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Neurodegenerative diseases: Epigenetic regulatory mechanisms and therapeutic potential

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ABSTRACT

Neurodegenerative diseases (NDDs) are a class of diseases in which the progressive loss of subtype-specific neurons leads to dysfunction. NDDs include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), among others. Previous studies have demonstrated that the pathogenesis of NDDs involves various mechanisms, including genetic factors, oxidative stress, apoptosis, and the immune response. Recent studies have shown that epigenetic regulation mediates the interactions between DNA methylation, chromatin remodeling, histone modification, and non-coding RNAs, thus affecting gene transcription. A growing body of research links epigenetic modifications to crucial pathways involved in the occurrence and development of NDDs. Epigenetics has also been found to regulate and maintain nervous system function, and its imbalance is closely related to the occurrence and development of NDDs. The present review summarizes focuses on the role of epigenetic modifications in the pathogenesis of NDDs and provides an overview of the key genes regulated by DNA methylation, histone modification, and non-coding RNAs in NDDs. Further, the current research status of epigenetics in NDDs is summarized and the potential application of epigenetics in the clinical diagnosis and treatment of NDDs is discussed.

1. Introduction

Neurodegenerative diseases (NDDs) are a class of diseases in which the progressive loss of specific subtypes of neurons leads to dysfunction. This progressive loss of neurons and/or deterioration in the myelin sheath over time results in dysfunction [1]. Since it is difficult to regenerate and recover after nerve damage, there remains a lack of effective strategies for preventing or postponing the occurrence and progression of NDDs.

Waddington first defined epigenetics as heritable modifications in gene expression without changes in the DNA sequence; epigenetics regulates processes such as cell differentiation, cell-specific gene expression, and genomic stability and structure [2]. Epigenetics encompasses DNA methylation, histone modifications, the expression of non-coding RNAs (ncRNAs), and chromatin accessibility. Epigenetics is now recognized to play an important role in the pathogenesis and progression of NDDs [3]. For example, the inhibition of histone deacetylase 1 (HDAC1) activity by the p25/Cdk5 complex can lead to double-stranded DNA breakage and neurotoxicity, which impairs synaptic plasticity and promotes neuronal apoptosis. Thus, overexpression of HDAC1 is an emerging therapeutic strategy to mitigate these neurotoxic effects and improve the symptoms of NDDs [4]. In addition, HDAC3 promotes tubulin-associated unit (tau) protein lesions, and the inhibition of HDAC3 may not only affect amyloid precursor protein (APP) processing but may also regulate the expression of neuroprotective genes *in vitro* and *in vivo* [5]. α-Synuclein (α-Syn) is considered to be a key effector of Parkinson's disease (PD) due to its functional activity in the cytoplasm. Through interaction with histone H3, α-Syn leads to the inactivation of a variety of histone acetyltransferases (KATs), such as CBP, p300, and pca86, thus inhibiting histone acetylation. *In vitro* studies and a drosophila model of PD have demonstrated that the inhibition of histone deacetylase SIRT2 activity can effectively prevent α-Syn-mediated neurotoxicity and reduce the formation of α-Syn inclusion bodies [6]. To date, in-depth studies of the role of epigenetics in

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NDDs and the underlying molecular mechanisms have provided crucial insight into the pathogenesis of NDDs, highlighting the clinical significance and application value of epigenetics. In addition, targeted therapy using epigenetics has become a breakthrough in the field of NDD therapy. This review aims to highlight potential epigenetic therapeutics and their targets of inhibition, serving as a summary of the literature on the novel candidates available in the continued search for effective clinical treatments for NDDs.

2. Epigenetics and neurodegenerative diseases

2.1. DNA methylation and neurodegenerative diseases

DNA methylation covalences occur on the cytosine pyrimidine ring, which inducing in a change in the structure of the major grooves [7]. It involves the addition of the methyl group (-CH3) of S-adenosylmethionine to the 5th carbon position of cytosine in CpG dinucleotides by enzymatic reaction. CpG sites comprise a specific combination of base pairs in a DNA sequence, and CpG islands are regions where these CpG sites congregate and play a crucial role in the regulation of gene expression. The 5mC modification at CpG sites is a reversible response catalyzed by DNA methyltransferases (DNMTs). DNA methylation is a three-phase process that involves the *de novo* synthesis, maintenance, and removal of methylation (Fig. 1). DNA methylation is mediated by the balance of DNMTs and DNA demethylating enzymes (TETs). For example, DNMT1, DNMT3A, and DNMT3B are the major DNMTs that act synergistically to regulate gene expression by adding methyl groups to DNA and then maintaining cell growth and multiplication. On the other hand, TET1, TET2, and TET3 act as TETs [8]. DNA methylation changes have known to regulate several regulatory proteins epigenetically during various neurodegenerative disorders. It has been reported that HSF1, BDNF and PSD95 participating in the synaptic fidelity were decreased, as well as the methylation levels were markly increase in the CpG islands of their gene promoter site, then affected the cognitive dysfunction and neurobehavioral alterations [9]. Fernandes also found DNMT enzymes could improve the synaptic transmission between neurons, and regulate neuroinfammation-related molecules iNOS and COX2 [10]. DNA methylation is a normal reversible process of gene expression regulation that participates in many biological processes, including embryonic development, transcription factor repression, and genome stability [11].

In recent years, significant advancements have been made in our understanding of the epigenetic regulatory mechanisms of NDDs, confirming that DNA methylation plays an important role in the regulation of neuroplasticity and memory formation [12] (Table 1). Martínez-Iglesias et al. [13]compared the DNA methylation status of healthy individuals with AD and PD patients and found that the AD and PD patients had a reduced global DNA methylation level. This suggests that abnormal DNA methylation levels are associated with NDD risk. AD patients exhibit significant changes in their cognitive trajectory [14]. A study of the association between DNA methylation and altered cognitive trajectories in AD brains showed that DNA methylation modifications of the tight junction protein claudin 5 (CLDN5) were differentially expressed and caused blood-brain barrier dysfunction, thereby participating in early cognitive decline in AD patients [15]. Using bisulfite genome sequencing analysis, Tohgi et al. [16]found that down-regulation of methylation levels in the promoter region of the APP in the cerebral cortex of AD patients promoted amyloid beta (Aβ) and tau protein production. Imbalanced production of Aβ and tau protein aggregates leads to extracellular amyloid plaque accumulation and intracellular neurofibrillary tangle (NFT) formation. These aggregates have multiple toxic effects on nerve cells, including the induction of neuroinflammation, synaptic toxicity, and mitochondrial dysfunction, thereby aggravating the pathological process of AD.

In the frontal cortex, temporal cortex, and cerebellum of ALS patients, Gijselinck et al. [17]detected a substantial elevation in the

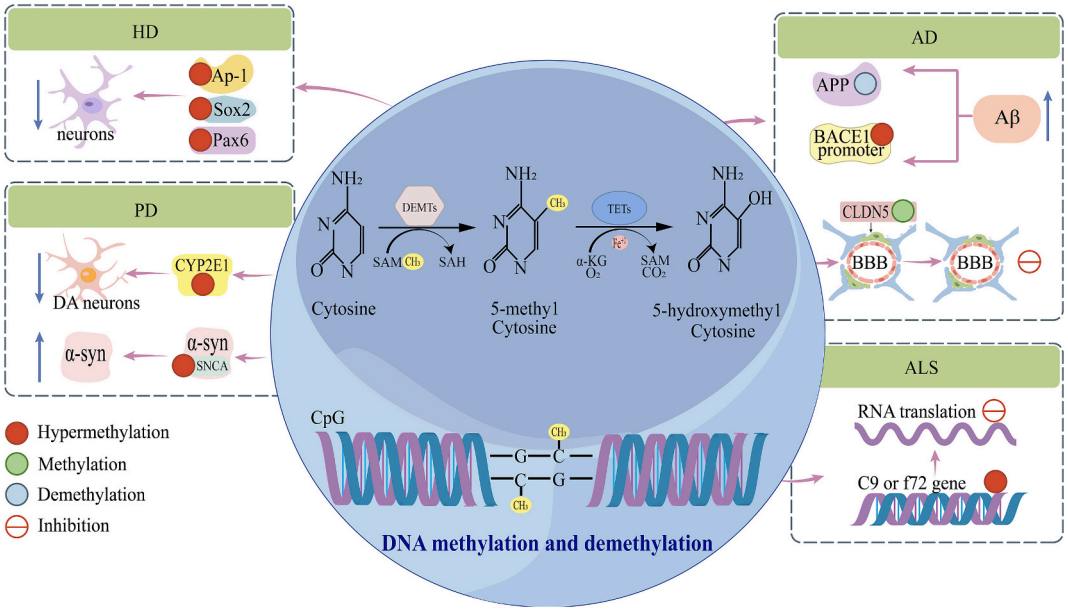

Fig. 1. The regulatory effects of DNA methylation on neurodegenerative diseases. DNA methylation mainly exists in the form of 5mC. It is a process that involves the replication of DNA genetic material under the catalysis of DNA methyltransferases. S-adenosyl methionine is a methyl donor for adding a methyl group (CH3-) to the fifth carbon atom of a particular cytosine ring. In the pathogenesis of Alzheimer's disease, demethylation of APP and hypermethylation of BCAE1 promote Aβ protein deposition. Methylation of the tight junction protein CLDN5 in the blood-brain barrier inhibits its function. In the pathogenesis of Parkinson's disease, hypermethylation of CYP2E1 leads to the functional degradation of DA neurons. The hypermethylation of the α-Syn-encoding gene SNCA leads to an increase in α-Syn protein content. In the pathogenesis of Huntington's disease, the hypermethylation of the Ap-1, Sox2, and Pax6 genes causes the degeneration of neuronal function. In the pathogenesis of amyotrophic lateral sclerosis, hypermethylation occurs in the C9 or f72 gene region, which inhibits RNA transcriptional activity. APP, amyloid precursor protein; BACE1, β-secretase 1; Aβ, amyloid beta; CLDN5, claudin 5; CYP2E1, cytochrome P450 family 2 subfamily E member 1; DA, dopaminergic neurons; α-Syn, α-Synuclein; SNCA, αlpha-synuclein; Ap-1, activator protein-1; Sox2, SRY (sex determining region Y)-box 2; Pax6, paired-box 6; C9 or f72, chromosome 9 open reading frame 72.

Table 1
Potential DNA methylation markers in neurodegenerative diseases.

Diseases	Model	Cell/Tissue Type	Main Findings	Ref.
AD	Human	Cerebral cortex	↓APP promoter methylation	[16]
	Human	Cerebral cortex	↓GCF binding sites methylation	[24]
	Human	Brain tissues	↓Immunoreactivity for 5mc	[25]
	Human	Brain tissues	↑BACE1 gene promoter methylation	[26]
ALS	Human	Brain tissues	↑C9 or f72 gene region methylation	[17]
	Human	Brain and spinal cord	↑DNMT1 and DNMT3A	[27]
HD	STHdhQ7 mice STHdhQ111 mice	Brain tissues	↑TET2	[23]
	R6/1 and R6/2 mice	Shell nucleus	↑ 5mC; ↓5hmC	[28]
PD	Human	Substantia nigra and shell nucleus	↓SNCA methylation	[19]
	Human	Brain tissues	↓ DNA methylation	[29]

Note: ↑increase; ↓decrease; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; BACE1, β-secretase 1; C9orf72, chromosome 9 open reading frame 72; DNMT, DNA methyltransferase; GCF, GC factor; HD, Huntington's disease; PD, Parkinson's disease; SNCA, alpha-synuclein; TET2, ten-eleven translocation 2; 5mc, 5-methylcytosine; 5hmC, 5-hydroxymethylcytosine.

methylation level at the DNA gene region of C9 or f72. Similarly, Ng et al. [18] found an obvious change in DNA methylation in the striata of Huntington's disease (HD) mice by genome-wide chromatin immunoprecipitation sequencing (ChIP-Seq). This change was particularly evident in the hypermethylation of neurodevelopmental-related promoter genes (Ap-1, Sox2, Pax6). It is suggested that an imbalance in DNA methylation is closely related to the functional degradation of damaged neurons. Research on the substantia nigra and nucleus accumbens of PD patients has revealed that the downregulation of the synuclein alpha (SNCA) (a gene encoding α-Syn) methylation level induces an increase in the expression of α-Syn proteins. This leads to the accumulation of the α-Syn protein, the formation of oligomers and insoluble fibrils, and ultimately, the formation of Lewy bodies (LBs), which trigger the apoptosis of nerve cells [19]. Gordevicius et al. [20] found that hypomethylation of SNCA caused epigenetic upregulation of SNCA expression and hypermethylation of Toll-like Receptor 9 (TLR9) and GTP cyclohydrolase-1 (GCH1) affected lysosomal function, epigenetic silencing of Glycoprotein nonmetastatic melanoma protein B (GPNMB) in the PD patients. In addition, PINK1, Unc-51 like autophagy activating kinase 1 (ULK1), the initiating enzyme in autophagy, sphingosine kinase 1 (SPHK1), nicotinamide phosphoribosyl transferase (NAMPT), and Sirtuin 1 (SIRT1) were found to be differentially methylated among PD patients and control group. Su et al. [21] found that increased cytosine methylation at promoter regions of PGC-1α and downregulated PGC-1α expressiom in substantia nigra pars compacta (SNpc), then results in mitochondrial dysfunction leading to PD disease progression. A study conformed that DNMT3B could mediate hypermethylation of the PGC1-α gene, and affect the α-ketoglutarate (a cofactor for DNA demethylases) levels, then modulates the mitochondrial dynamics, the fission and fusion, as well as the mitochondrial DNA levels [22]. Marshall et al. [23]revealed that the level of the DNA demethylation enzyme ten-eleven translocation 2(TET2)was upregulated in the brains of PD patients, but deficiency of the TET2 gene in PD mice mitigated the inflammation-induced damage to nigral dopaminergic neuronal loss and impaired the inflammation-triggered immune response, thus reversing the progression of PD. This results suggested that targeting TET2 activity may be considered a potential therapy for PD.

2.2. Histone modifications and neurodegenerative diseases

Except DNA methylation, most of studies investigated the contribution of histone modifications dysregulation to NDDs pathogenesise and development. Histones are octamers consisting of H2A, H2B, H3, and H4; their amino-terminal residues are loose in structure. Histones are also the main sites for post-translational covalent modifications, including methylation, acetylation, crotonylation, guanosine, ubiquitylation, and ADP-ribosylation. These modifications alter the chromosomal tertiary structure and thus, regulate gene expression [30].

2.2.1. Histone acetylation and neurodegenerative diseases

Acetylation, a key post-translational modification, plays a crucial role in the regulation of gene expression. Dynamic acetylation and deacetylation processes are regulated by the interaction between acetyltransferases (HATs) and deacetylases (HDACs) (Fig. 2). These processes regulate a variety of cellular activities, including DNA transcription, protein balance, senescence, autophagy, and metabolism [31]. They also play an important role in maintaining neuroplasticity and memory and learning activities [32]. Experimental studies have demonstrated that acetylation is vital for the development of the brain; the proliferation and differentiation of neural stem cells; the maturity of glial cells such as astrocytes, oligodendrocytes, and microglia; and for neuronal circuit formation in HAT and HDAC mutant mouse models [33]. In NDDs such as AD, PD, and HD, the regulatory process of acetylation is changed. This manifests as over-acetylation and deacetylation, which impairs the physiological homeostasis of neurons and increases the accumulation of disease-related proteins (Table 2). Moreover, deacetylation has been implicated in axonal transport disorder [34]. Consequently, acetylation could provide a new perspective for understanding disease pathogenesis and developing novel potential therapeutic strategies for NDDs.

Histone acetylation has emerged as a key regulator of memory storage and is involved in the restructuring of chromatin in different brain regions, including the hippocampus [35]. Mews et al. [36]used the Cath.-a-differentiated (CAD) cell line to study the neuronal function of acetyl coenzyme A synthetase 2 (ACSS2) and found that the whole-cell and nuclear levels of ACSS2 increased during the differentiation of CAD neurons, and these were closely related to the up-regulation of genes near the region with an increased histone acetylation level. Decreased ACSS2 expression led to decreased nuclear acetyl-coenzyme A (acetyl-CoA) levels, which, in turn, affected histone acetylation and the responsive expression of multiple neuronal genes. Subsequent experiments revealed that a decrease in hippocampal ACSS2 impaired long-term spatial memory and altered the expression of neuronal genes linked to memory formation *in vivo*; this process was dependent on histone acetylation. These findings emphasize the role of acetyl-CoA synthesis within chromatin regions in the modification of essential neuronal gene transcription activation during histone acetylation processes. Cai et al. [37] integrated and analyzed epigenetic markers and single-cell transcriptomic data from brain samples of AD patients. The authors found that differentially expressed genes (DEGs) caused histone acetylation alterations in astrocytes, oligodendrocytes, and microglial cells, disrupted the synaptic plasticity of neurons, and affected the expression of the key AD-related genes, thus influencing the progression of the disease. The levels of neurospecific promoter histone H3 lysine 27 acetylation (H3K27ac) were markedly down-regulated in the AD brain, leading to decreases in the expression of genes associated with synaptic plasticity [38]. Another study found that the H3K27ac level was reduced in the entorhinal cortex of AD patients [39]. HDAC inhibition could cause hyperacetylation of histone proteins involved in regulating proteostasis and promotes the expression of HSP70, HSP 90, HSP40, and GRP78, thereby activating or inhibiting transcription of proteostasis related genes [40]. It has been reported that inhibiting the HDACs (Class-I and IIa) could upregulate DJ-1 expression, which results in protecting MPTP-induced PD in mice [41]. Research from Merienne

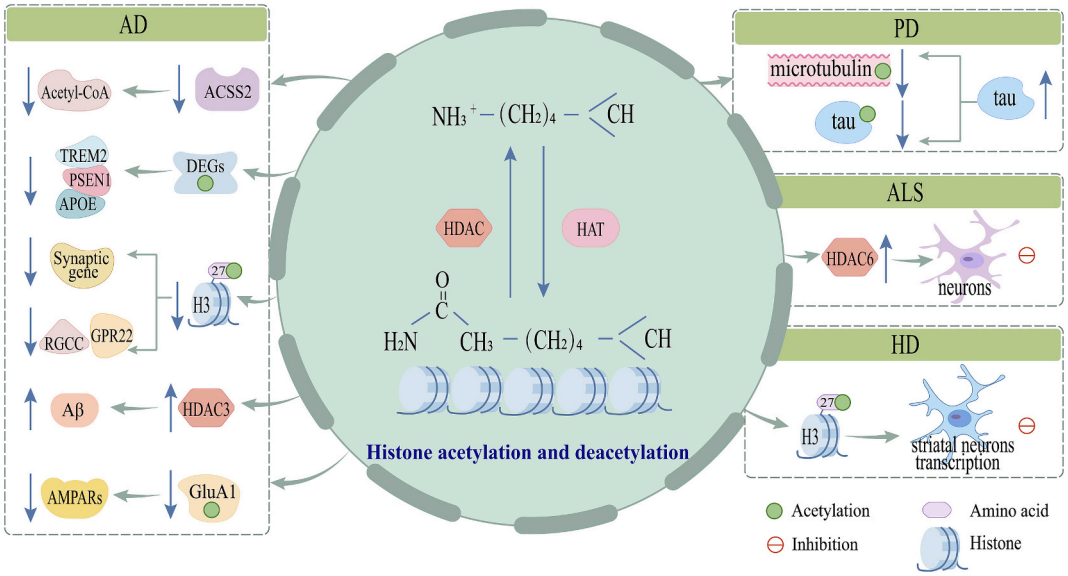

Fig. 2. The regulatory effects of histone acetylation on neurodegenerative diseases. Histone tail lysine residues protruding from the nucleosome core offer acetylation and deacetylation by adding or removing acetyl groups, these reactions are usually catalyzed by histone acetyltransferases or histone deacetylases. In the pathogenesis of Alzheimer's disease, the decreased expression of ACSS2 leads to a decrease in the acetyl-CoA level, which impairs spatial memory. The expression levels of the Alzheimer's disease-related genes TREM2, APOE, and PSEN1 decrease due to acetylation of DEGs. The decreased acetylation level of H3K27 leads to the downregulation of the synaptic genes RGCC and GPR22. The up-regulation of HDAC3 expression promotes the deposition of Aβ protein. The decrease in GluA1 acetylation causes an increase in the number of AMPARs. In the pathogenesis of Parkinson's disease, the acetylation of tubulin and tau protein leads to tau protein aggregation. In the pathogenesis of amyotrophic lateral sclerosis, the up-regulation of HDAC6 expression suppresses neuronal function. In the pathogenesis of Huntington's disease, acetylation of H3K27 inhibits the transcriptional function of striatal neurons. ACSS2, acetyl coenzyme A synthetase 2; TREM2, transmembrane protein 2; APOE, apolipoprotein E; PSEN1, presenilin 1 gene; DEGs, differentially expressed genes; H3K27, histone H3 lysine 27; RGCC, response gene to complement component C5; GPR22, G protein-coupled receptor 22; HDAC3/6, histone deacetylase 3/6; Aβ, amyloid beta; GluA1, Glutamate ionotropic receptor AMPA type subunit 1; AMPARs, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors; tau, tubulin-associated unit.

Table 2
Potential histone acetylation markers in neurodegenerative diseases.

Diseases	Model	Cell/Tissue Type	Main Findings	Ref.
AD	Human	Excitatory and inhibitory neurons; Microglia	↓H3K9ac of the DEGs	[37]
	Human	Entorhinal cortex	↓H3K27ac	[39]
	Human	Entorhinal cortex	↓Microtubulin and tau protein acetylation	[46]
	CAD cells	Hippocampus	↓ACSS2	[36]
	CK-p25 mice	Brain tissues	↓H3K27ac	[38]
	CK-p25 mice	Brain tissues	↑HDAC2	[52]
	HEK-293 cells; 3xTg-AD mice	Brain tissues	↓HDAC3	[56]
	APP/PS1 mice	Brain tissues	↑GluA1 acetylation	[51]
ALS	SOD G93A mice	Brain tissues	↓HDAC6	[57]
HD	Hdh(Q7/Q111) mice	Brain tissues	↓H3K27ac	[58]
PD	Human	Cerebral cortex, Hippocampus, SNpc	↓Microtubulin and tau protein acetylation	[47]

Note: ↑increase; ↓decrease; AD, Alzheimer's disease; ACSS2, acyl-CoA synthetase short-chain family member 2; ALS, amyotrophic lateral sclerosis; DEGs, differentially expressed genes; GluA1, glutamate AMPA receptor subunit 1 gene; HD, Huntington's disease; HDAC, histone deacetylase; H3K9, histone H3 lysine 9; H3K27, histone H3 lysine 27; PD, Parkinson's disease.

et al. [42] showed that H3K27ac was also decreased in the brain tissue of HD mice and patients. Transcription dysregulation is one of the core features of HD. It has been reported that the Huntington protein (HTT) can directly interact with the CREB-binding protein (CBP), a member of the HATs family, leading to its consumption and thus, a reduction in the acetylation level of histones [43]. In addition, the absence of CBP in the nucleus can impair HAT acetyltransferase activity and CBP-mediated gene expression, inducing neuronal dysfunction and death [44].

It has been reported that microtubule acetylation can control the migration, differentiation, and synaptic maturation of neurons during neurodevelopment. Alterations in microtubule acetylation are strongly associated with NDDs [45]. Esteves et al. [46] reported a remarkable reduction in the microtubule acetylation level in the brains of PD patients. Another study from the same group [47] confirmed that both microtubule acetylation and tau protein acetylation were reduced in the cerebral cortex, hippocampus, and SNpc of PD patients. This is consistent with what is observed in AD patients. Inhibition of silent information regulator sirtuin 2 (SIRT2) can enhance the acetylation of the alpha-tubulin protein and promote the formation of α-Syn aggregates by interacting with microtubules, highlighting the crucial role of microtubule stability in neuroprotection [48]. At the same time, the up-regulation of SIRT2 expression can prevent microtubule hyperacetylation and axonal degeneration [49]. In addition, the overexpression of SIRT1 can significantly increase the survival period of α-Syn A53T PD mice and effectively prevent the formation of α-Syn aggregates [50].

Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA)-type glutamate receptors (AMPARs), which are primarily responsible for excitatory synaptic transmission, serve as critical regulators of learning and memory processes. O'Connor et al. detected significant decreases in the acetylation levels of AMPARs in AD brains and Aβ-treated neurons. To explore the potential influence of AMPAR acetylation on AD pathology, AD mice were injected with the GluA1 gene (a subunit of AMPARs). GluA1 acetylation was increased, which reversed the reduction in both the number and cell localization of AMPARs caused by the Aβ protein. This ultimately antagonized the synaptic plasticity

alterations and memory deficits induced by AD [51]. These findings indicate that AMPAR acetylation may be a potential target for the treatment of AD.

In addition, increased expression of HDAC enzymes has been observed in multiple NDDs. For example, HDAC2 levels were elevated in the brains of AD mice and patients, accelerating neurodegenerative processes by promoting chromatin condensation and transcriptional repression. Administering an HDAC inhibitor to AD mice enhanced learning and cognitive function [52]. In the brains of AD mice, excessive SIRT1 effectively inhibited the formation of Aβ protein aggregates while improving behavioral disorders, suggesting that SIRT1 may have a potential neuroprotective function. Furthermore, in AD-derived cell models, SIRT2 loss promoted microtubule stability and activated subsequent autophagy-lysosomal pathways that degrade pathological Aβ proteins [53]. These findings contribute to our understanding of the effect of histone acetylation on brain development and NDD progression. Increasing evidence showed that major depressive disorder (MDD) is commonly associated with neurodegenerative diseases such as AD, PD and HD, and has a significant impact on the increasing burden of these neuropathologies [54]. A study reported that hippocampal sirt1 (a class III HDAC) could be participate in blockade in depression induced by chronic stress, after the blockade of hippocampal Sirt1 activity, the depressive behavior is significantly increased, contrarily, Sirt1 activation could result in the blockade of depressive behavior and abnormal dendritic structures, it maybe associated with the increasing of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) phosphorylation [55].

2.2.2. Lactation, crotonylation, citrullination, and neurodegenerative diseases

In addition to acetylation, the development and application of modern massectrometry (MS) has revealed a variety of other post-translational histone modifications, such as lactation [59], crotonylation [60], and citrullination [61] In contrast to acetylation, these novel modifications are associated with the regulation of gene expression, cell metabolism, and the stress response, depending on the specific location and degree of modification. Lactation is a process by which lactate acid regulates histone modification by adding lactic acid groups to lysine residues. It can mediate cell metabolism and coordinate gene expression and cell recombination [62]. Crotonylation is a dynamic process co-regulated by crotonyltransferases and decrotonylases and plays an important role in chromatin remodeling, the cell cycle, and cell recombination [63]. Citrullination, also known as deimination, is a post-translational protein modification catalyzed by peptidyl arginine deiminases (PADs) that converts positively charged arginine to neutral citrulline, thereby altering DNA charge, densifying chromatin, and promoting transcription [64,65]. These novel modifications are recognized to play a role in the development of NDDs.

Pan et al. [66] initially employed the CUT&Tag technique to detect significant Pan lysine lactation (Pan Kla) and histone lactation in the prefrontal cortex and hippocampus of AD mice and patients. Significant up-regulation of histone H4 lysine 12 lactylation (H4K12la) levels was observed nearby Aβ plaque-adjacent microglia. Further analysis showed that H4K12la was rich in several promoter regions of glycolytic genes, including pyruvate kinase M2 (PKM2). This discovery suggests that the interaction between H4K12la and PKM2 can promote the action of microglia in the prefrontal cortex and hippocampus, thereby affecting learning and memory abilities. Subsequently, Wei et al. [67] quantitatively analyzed lactate levels in microglial cells and the hippocampus of AD mice and naturally aging mice. Their findings revealed significant increases in lactic acid levels and H3 lysine 18 lactylation (H3K18la) in the hippocampus and in senescent microglia as compared with the control group. This study also reported that the enhancement of H3K18la could facilitate the interaction between the Rela (p65) promoter and the NF-kappaB1 (p50) promoter, thereby activating the NF-κB signaling pathway and leading to elevated expression of IL-6 and IL-8 in the senescence-associated secretory phenotype (SASP), consequently impacting the progression of AD. The results showed that the expression level of paraspeckle assembly transcript 1 (NEAT1) was reduced in the hippocampus. Further experiments confirmed that NEAT1 can inhibit the production of acetyl-CoA, promote the expression of H3K27 crotonylation, and up-regulate the expression of genes related to endocytosis-related genes. This regulatory mechanism may help glial cells effectively eliminate Aβ protein [68].

In addition, the up-regulation of citrullinated regulatory enzyme PAD levels has been reported in multiple NDDs. For example, the PAD subtypes PAD2 and PAD4 are specifically expressed in astrocytes and neurons, respectively, and the expression of PAD4 is closely related to the accumulation of citrullinated protein in the hippocampus and cerebral cortex of AD patients [69]. This suggests a potential role of citrulline in the production of neural reactive autoantibodies in AD. Compared with healthy individuals, myelin basic protein (MBP) in the cerebral myelin sheath of multiple sclerosis (MS) patients showed hypercitrullination and a significant increase in PADs was observed in the cerebral white matter [70]. To further determine the relationship between MBP protein citrullination and PADs, an experimental study examined the levels of PAD activity, protein, and mRNA expression. The results indicated that all levels were increased and citrullination of MBP was enhanced in the brain tissue of PAD transgenic mice. PAD activity was also positively correlated with the citrullination expression of MBP [71]. Yusuf et al. [72] found that with the development of myelopathy, the expression of protein citrullination and PAD2 gradually increased in the spinal cord and astrocytes of ALS mice. This correspond with these regions of the central nervous system (CNS) containing degenerated motor neurons. Furthermore, citrullinated proteins were overwhelmingly enriched in the brain white matter of ALS mice and were mainly colocalized with the myelin proteins MBP. This suggests that they play a role in neural reactive autoantibody production.

2.2.3. Ubiquitination and neurodegenerative diseases

Ubiquitination is one of the most important post-translational modifications in protein transport and turnover regulation (Fig. 3). The ubiquitin-proteasome system (UPS) is the main protein degradation system in cells; it is composed of ubiquitin (Ub), E1 ubiquitin-activating enzyme (E1), E2 ubiquitin-binding enzyme (E2), E3 ubiquitin-ligase (E3), 26S proteasome and deubiquitination enzyme (DUBs), and so on. The protein substrates modified by ubiquitination then participate in different ubiquitin chain-regulated physiological processes [73]. The UPS regulates protein degradation in cells and also participates in cell development and physiological processes, including transcriptional regulation, DNA damage repair, the cell cycle, and apoptosis [74,75]. NDDs such as AD, PD, and HD are characterized by excessive accumulation of protein aggregates, which results in the disruption of cell homeostasis and neuronal function. Although the composition and localization of protein aggregates are different in the various NDDs, they all exhibit immune activity against ubiquitin antibodies. A growing body of literature has demonstrated that abnormalities in the ubiquitin-dependent UPS are closely related to the formation of protein aggregates and thus, participate in neurodegeneration [76,77].

Extracellular amyloid plaques and intracellular neurofibrillary tangles are the pathological features of AD. Zhang et al. [78] found that the increased activity of AMPAR E3 ligase Nedd4 and decreased expression of AMPAR deubiquitinase USP46 in the cerebral cortex and hippocampal neurons of AD mice promoted the ubiquitination of AMPAR, driving the protein degradation process of Aβ, ultimately resulting in a decrease in the Aβ protein content. These results suggest that the ubiquitination mechanism of the AMPAR may be a key molecular pathway in the occurrence and development of AD. Another study by Gong et al. showed that the level of ubiquitin carboxy-terminal hydrogenase L1 (UCHL1) was significantly reduced in the brain tissue of AD mice, and the absence of UCHL1 led to impairment of long-term potentiation (LTP) and aggravation of cognitive impairment in AD [79]. Further, the author

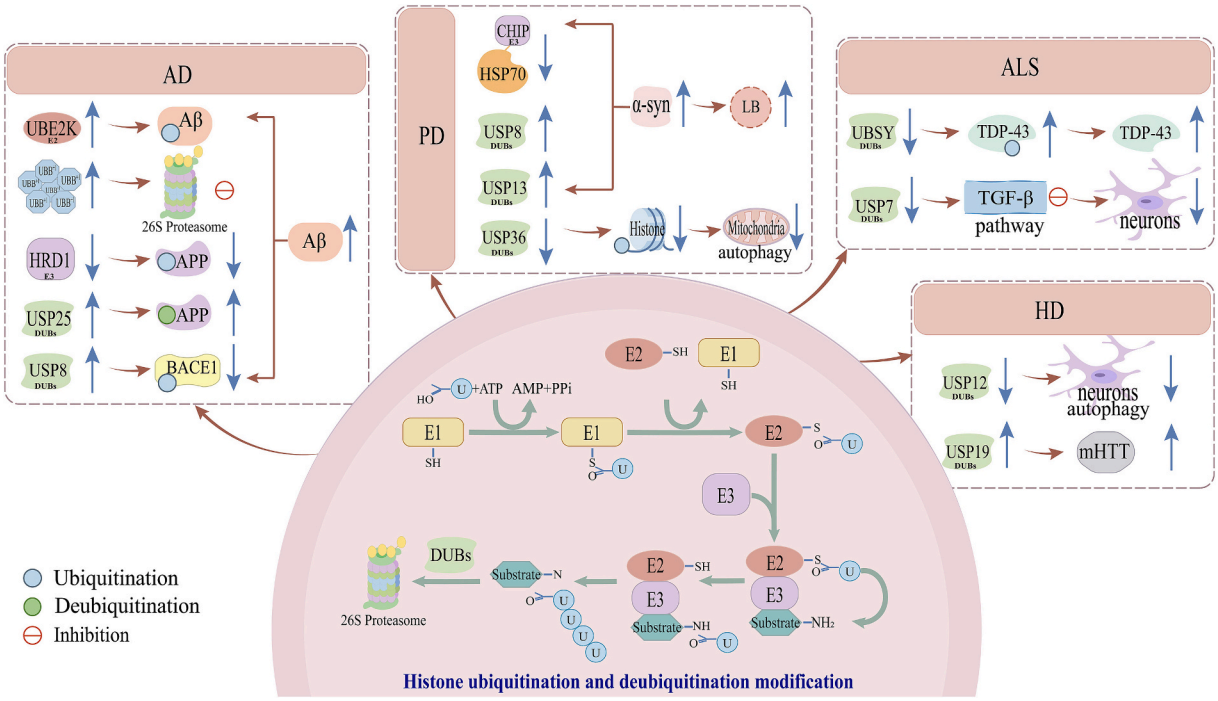

Fig. 3. The regulatory effects of histone ubiquitination on neurodegenerative diseases. Ubiquitin (Ub) is activated by the E1 enzyme in an Adenosine triphosphate (ATP)-dependent reaction. Activated Ub binds to a specific Ub-binding enzyme (E2), and this complex binds to Ub ligase (E3). The new Ub-binding complex then binds to a specific protein, resulting in polyubiquitination. The polyubiquitinated protein can be identified and directed to the 26S proteasome for degradation. In the pathogenesis of Alzheimer's disease, up-regulation of UBE2K expression leads to Aβ ubiquitination; mutant ubiquitin (UBB^{+1}) accumulation in the body inhibits 26S proteasome activity; HRD1 expression reduces the APP ubiquitination level; up-regulation of USP25 expression increases the APP deubiquitination degree; up-regulation of USP8 expression decreases BACE1 ubiquitination. These processes eventually lead to the deposition of the Aβ protein. In the pathogenesis of Parkinson's disease, down-regulation of the HSP70 protein and the expression of its carboxy-terminal CHIP protein, and up-regulation of USP8 and USP13 expression, lead to an increase in the α-Syn level. This promotes LB formation. The down-regulation of USP36 expression reduces histone ubiquitination and leads to a decrease in mitochondrial autophagy function. In the pathogenesis of amyotrophic lateral sclerosis, down-regulation of UBSY expression leads to an increased ubiquitination level of the TDP-43 protein, which, in turn, promotes the aggregation of the TDP-43 protein. Down-regulation of the USP7 level inhibits the TGF-β pathway, leading to a decline in neuronal function. In the pathogenesis of Huntington's disease, down-regulation of USP12 expression attenuates neuronal autophagy. Up-regulation of USP19 promotes the formation of the mHTT protein. UBE2K, ubiquitin-conjugating enzyme E2K; Aβ, amyloid beta; HRD1, E3 ubiquitin ligase HMG-CoA reductase degradation protein 1; USP7, USP8, USP12, USP13, USP19, USP25, USP36, UBSY, deubiquitination enzyme (DUB) family; APP, amyloid precursor protein; BACE1, β-secretase 1; HSP70, heat shock protein 70; CHIP, carboxyl terminus of Hsc70-interacting protein; α-Syn, α-synuclein; LB, Lewy body; TDP-43, TAR-DNA/RNA binding protein; TGF-β, transforming growth factor beta; mHTT, mutated Huntington's protein.

showed that exogenous UCHL1 reversed or repaired synaptic insufficiency in AD mice and mitigated similar injury induced by the Aβ protein. The UPS can enhance the release of neurotransmitters by degrading cAMP-response element binding protein (CREB), thereby regulating the metabolism and synaptic efficiency of presynaptic proteins and enhancing the plasticity of LTP, which contributes to the formation of long-term memories [80].

α-Syn is a synaptic nucleoprotein that is involved in synaptic function and dopaminergic neurotransmitter synthesis and transmission; it is also the main component of LBs [81]. Singleton et al. [82] found that an increased level of the α-Syn protein can cause PD. Tofaris et al. [83] analyzed the brains of PD patients through immunohistochemistry and western blotting and found that a large amount of α-Syn ubiquitination accumulated in LBs, suggesting that α-Syn ubiquitination is closely related to the pathogenesis of PD. Mutations in the α-Syn protein can lead to its aggregation, resulting in the formation of atypical β-fold structure. The mutant α-Syn protein becomes resistant to degradation by the UPS and consequently accumulates in LBs. In addition, the mutant α-Syn protein can also increase the sensitivity of cells to proteasome inhibitors, thus inhibiting the function of the UPS [84].

Increasing evidence has confirmed that the loss of the ubiquitin B mRNA dinucleotide causes a ubiquitin mutant called UBB^{+1}. This leads to dysfunction of the UPS in NDDs and ultimately, participates in the development of diseases [85,86]]. Pril et al. [87] reported that a large amount of UBB^{+1} accumulates in the striatum of HD mice, aggravating the polyglutamine-induced ubiquitination protein degradation process and inducing neuronal cell death and the formation of protein aggregates. This accelerates the pathological process of HD. These findings highlight the crucial function of the UPS in the neurodegeneration of HD. The accumulation of mutated Huntington's protein (mHTT) and the UPS dysfunction were closely related to HD. Corti et al. [88] confirmed that mHTT can inhibit proteasome activity, leading to the aggregation of inclusion bodies in neurons and the induction of neurotoxicity. This triggers nerve cell dysfunction and death. John et al. [89] reported that abnormal HTT protein in the brains of HD patients damages the function of the UPS by affecting protein aggregation, subcellular localization, and the cell microenvironment. The inclusion bodies formed by these mHTTs can recruit other proteins, including UPS components such as the Ub, 20S, and 19S subunits, causing the depletion of UPS components and functional abnormalities. Moreover, UPS activity is inhibited by binding with molecular chaperones such as the Hsp70/Hsp40 complex, and oxidative stress is induced. This leads to the dysfunction of proteasome function and causes endoplasmic reticulum (ER) stress through the c-Jun NH2-terminal kinase (JNK) signaling pathway, which participates in the pathological process of HD.

2.3. *RNA modification and neurodegenerative diseases*

Recent studies have highlighted the crucial role of RNA modification in neurodegenerative diseases and investigating its role in NDDs could

provide valuable insights for drug development. Various RNA modification types have been found, including N6-methyladenosine (m^6A) [90] 5-methylcytosine(m^5c) [91], and N1-methyladenosine modification (m^1A) [92]. M^6A modification is a well-known form of RNA methylation that is synergically regulated by a variety of enzymes and protens, including the methyltransferases METTL3, METTL14, WTAP, VIRMA, and RBM15, the demethylases FTO and ALKBH5, as well as the methylated binding proteins YTHDC1, YTHDC2, YTHDF1, and YTHDF2 (Fig. 4). M^6A methylation modification is highly expressed in the brain. It regulates the self-renewal of neural stem cells, learning and memory processes, brain development, synaptic growth, and glioma cell proliferation, playing a key role in nervous system diseases [93–96] (Table 3).

Studies have found that m^6A has obvious tissue specificity, especially in the hypothalamus. A significant increase in m^6A sites has been observed during the aging process in mice and humans. The changes to the m^6A sites are mainly concentrated in the relevant signaling pathways regulating the aging process and are negatively correlated with the corresponding mRNA expression [97]. Shi et al. [98] demonstrated that knockout of the Ythdf1 gene, which binds m^6A-modified methylation, in male adult mice led to learning and memory deficits along with synaptic transmission and LTP function impairments in the hippocampus. These results highlight the involvement of m^6A methylation in cognitive abilities and Ythdf1-mediated mechanisms. By combining m^6A sequencing and high-throughput liquid chromatography tandem mass spectrometry echnology, Shafik et al. [99] found that the m^6A methylation levels of the AD-related genes Mapt and Ltp1 were markedly reduced, and the level of the methyltransferase METTL3 was decreased, while the mRNA and protein expression levels of the demethylase FTO

Table 3
Potential RNA modification markers in neurodegenerative diseases.

Diseases	Model	Cell/Tissue Type	Main Findings	Ref.
AD	Human	Hippocampus	↑METTL3; ↑tau	[101]
	APP/PS1 mice	Brain tissues	↑METTL3; ↓FTO	[100]
	YTHDF1-KO mice	Brain tissues	↓m^6A modification	[98]
	5XFAD mice	Brain tissues	↓Mapt and Ltp1 gene m6A methylation; ↓METTL3; ↑FTO	[99]
	C57BL/6 J mice	Brain tissues	↓m^6A modification	[111]
	$M14^{f/f}$ mice	Striatum	↓mRNAs of the neuron and synapse-specific proteins	[112]
	Human	Peripheral blood mononuclear cells	↓METTL3, METTL14, YTHDF2	[114]
PD	Sprague-Dawley rat	Striatum	↓m^6A methylation	[104]
	Sprague-Dawley rat	Striatum	↓mRNA methylation; ↑ALKBH5	[113]
ALS	Human	Medulla Spinalis	↑RNA methylation	[108]
PD	Human	Hippocampus	↑METTL14; ↓FTO	[109]

Note: ↑increase; ↓decrease; AD, Alzheimer's disease; ALKBH5, AlkB homolog 5; ALS, amyotrophic lateral sclerosis; FTO, fat and obesity-associated gene; HD, Huntington's disease; Mapt, microtubule-associated protein tau; Ltp1, lipid transfer protein 1; METTL, methyltransferase-like proteins; PD, Parkinson's disease; YTHDF, YTH N6-methyladenosine RNA binding protein.

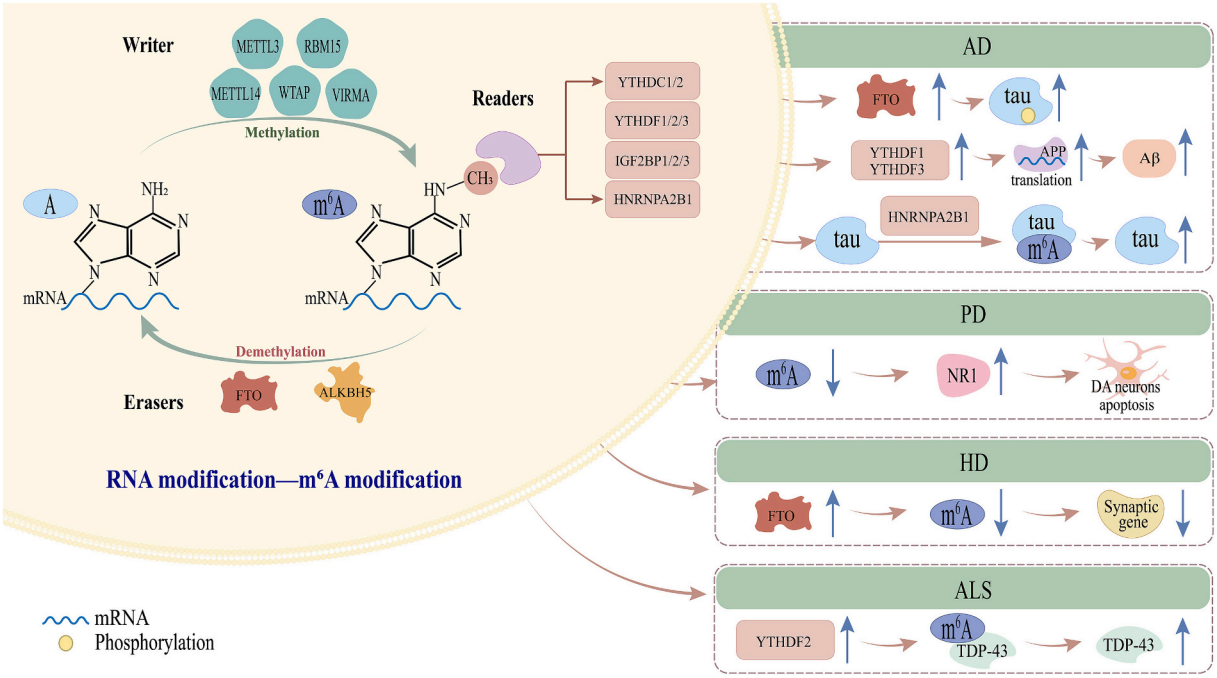

Fig. 4. The regulatory effects of RNA modification-m^6A modification on neurodegenerative diseases. mRNA modifications play an important role in mRNA synthesis, processing, and translation. N6-methyladenosine (m^6A) is the most abundant chemical modification in mRNA. m^6A modifications are dynamically and reversibly regulated by m^6A methyltransferases (METTL3/14, WTAP, RBM15, and VIRMA, termed "Writers"), demethylases (FTO and ALKBH5, termed "Erasers"), and m^6A binding proteins (YTHC1/2, YTHDF1/2/3, IGF2BP1/2/3, and HNRNPA2B1, termed "Readers"). In the pathogenesis of Alzheimer's disease, the up-regulation of FTO expression promotes tau protein phosphorylation. The increase in the YTHDF1 and YTHDF3 levels increases the transcriptional activity of APP-related mRNA, which leads to the deposition of the Aβ protein. The tau protein forms an m^6A RNA complex of tau proteins mediated by HNRNPA2B1, which eventually leads to tau protein aggregation. In the pathogenesis of Parkinson's disease, the down-regulation of the m^6A modification level leads to increased NR1 receptor expression, causing dopamine neuron apoptosis. In the pathogenesis of Huntington's disease, the up-regulation of FTO expression leads to the down-regulation of m^6A modification levels, which ultimately leads to decreased expression of synaptic-related genes. In the pathogenesis of amyotrophic lateral sclerosis, the up-regulation of YTHDF2 expression facilitates TDP43 substrates carry m6A modifications, thus promotes facilitates TDP43-related toxicity. FTO, fat and obesity-associated gene; tau, tubulin-associated unit; YTHDF1/2/3, YTH N6-methyladenosine RNA binding protein 1/2/3; APP, amyloid precursor protein; Aβ, amyloid beta; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2B1; NR1, *N*-methyl-D-aspartate receptor subunit 1; TDP-43, TAR-DNA/RNA binding protein.

were increased in the brains of 5XFAD mice, as compared with the control group. This suggests that the dysregulation of m^{6}A modification plays a role in AD. Han et al. [100] found increased METTL3 expression and decreased FTO levels in the brains of AD mice compared with the control group, these inconsistent results about METTL3 expression may be due to the selection of different AD models or the stages of disease development. Huang et al. [101] also found abnormal expression of the methyltransferase METTL3 and the RNA binding motif protein 15B (RBM15B) in the hippocampus of AD patients. Studies have shown that METTL3 accumulation is positively correlated with the level of the tau protein, thus confirming that disruption of the m^{6}A pathway is closely related to neuronal dysfunction in AD. In addition, Reitz et al. [102] found that genetic variation in intron 1, 2, or 3 in the FTO gene was related to AD, and the expression of FTO in AD patients was significantly down-regulated.

A comprehensive analysis of m^{6}A-modified genes was conducted on 1647 sporadic PD patients and 1372 controls. The analysis of rare mutations based on gene load revealed 214 rare mutations in all m^{6}A modification-related genes, underscoring the genetic complexity of PD [103]. Chen et al. [104] found no significant changes in the m^{6}A methylation level in the whole brain, hippocampus, cortex, and midbrain of PD rats, but the m^{6}A methylation level in the striatum was significantly reduce. In addition, decreased m^{6}A methylation induced the expression of *N*-methyl-D-aspartate receptor 1 (NMDAR1), as well as oxidative stress and Ca^{2+} influx, thus leading to apoptosis of dopaminergic neurons [105]. Chen et al. [106] found that m^{6}A modification also plays an important role in the death of dopaminergic neurons. At present, the specific function and mechanism of m^{6}A modification in PD remain unclear. A comprehensive investigation of the interaction of m^{6}A modification and PD will increase our understanding of the pathological mechanism of PD and pave the way for new therapeutic approaches for PD.

TAR-DNA/RNA binding protein (TDP-43) is a key protein in nuclear RNA binding. Its aggregation can reduce the mRNA stability of encoded ribosomal proteins and oxidative phosphorylation enzymes [107]. McMillan et al. [108] found that the majority of TDP43 substrates carry m6A modifications and the m6A reader protein YTHDF2 facilitates TDP43-related toxicity in rodent and human neuron models of ALS, then confirmed a link between TDP43-dependentmisprocessing of m6A-modified RNA and ALS pathogenesis. Pupak et al. [109] found m^{6}A hypermethylation of synaptic-related genes, in the hippocampus of HD mice using methylated RNA immunoprecipitation sequencing (MeRIP-seq). The expression levels of the m^{6}A modification proteins FTO and METTL14 were significantly increased, and inhibition of FTO expression in hippocampal CA1 partially restored the memory impairment in HD mice. This suggests that RNA methylation is involved in cognitive dysfunction in HD, providing a new scientific basis for considering m^{6}A as a potential therapeutic target for HD. RNA modification plays a critical role in neurological diseases, and abnormality in RNA modification may trigger NDDs.

2.4. Non-coding RNA modification and neurodegenerative diseases

The characteristic events in neurodegenerative diseases (NDDs) included protein misfolding, aggregation, accumulation and so on. It has been reported that non-coding RNAs (ncRNAs) could influence the formation of protein aggregates by facilitating protein overexpression through the regulation of gene transcription and translation, inhibiting protein degradation *via* lysosomal and autophagic pathways, and targeting aberrant modifications and phase transitions of proteins [110]. Non-coding RNAs (ncRNAs) are a class of RNA which do not code proteins that are highly heterogeneous in sequence, structure, and biological function (Fig. 5). The role of ncRNAs in the nervous system has attracted increasing attention from neuroscientists. To date, studies

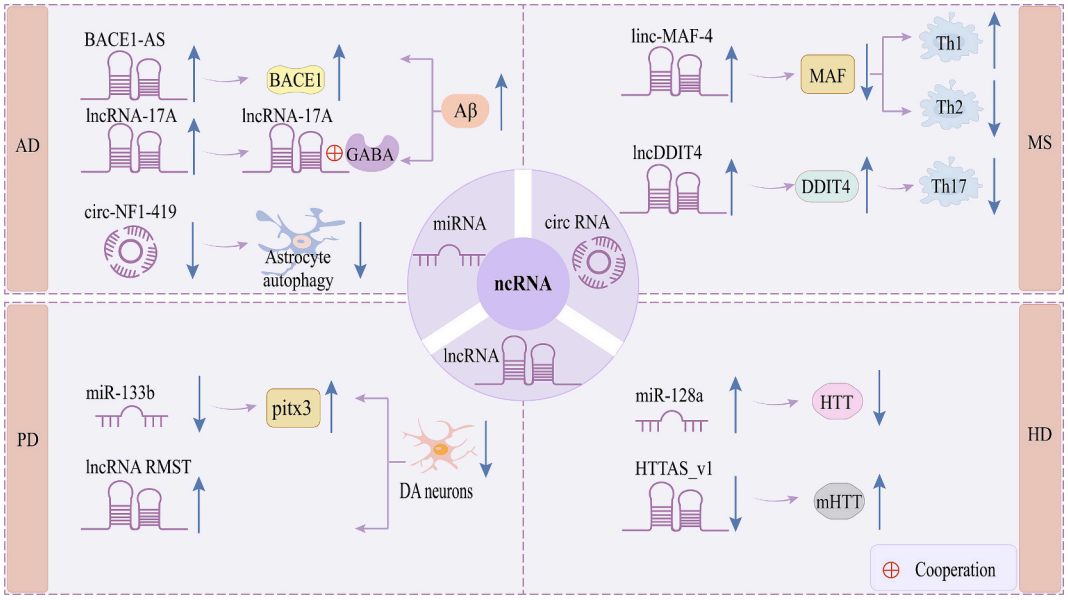

Fig. 5. The regulatory effects of non-coding RNAs on neurodegenerative diseases. ncRNAs include circular RNAs (circRNAs), microRNAs (miRNAs), and long non-coding RNAs (lncRNAs). In the pathogenesis of Alzheimer's disease, the up-regulation of BCAE1-AS levels promotes BACE1 expression, and the up-regulation of lncRNA-17 A expression promotes a synergistic interaction between lncRNA-17 A and GABA receptors. These processes ultimately lead to the deposition of Aβ protein. The down-regulation of circ-NF1–419 expression attenuates astrocyte autophagy. In the pathogenesis of Parkinson's disease, the down-regulation of miR-133b expression leads to an increase in the pitx3 level; up-regulation of the expression of the lncRNA RMST leads to a reduction in dopamine neuron function. In the pathogenesis of multiple sclerosis, the up-regulation of linc-MAF-4 (an intergenic lncRNA) expression leads to decreased MAF levels, which, in turn, leads to increased Th1-cell differentiation and inhibition of Th2-cell differentiation. The up-regulation of lncDDIT4 expression promotes the expression of DDIT4 and inhibits IL-17 transcription and Th17-cell differentiation. In the pathogenesis of Huntington's disease, the up-regulation of miR-128a expression leads to a decrease in Huntington's protein. The down-regulation of HTTAS_v1 levels promotes the formation of mutant Huntington's protein. BACE1, β-secretase 1; GABA, gamma-aminobutyric acid; pitx3, paired-like homeodomain transcription factor 3; RMST, rhabdomyosarcoma 2-associated transcript; MAF, MAF transcription factors; Th1/2/17, T-helper 1/2/17; DDIT4, DNA damage-induced transcript 4.

have mainly focused on circular RNAs (circRNAs), long non-coding RNAs (lncRNAs), and microRNAs (miRNAs). ncRNAs regulate many signaling pathways and affect the occurrence and development of various NDDs [114].

CircRNAs are covalent closed endogenous RNAs without 5′ end caps or 3′ poly(A) tails. They bind sequester-specific proteins to appropriate subcellular locations and are involved in the regulation of protein-protein and protein-RNA interactions [115]. Diling et al. [116] extracted primary astrocytes from AD mice and identified 7376 circRNAs through computational analysis techniques. The authors found that circNF1–419 regulated astrocyte autophagy and affected the PI3K-I/Akt-AMPK-mTOR pathway. Additionally, the overexpression of circNF1–419 enhanced autophagy activity, thereby affecting the expression of many proteins and factors associated with aging and AD, such as p21, p35/25, p16, TNF-α, NF-κB, Tau, p-Tau, Aβ1–42, and APOE. These findings suggest that circRNAs play a crucial role in the regulation of protein-protein and protein-RNA interactions in astrocytes, thereby affecting AD-related pathways and potentially halting disease progression. Further, Xu et al. [117] treated the SH-SY5Y and SK-N-SH cell lines with Aβ1–42 to simulate the pathological process of AD and found that silencing of the lncRNA SOX21 antisense RNA 1 (SOX21-AS1) alleviated the decline in cell activity and apoptosis caused by AD. This protective effect suggests that SOX21-AS1 may regulate neuronal survival under AD-related stress conditions. Further, SOX21-AS1 may serve as a biomarker and therapeutic target in AD.

LncRNAs are composed of non-coding RNA molecules with a length greater than 200 nucleotides. They can affect chromatin structure and gene expression by binding to chromatin [118]. β-amyloid precursor protein lyase 1 (BACE1), also known as β-secretase, is involved in the abnormal cleavage of APP into Aβ. Aβ is considered to be one of the main pathological markers of AD [119]. BACE1 antisense transcript (BACE1-AS) is a lncRNA that can competitively overlap with miRNA binding sites of target mRNA, thereby stabilizing the BACE1 mRNA level by inhibiting miRNA silencing on BACE1. This may lead to BACE1 overexpression, which triggers the overproduction and aggregation of Aβ, resulting in the dysregulation of synaptic function [120]. According to a recent study, reducing the expression of BACE1-AS, down-regulating the production of the BACE1 and Aβ proteins, and inhibiting tau protein phosphorylation in the hippocampus can improve the learning and memory abilities of AD mice. Therefore, BACE1 and BACE1-AS may be biomarkers and therapeutic targets for AD [121]. Kraus et al. [122] analyzed the expression profiles of lncRNAs in brain samples from 20 PD patients at different onset stages and 10 healthy controls. The results revealed that the expression levels of five lncRNAs (H19 upstream gene, lincRNA-p21, Malat1, SNHG1, and TncRNA) in the brains of PD patients were significantly higher than those of the control group. Interestingly, dysregulation of these lncRNAs is observed in the early stages of PD, usually before the clinical symptoms, suggesting that these lncRNAs may be early biomarkers of PD. Subsequently, Elkouris et al. [123] identified the strong associations between the lncRNAs (SNCA-AS1, AK127687, UCHL1AS1, PinK1-AS1, AX747125, and MAPT-AS1) and PD-related genes (SNCA, LRRK2, CUHL1, PINK1, DJ1, and MAPT), which may indicate that lncRNAs play a role in PD-related gene expression and function. Ma et al. [124] studied the mechanism of action of lncRNA-associated transcripts (RMST) in dopaminergic neuron injury in PD rats. The authors found that the expression level of RMST in the substania nigra of PD rats was upregulated. When RMST expression was inhibited, oxidative stress and dopaminergic neuron apoptosis were significantly reduced, and this reversed the cognitive impairment and dyskinesia in PD rats. This study highlights the therapeutic potential of targeting specific lncRNAs to alleviate PD symptoms through the modulation of neuronal pathways.

It has been confirmed that miRNAs can bind to the 3'-Untranslated regions (3 '-UTR) or 5'-Untranslated regions (5′ -UTR) of target mRNAs, affecting the translational process, which reduces the expression of proteins related to neurogenic differentiation [125]. Abnormal miRNA levels not only exist in the brain and spinal cord but can also be detected in cerebrospinal fluid, serum, plasma, peripheral blood mononuclear cells, and exosomes of neurodegenerative disease samples. Thus, they could serve as biomarkers for NDD diagnosis and prediction [126]. It has been reported that numerous miRNAs were dysregulated in PD patients, such as MiR-17 is a negative regulator of DNMT1, increased miR-17 is related to abnormal methylation patterns in PD [127]. MiR-29 family could target DNMT3a/3b directly and DNMT1 indirectly, it could be downregulate in PD, these results suggested that miRNAs may be used as biomarkers of cognitive impairment in PD patients [128]. MiR-128 was found to not only exert neuroprotective effect on dopaminergic neurons by downregulating AXIN1 and thereby upregulating excitatory amino-acid transporter (EAAT) 4, but also directly target 3'UTR of EZH2 and suppresses its expression in PD disease [128].

3. Considerations for therapy

At present, remarkable progress has been made in the development of drugs based on epigenetic principles. Accordingly, several drugs have been developed to treat degenerative diseases of the CNS, such as AD, PD, and HD. DNMT and HDAC inhibitors have been approved for clinical studies of related diseases [129]. DNMT inhibitors are considered demethylation agents and have been studied in preclinical and clinical trials for more than 30 years. Among them, 5-azacytidine (AZA) and decitabine (DAC) are two of the most studied DNMT inhibitors. These are cytosine analogues. Animal experiments have shown that synaptic plasticity and learning and memory abilities are damaged after the injection of cytosine analogues into the brain [130,131].

Changes in HDAC activity are associated with a variety of NDDs and neural injuries [132]. Studies have shown that HDAC inhibitors can alter gene expression and are efficacious in experimental models and clinical trials of NDDs. Thus, they are highly promising therapeutic candidates [133]. For example, CKD-504 (an inhibitor of HDAC6), was found to not only significantly degrade pathological tau proteins in the brains of animal models of AD but also showed similar effects in brain-like organs derived from AD patients [134]. HDAC3 inhibitors can inhibit the phosphorylation and acetylation of tau proteins and reduce Aβ protein aggregation, thereby improving cognitive function in AD mice [135]. Another study found that the HDAC inhibitor sodium butyrate regulated the level of histone acetylation, improved α-Syn protein-induced neurotoxicity, and delayed disease progression in PD [136]. Hathorn et al. [137] found that another HDAC inhibitor niacinamide effectively delayed the appearance of motor symptoms in HD mice. These findings support the possible role of HDAC inhibitors in HD treatment.

4. Summary and future perspectives

Epigenetics regulating gene expression in different cell types plays a critical role in NDDs. Here we reviewed various epigenetic mechanisms and discussed in detail each epigenetic modification involved in the NDDs process. The changes of the epigenetic factors in the brain during the NDDs provides new insight in understanding how epigenetic based therapy is emerging as an potential approach to treat neuro-related diseases. In addition, most experimental data on NDDs are derived from cell and mouse models; living patient-based studies remain limited. Drug development and clinical trials targeting epigenetic targets are expected to yield effective new drugs with low toxicity and high biocompatibility for the treatment of NDDs. With an in-depth understanding of the molecular structure and regulatory mechanism of epigenetics, the epigenetic therapy of NDDs will have a broader research landscape.

CRediT authorship contribution statement

Jianbing Men: Writing – review & editing, Writing – original draft. **Xinyue Wang:** Writing – review & editing, Validation, Investigation.

Yunnuo Zhou: Writing – review & editing, Project administration, Investigation. **Yumeng Huang:** Validation, Resources, Investigation. **Yue Zheng:** Validation, Resources, Investigation. **Yingze Wang:** Writing – review & editing. **Shuang Yang:** Resources, Investigation, Data curation. **Nan Chen:** Investigation, Resources, Validation. **Nan Yan:** Writing – review & editing. **Xiaoxu Duan:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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