normal conditions, cells sustain basal levels of autophagy to maintain homeostasis. However, a variety of stimuli, including nutrient deprivation, metabolic imbalance or cellular stress, can activate autophagy. Autophagosome biogenesis includes three early stages: initiation, nucleation, and expansion of the isolation membrane (Fig. 1), and the process is mediated by autophagy-related proteins (ATGs), which were initially discovered in yeast. Many ATG proteins can be regulated by PTMs, such as phosphorylation, ubiquitination and acetylation. The Unc-51-like autophagy-activating kinase (ULK) 1/2 complex (consisting of ULK1, ATG13, RB1-inducible coiled-coil protein 1 (FIP200) and ATG101) plays a major role in autophagy as a signaling node for several pathways and by phosphorylating downstream effectors. During the initiation of autophagosome formation, this complex acts as a serine/threonine kinase that phosphorylates Beclin 1 in the vacuolar protein-sorting 34/PI3-kinase (VPS34)/PI3K complex. Additionally, the ULK1 complex recruits ATG9, which is thought to be involved in delivering membranes to autophagosomal structures and may act as a lipid scramblase. The VPS34/PI3K complex generates phosphatidylinositol 3-phosphate (PI3P), which facilitates the recruitment of WD-repeat protein-interacting with phosphoinositides (WIPI2) that recruits the ATG5-ATG12-ATG16L1 complex to the sites of phagophore formation. This complex enables the conjugation of LC3 and its family members to phosphatidylethanolamine in phagophore membranes. To degrade the autophagosomal content, autophagosomes must fuse with a functional lysosome, and SNARE proteins mediate this fusion.

Autophagy is tightly regulated by intracellular and extracellular signals. Mechanistic target of rapamycin (mTOR) complex 1 (mTORC1) integrates signals related to growth and metabolism in response to nutrient and energy levels and negatively regulates autophagy through the phosphorylation of ULK1, ATG13, transcription factor EB (TFEB) and other autophagy-related proteins under nutrient-rich conditions.

Regulation of acetylation in cells

Nt-acetylation

Six different NATs have been identified in mammals (NatA to NatF). NATs regulate the transfer of an acetyl group from Ac-CoA to the free α-amino group of a polypeptide chain that is being synthesized. NATs can differ in their subunit composition and substrate specificity. Nt-acetylation can regulate the subcellular localization of proteins, protein stability, and protein-protein interactions.

K-acetylation

Lysine (K) acetylation depends on the use of Ac-CoA, and also nicotine adenine dinucleotide (NAD+) in the case of sirtuins, a class of lysine deacetylases (KDACs; HDACs), which use it as a co-substrate. This type of acetylation links metabolism with cell signaling, as Ac-CoA and NAD+ are key metabolites, and modifies pathways that can be reversibly altered by deacetylases (Fig. 2). The K-acetylation and deacetylation of proteins were first studied in histones because of their roles in gene expression.

Fig. 1 Overview of the autophagy pathway. mTORC1 inhibition and AMPK activation positively regulate the ULK1 complex through a series of phosphorylation events. The ULK1 complex subsequently activates VPS34/PI3K complexes, which leads to PI3P synthesis and the nucleation of preautophagosomal structures. PI3P then recruits PI3P effector proteins, namely, WIPIs and the ATG12-ATG5-ATG16L1 complex, which is essential for autophagosome membrane elongation. Subsequent fusion to lysosomes results in the degradation of a variety of substrates, such as protein aggregates, infectious agents, and damaged mitochondria.
regulation. However, KATs and KDACs also acetylate nonhistone proteins in the nucleus or cytoplasm to regulate major biological processes. Acetylation also occurs through nonenzymatic mechanisms and is affected by the availability of Ac-CoA.

KATs and KDACs and autophagy regulation

To date, approximately 40 mammalian proteins have been proposed to possess endogenous KAT activity. Thirteen are well characterized (canonical) and can be classified into three major families: the GCN5 (also known as KAT2A) and PCAF (also known as KAT2B) family; the E1A binding protein p300 (encoded by EP300, also known as KAT3B) and CREB-binding protein (CBP, also known as KAT3A) family; and the MYST family, named for its founding members MOZ (also known as KAT6A), yeast Ybf2, Sas2, and Tip6 (also known as KAT5) (Fig. 2). All canonical KATs are predominantly localized in the nucleus and acetylate histones and nonhistone proteins. However, some KATs, such as p300, are nuclear but can be exported to the cytoplasm depending on intracellular signaling. The substrate specificities of KATs are thought to be defined by their specific subcellular localization, their interacting proteins and the accessibility of lysine residues in substrate proteins. KATs are found in unique complexes that influence their target specificities and their abilities to interact with other proteins. More than 2,000 acetylation targets in the nucleus, cytoplasm, mitochondria and endoplasmic reticulum have been identified in human cells.

The human genome encodes 18 KDACs, and they are divided into two major categories: zinc-dependent KDACs and NAD+-dependent sirtuin deacetylases (Table 1). On the basis of phylogenetic conservation and sequence similarities, zinc-dependent KDACs are further divided into four classes: class I, class IIa, class IIb and class IV. Class I and class IV KDACs are localized in the nucleus, class IIb KDACs are cytoplasmic, and class IIa KDACs are primarily localized in the nucleus but are also found in the cytoplasm. Sirtuin (SIRT) deacetylases localize to different cellular compartments, including the nucleus (SIRT1, SIRT6 and SIRT7), cytoplasm (SIRT2) and mitochondria (SIRT3, SIRT4 and SIRT5).

In mammalian cells, KATs and KDACs play pivotal roles in autophagy regulation at multiple steps (Table 1). As protein acetylation is a major regulator of gene transcription, the epigenetic regulation of autophagy genes by KATs or KDACs may be important for autophagy regulation. Depending on the target proteins of KATs and KDACs, acetylation has the potential to induce or inhibit autophagy (Table 1).

Regulation of autophagy by p300-dependent acetylation

Among KATs, p300 appears to acetylate many ATG proteins that regulate autophagy at multiple steps. p300 depletion or specific p300 inhibitors can induce autophagy, whereas the overexpression of p300 inhibits autophagy. Recently, we reported that under nutrient-depleted conditions, such as amino acid (AA) or leucine starvation, p300-dependent acetylation regulates autophagy through the acetylation of the mTORC1 component Raptor at K1097. This acetylation of Raptor enables the interaction of mTORC1 with the Rag complex on the lysosomal membrane, where mTORC1 is activated. In this way, Raptor acetylation is mediated by leucine, and p300 activation results in mTORC1 activation and autophagy repression. Cells expressing an acetylation-dead mutant of Raptor (Raptor K1097R; KR) manifested autophagy activation without altered acetylation of autophagy-related proteins. Furthermore, p300 activation had no discernible effects on autophagy levels in Raptor KR-expressing cells or in cells where mTORC1 was inhibited. Thus, our data suggest that p300 activity (and leucine) inhibits autophagy primarily by activating mTORC1 rather than by altering the acetylation of other proteins. This Ac-CoA-p300-Raptor regulation of autophagy via mTORC1 occurs in most cell types, including neurons (Fig. 3).
The regulation of autophagy by other KATs

1. GNAT family In mammalian cells and Drosophila, GCN5 inhibits the biogenesis of autophagosomes and lysosomes by regulating the acetylation of TFEB at lysine 274 and lysine 279. The acetylation of TFEB disturbs its dimerization and its subsequent binding to target gene promoters, many of which regulate autophagy or lysosomal biogenesis. PCAF, another member of the GNAT family, is reported to regulate autophagy through the inhibition of the mTORC1 pathway in some cancers, such as hepatocellular carcinoma.

2. MYST family The MYST acetyltransferase family also appears to regulate autophagy. Serum deprivation leads to the association of the protein kinase GSK3β with TIP60/KAT5 and subsequent phosphorylation at serine 86 of TIP60. Phosphorylated TIP60 acetylates and activates ULK1, which is essential for serum deprivation-induced autophagy. Additionally, under nutrient starvation, the induction of autophagy is coupled...
to a reduction in histone H4 lysine 16 (H4K16) acetylation through the downregulation of MOF/KAT834. The regulation of autophagy by KDACs

1. KDACs family
   KDAC family members are important for the regulation of autophagy at several levels. HDAC1 has been reported to be overexpressed in hepatocellular carcinoma, and inhibition of HDAC1 induces autophagy to repress tumor cell growth35. Chemical or genetic HDAC1 inhibition also induces autophagy and lysosomal activity in HeLa cells36. However, knocking down HDAC2, but not HDAC1, inhibited autophagy in cardiomyocytes37. In contrast, the deletion of both HDAC1 and HDAC2 in mice blocked autophagic flux in skeletal muscle38. Knocking down class IIa HDAC4 leads to autophagy induction by increasing the expression levels of ATG proteins, including Beclin 1 and ATG739. MicroRNA-dependent protein acetylation can also regulate autophagy. The regulation of HDAC4 and HDAC5 by miRNA-9 increased total LC3B and Rab7 levels40. Another study showed that the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) decreased HDAC7 protein levels in endometrial stromal sarcoma cells, producing an accumulation of autophagic vacuoles41. Recently, the HDAC8-selective inhibitor HMC was shown to induce autophagy in MCF-7 cells42.

2. Sirtuins
   The sirtuin family of class III HDACs are NAD$^+$-dependent deacetylases that modulate a variety of cellular processes, including energy metabolism, stress responses, cell survival and proliferation. The deacetylation reactions catalyzed by sirtuins are coupled to the cleavage of NAD$^+$ into nicotinamide and 1-O-acetyl-ADP ribose. Therefore, sirtuin activities are dependent on the availability of cellular NAD$^+$ and are influenced by cellular metabolic status. Seven sirtuins (SIRT1 to SIRT7) have been identified in the human genome, and recent studies have proposed important roles for all sirtuins in the regulation of autophagy49–56. In particular, SIRT1 deacetylates ATG5, ATG7 and LC3 and appears to positively regulate autophagy at several steps49.

KATs and KDACs in neurodegenerative disease

Most of the neurodegenerative diseases in humans are caused by toxic intracytoplasmic, aggregate-prone proteins. Alzheimer’s disease (AD) pathology is characterized by amyloid-beta, an extracellular product derived from amyloid precursor protein (APP), and intracellular aggregated tau57. Parkinson’s disease (PD) is associated...
with the accumulation of alpha-synuclein (α-syn), and excess levels of this protein are sufficient to cause disease. Huntington’s disease is a monogenic autosomal dominant disease caused by polyglutamine tract expansions in the huntingtin protein, while amyotrophic lateral sclerosis (ALS) can be either monogenic or complex. The monogenic causes of ALS include mutations in SOD1, FUS and TDP-43. Importantly, all of these disease-causing intracytoplasmic proteins are autophagy substrates, and autophagy-upregulating drugs and genes enhance the clearance of these proteins and attenuate their toxicities in a range of animal models (flies, zebrafish and mice). Autophagy may also protect against neurodegeneration by dampening inflammatory-type processes and apoptosis.

The importance of acetylation regulated by KATs and HDACs in neurodegenerative diseases has been highlighted by observations that imbalanced acetylation causes progressive neuron-specific loss, impaired neuronal function, and eventual neuronal death. Many studies have reported that abnormal acetylation and deacetylation are linked to the pathogenesis of a variety of neurodegenerative diseases (Table 2). We briefly review the relationships between acetylation and different neurodegenerative diseases to reveal some of the complexities that may emerge when perturbing relevant modifying enzymes, as these may impact not only autophagy but also numerous other cellular processes pertinent to neurodegeneration.

1. Alzheimer’s disease (AD) While p300-mediated histone H3 acetylation at the presenilin 1 (PS1) and beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1) promoters is upregulated, consequently enhancing the expression levels of these genes in an AD model cell line. Interestingly, p300 levels are significantly increased in an AD model cell line, suggesting that p300 regulates the expression of AD-related genes by controlling acetylation or their promoters. The overexpression of CBP leads to recovered loss of learning and memory in AD triple transgenic mice. On the other hand, acetylation of tau can be modulated by p300 and SIRT1, and excess acetylated tau may contribute to tau-mediated neurodegeneration. Interestingly, hyperactivation of p300/CBP activity has been reported to disrupt autophagic flux and cause excessive tau secretion. PCAF knockout mice are resistant to Aβ-induced toxicity and memory deficits, an effect that has been attributed to the upregulation of the activity of the Aβ-degrading enzyme Neprilysin. Impaired function of TIP60 has been described in the human AD hippocampus, and imbalanced TIP60/HDAC2 activity is observed in the brain of an APP Drosophila AD model, suppressing the activities of neuroplasticity genes, which can be rescued by overexpression of TIP60. Inactivation of HDAC1 activity by the p25/Cdk5 complex, which is involved in neurodegenerative diseases, including AD, causes double-strand DNA breaks and neurotoxicity, which can be restored by HDAC1 overexpression. Moreover, HDAC3 promotes tauopathy, whereas suppression of HDAC3 may affect not only nonamyloidogenic APP processing but also neuroprotective gene expression in vitro and in an AD mouse model. Nuclear translocation of class II HDACs such as HDAC4 and HDAC6 is regulated by Aβ oligomers and the apolipoprotein E ε4 allele (apoE4), which is a critical AD risk factor, resulting in the downregulation of BDNF expression, which is important for controlling synaptic repair and synaptic plasticity. HDAC6 binds to tau in the perinuclear aggresomal compartment, and HDAC6 levels are upregulated in the hippocampus of AD patients and AD mice. By contrast, loss of HDAC6 improves learning and memory, α-tubulin acetylation and cognitive function in an AD mouse model. In the brains of an AD mouse model, overexpression of SIRT1 inhibits Aβ oligomers and plaque burden and ameliorates behavioral deficits, suggesting a neuroprotective role for SIRT1 in AD. Loss of SIRT2 induces microtubule stabilization and initiation of the subsequent autophagic-lysosomal pathway to degrade toxic Aβ oligomers in an AD-derived cell model.

2. Parkinson’s disease (PD) While α-syn is believed to be an important effector of PD because of its activities in the cytoplasm, α-syn may also mediate neurotoxicity by interacting with histone H3, thereby inhibiting histone acetylation by inactivating several KATs, including CBP, p300 and PCAF. The suppression of SIRT2 by either siRNA or a potent inhibitor prevents α-syn-dependent neurotoxicity, as well as the formation of α-syn inclusions in vitro and in a Drosophila model of PD. However, the relationship between SIRT2 inhibition and α-syn aggregation is still unclear. In cortical Lewy bodies, α-syn colocalizes with the microtubule-binding proteins MABP1 and tau. Increased acetylation of α-tubulin by the inhibition of SIRT2 may promote the formation of α-syn aggregates by binding to microtubules, suggesting that stabilized microtubules can play an important role in neuroprotection. Furthermore, the upregulation of SIRT2 prevents microtubule hyperacetylation and axonal degeneration. The overexpression of SIRT1 increases the lifespan of an α-syn A53T PD mouse model and prevents the
| Disease | Class | Prognostic relevance | Molecular evidence | Molecular consequence | Opposite effect | Ref. |
|---------|-------|----------------------|--------------------|----------------------|----------------|-----|
| AD KAT | p300  | Upregulated in N2a/ APPswe cells | Binding to the PS1 and BACE1 promoters and acetylation | p300 increases PS1 and BACE1 expression levels and increases the expression of Aβ. | Overexpression of p300 induces neuronal cell death linked to AD pathology. | 74  |
|         |       | Increased p-p300 (Ser1834) in CA1 of AD brain | p-p300-positive neurons colocalize with p-tau | p300 leads to tauopathy. | | 107 |
|         |       | Decreased in AD brain | | | | 108 |
| CBP     | Decreased in AD brain | | | Aβ induces posttranslational degradation of p300. | Overexpression of CBP rescues learning and memory loss in AD mice. | 75,108 |
| PCAF    | Decreased in AD brain | | Regulation of NEP and low level of SRIH | | Knocking out PCAF reduces Aβ-mediated toxicity. | 78,108 |
| TIP60   | Human AD hippocampus, APP Drosophila Drosophila CNS | Suppression of synaptic plasticity gene Binding to APP through AICD | TIP60 suppresses synaptic plasticity. Tip60 functions neuroprotection. | | | 79,109 |
| KDAC    | HDAC1  | Decreased in frontal cortex and hippocampal region of AD patients | Inactivation by the p25/Cdk5 complex | Inactivated HDAC1 causes dsDNA breaks and neurotoxicity. | Overexpression of HDAC1 leads to neuroprotection. | 80,108 |
|         | HDAC2  | Upregulated in AD brain | Inhibition of neuronal gene expression | HDAC2 causes disruption of synaptic plasticity and neuronal development. | HDAC2 deficiency improves the increased synapse numbers and memory. | 81,108 |
|         | HDAC3  | In vitro and AD mice model | | HDAC triggers not only tau phosphorylation but also Aβ metabolism in AD cellular and animal models. | Inhibition of HDAC3 decreases tau phosphorylation and Aβ production, leading to a neuroprotective effect. | 81 |
|         | HDAC4/ HDAC6 | Increased nuclear localization Nuclear localization by Aβ oligomers and ApoE4 Binding to tau in perinuclear aggresome, deacetylation α-tubulin and tau. | HDAC4/6 affect inhibition of BDNF expression, which controls synaptic repair and plasticity. | | | 82,83,111 |
|         | HDAC6  | Upregulated in AD patient, mice model and during AD progression | | HDAC6 leads to tauopathy. | | 84,111 |
|         | SIRT1  | Decreased in AD brain | Binding to tau | Loss of SIRT1 promotes p-tau and consequent tauopathy. Reduced level of SIRT1 induces Aβ oligomers. | Overexpression of SIRT1 prevents tauopathy. | 85,112 |
| SIRT2   | AD-derived cell model | Inhibition of microtubule stabilization | | | Uppregulation of SIRT1 suppresses Aβ production through control of γ-secretase activity. | 85 |
| Disease | Class | Prognostic relevance | Molecular evidence | Molecular consequence | Opposite effect | Ref. |
|---------|-------|----------------------|--------------------|----------------------|----------------|-----|
| HD      | KAT CBP | Decreased in the hippocampus of mutant HdhQ7/Q111 mice | Low expression of CBP in HD | Acetylation of mHtt at K444 | Reduced level of CBP impairs memory and induces neuron death. | Loss of SIRT2 induces microtubule stabilization and degrades toxic Aβ oligomers by autophagy. | 113 |
|         |       |                      | Binding to polyQ expansions |                      | Low level of CBP reduces acetyltransferase activity, leading to mHtt accumulation and impaired intracellular trafficking. | CBP overexpression promotes increased acetylation and degradation of mutant Htt. | 95 |
|         |       |                      | Loss of CBP in HD Drosophila model and primary neurons | Acetylation of mHtt at K444 | CBP-mediated mHtt acetylation at K444 triggers trafficking to autophagosome for mHtt degradation by autophagy. | 95 |
| PCAF    | Loss of PCAF in HD Drosophila model | Binding to mHtt | | Reduced PCAF level triggers neurodegeneration. | 114 |
| KDAC    | HDAC6 SBMA Drosophila model | Controls BDNF expression and mTORC1-CREB-regulated transcription | | SIRT1 inhibits mHTT-mediated interference with mTORC1 activity and improves mHtt toxicity. | 116 |
| SIRT2   |       |                      |                      |                      | SIRT2 inhibition offers neuroprotection by decreasing sterol biosynthesis. | 117 |
| PD      | KAT CBP, p300, PCAF | Downregulated in PD brain | Extension of the life span of αSyn A35T-expressing mice Deacetylation of HSF1 and increase in Hsp70 | SIRT1 prevents the formation of αSyn aggregates. | Inhibition of SIRT2 promotes αSyn mediated neurotoxicity through α-tubulin hyperacetylation. | 87,88 |
|         |       |                      | Binding to α-tubulin | SIRT1 Inhibits αSyn-mediated neurotoxicity by activating molecular chaperones. | 89 |
| ALS     | KAT CBP | Low level of CBP in motor neuron of ALS patients | Acetylation of p53 K320 | Neuroprotection | Inhibition of SIRT2 promotes αSyn mediated neurotoxicity through α-tubulin acetylation. | 99 |
|         | P300, CBP, PCAF | | | | 106 |
formation of α-syn aggregates. SIRT1 deacetylates HSF1 (heat shock factor 1) and thereby increases Hsp70 levels, suggesting that Hsp70 activation can inhibit the α-syn-mediated neurotoxicity of Hsp70.

3. Huntington’s disease (HD) CBP is observed in the aggregates formed by mutant huntingtin (mHtt). PolyQ expansions, the mutations in the huntingtin protein, directly interact with and sequester CBP and PCAF in animal models, leading to transcriptional dysregulation. In addition, loss of CBP from the nucleus impairs HAT activity and CBP-mediated gene expression, resulting in neuronal dysfunction and neuronal death. Furthermore, soluble mHtt may enhance ubiquitination to accelerate CBP degradation via the ubiquitin-proteasome system. mHtt acetylation at lysine 444 (K444) by CBP activation or HDAC1 inhibition promotes its trafficking to autophagosomes and subsequent clearance in primary neurons and a C. elegans HD model, suggesting a role in neuroprotection. Similarly, HDAC6-mediated retrograde transport on microtubules may facilitate mHtt degradation through autophagy. Several studies have reported that SIRT1 activity ameliorates mHtt-mediated toxicity in both cellular and animal models. In addition, mHtt suppresses SIRT1 deacetylase activity through a direct interaction causing SIRT1 to remain hyperacetylated, leading to the attenuation of SIRT1-regulated neuroprotective effects. However, SIRT2 controls HD-related metabolism, such as cholesterol biosynthesis, leading to increased production of cholesterol, further increasing mHtt aggregation.

4. Amyotrophic lateral sclerosis (ALS) Transgenic mice expressing the disease-causing mutant protein SOD1 G86D have low levels of histone H3 acetylation and CBP in motor neurons. Similar to SOD ALS mouse models, low levels of CBP are found in the motor neurons of sporadic ALS patients. Furthermore, SOD1 mutants may cause disrupted axonal transport and contribute to the loss of mitochondria from axons because of defective microtubule-dependent trafficking. Interestingly, decreased acetylation of α-tubulin is observed in HAT Elp3-deficient cortical neurons. Knocking out HDAC6 in SOD1 G93A-expressing mice reduces motor neuron degeneration and increases acetylated α-tubulin without affecting disease onset. However, conflicting functions of HDAC6 in mice harboring mutant SOD1 have also been reported. Inhibition of HDAC6 promotes the formation of large mutant SOD1 aggregates, which is accompanied by the increased acetylation of α-
Concluding remarks

Although the mechanisms remain incompletely understood, accumulating evidence indicates that different KATs and KDACs play pivotal roles in autophagy regulation at multiple steps of the pathway. New links between protein acetylation and autophagy control are likely to emerge. Acetylation also plays a crucial regulatory role in pathological conditions, particularly in neurodegenerative diseases and cancer. Thus, identifying how acetylation impacts various processes involved in neurodegenerative diseases, including autophagy, will help to inform suitable therapeutic strategies.

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Conflict of interest

D.C.R is a consultant for Aladdin Healthcare Technologies, Nido Biosciences and Drishti Discoveries. The remaining authors declare no competing interests.

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