Epigenetics-Based Therapeutics for Neurodegenerative Disorders

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Abstract

Epigenetic regulation, such as DNA methylation and histone modification, is implicated in the aberrant changes in gene expression that occur during the progression of neurodegeneration. Many epigenetics-based drugs have been developed recently for the treatment of some neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's diseases. Here we review recent studies that highlight the role of epigenetic modifications in neurodegeneration, among them DNA methylation and demethylation and histone acetylation and deacetylation; we also explore the possibility of using epigenetics-based therapeutics to treat neurodegenerative disorders.

Keywords

Introduction

The term "epigenetics" encompasses all meiotically and mitotically heritable changes in gene expression that are not coded in the DNA sequence itself, and only alter phenotype without changing genotype [1]. Epigenetic modifications include DNA methylation, histone modifications, the action of small RNAs, and nucleosome positioning [2–4]. These modifications form a network of covalent alterations to DNA and histone proteins, which in turn interact with other cellular proteins, typically in multi-component mediator complexes, the end result being altered gene expression. The recognition of the role epigenetics plays in human disease began with oncology, but has now extended to other diseases, such as neurodevelopment and neurodegenerative disorders. Epigenetic interventions affect the compaction of chromatin and alter the binding of histones to promoter regions of their associated DNA surrounding the nucleosomal core, thereby influencing the accessibility of transcription factors and their ability to regulate gene expression.

There has been considerable progress in the development of epigenetic drugs for the treatment of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease,

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and Huntington's disease. Several drugs that target epigenetic alterations, including inhibitors of histone deacetylase (HDAC) and DNA methyltransferase (DNMT), are currently approved and available for clinical investigation in these disorders [5••]. In this review, we will discuss the role of epigenetic modifications in neurodegeneration, including DNA methylation and demethylation and histone acetylation and deacetylation; we also explore the possibility of using epigenetics-based therapeutics to treat neurodegenerative disorders.

Epigenetic Alterations in Neurodegeneration

DNA Methylation and Demethylation

DNA methylation, the most widely studied epigenetic mechanism, is catalyzed by a family of DNA methyltransferases (DNMTs) that transfer a methyl group from S-adenosylmethionine (SAM) to the fifth carbon of a cytosine residue to form 5mC. In mammals, there are five known members of the DNMT family: DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L (DNMT3-like), but only DNMT1, DNMT3a, and DNMT3b possess methyltransferase activity [4]. The catalytic members of the DNMT family are customarily classified into de novo DNMTs (DNMT3a and DNMT3b) and maintenance DNMTs (DNMT1). DNMT3a and DNMT3b can establish a new methylation pattern in unmodified DNA and are thus known as de novo DNMTs. These DNMTs are highly expressed in embryonic stem (ES) cells and downregulated in differentiated cells [6]. On the other hand, the maintenance DNMTs function during DNA replication to copy the DNA methylation pattern from the parental DNA strand onto the newly synthesized daughter strand [7•]. DNMT1 has a 30-fold to 40-fold preference for hemimethylated DNA, and also has de novo DNMT activity. DNMT1 is the most abundant DNMT in the cell and is transcribed mostly during the S-phase of the cell cycle. It is most often needed to methylate hemimethylated sites that are generated during semi-conservative DNA replication. In a cellular context, the affinity of DNMT1 for newly synthesized DNA is increased by its interaction with the DNA polymerase processing factor proliferating cell nuclear antigen (PCNA), ensuring localization to the replication fork [8]; the ubiquitin-like plant homeodomain and RING finger domain-containing protein 1 (UHRF1) could perform a similar function, tethering DNMT1 to hemimethylated DNA [9].

Most DNA methylation occurs on cytosines that precede a guanine nucleotide or CpG sites. It is essential for silencing retroviral elements, regulating tissue-specific gene expression, genomic imprinting, and X chromosome inactivation. Importantly, DNA methylation in different genomic regions may exert different influences on gene activities based on the underlying genetic sequence [7•]. The proteins that bind to and recognize 5-methylcytosines are the methyl-CpG binding domain (MBD) proteins: in mammals, these are MeCP2, MBD1, MBD2, MBD3, and MBD4. MeCP2 was the first of these proteins to be characterized [10]. Almost all MBD proteins are localized in highly methylated chromatin regions involved in silencing imprinted genes and in endoparasitic sequences [11], where they promote genomic stability and transcriptional repression.

DNA demethylation occurs via a series of chemical reactions that further modify 5mC. Several mechanisms of active DNA demethylation have been proposed. 5mC can be chemically modified at two sites, the amine group and the methyl group. Deamination of the amine to a carbonyl group by AID/APOBEC (activation-induced cytidine deaminase/ apolipoprotein B mRNA-editing enzyme complex) effectively converts 5mC into thymine, thus creating a G/T mismatch and inducing the base excision repair (BER) pathway to correct the base. Overexpression of AID/APOBEC promotes DNA demethylation in zebrafish [12], whereas knockdown or knockout inhibits the DNA demethylation of various genes necessary for cellular reprogramming and development [13, 14]. Another active DNA

demethylation mechanism could be mediated by the ten–eleven translocation (TET) enzymes TET1, TET2, and TET3. TET enzymes add a hydroxyl group onto the methyl group of 5mC to form 5hmC [15••, 16]. The mature brain contains significant 5hmC levels in multiple regions, ranging from 0.3 % to 0.7 %, which is approximately tenfold lower than the average abundance of 5mC [17]. Once 5hmC is formed, two separate mechanisms can convert 5hmC back into cytosine in mammals: iterative oxidation by TET enzymes continues to oxidize 5hmC first to 5-formyl-cytosine (5fC) and then to 5-carboxy-cytosine (5caC) [18]; alternatively, 5hmC is deaminated by AID/APOBEC to form 5-hydroxymethyl-uracil (5hmU) [19•]. 5fC, 5caC, and 5hmU could be further converted into unmodified cytosine.

Histone Modifications

Histone modifications are the other major epigenetic marks. DNA is packed in the nucleus of eukaryotic cells through its chromatin organization. The nucleosome, the fundamental unit of chromatin structure, consists of 146 base pairs of DNA wrapped around an octamer of histones made up of two copies of each of the core histones: H2A, H2B, H3, and H4 [20]. These proteins not only provide a solid structure, N-terminal regions of histones protrude from the nucleosome and are susceptible to interactions with other proteins. There are many types of post-translational modification of the residues at histone tails, including methylation of lysines and arginines, acetylation, phosphorylation, ubiquitination, SUMOylation, and ADP-ribosylation.

The post-translational modification of histones is often a dynamic and reversible process mediated by two antagonistic sets of enzymatic complexes that attach or remove the corresponding chemical groups in a site-specific manner. One of the most thoroughly studied modifications of histone tails is the acetylation at lysine residues, which is associated with transcriptional activation [20]. Histone acetyltransferases (HATs) carry out these modifications, which can be reverted by histone deacetylases (HDACs). HATs are evolutionarily conserved from yeast to humans, and are categorized into three main families, GNAT, MYST, and CBP/p300, according to the structure of the catalytic domains [20, 21]. Acetylated histones serve as epigenetic markers, which could recruit HATs and other bromodomain-containing proteins. Histone deacetylases (HDACs) remove acetyl groups from lysine/arginine residues in the amino-terminal tails of core histones and other proteins, thereby reversing the effects of the HATs [20, 21]. Mammalian HDACs fall into four main classes, classes 1–4, with class 1 and class 2 HDACs receiving the most attention in the nervous system [38]. Class 1 HDACs (HDACs 1, 2, 3, and 8) are homologs of the yeast HDAC RPD3, are constitutively nuclear proteins, and are widely expressed. Class 2 HDACs (HDACs 4, 5, 6, 7, 9, and 10) are homologs of yeast Hda1, are expressed in a tissue-specific and cell-specific manner, and are regulated, at least in part, by shuttling between the nucleus and cytoplasm, where they are stabilized by interactions with 14-3-3 proteins. Sequence specificity of HDAC action is acquired by recruitment of HDACs to specific genetic loci by repressors, co-repressors, and methyl-DNA binding proteins [38].

Other histone modifications also take place on lysines at their tails, which can be monomethylated, dimethylated, or trimethylated. The effect of each modification depends on both the identity of the modified residue and the extent of methylation. For example, methylation of histone H3 on lysines 4 and 36 (H3K4 and H3K36) is generally associated with an "open" euchromatin structure and transcriptional activation, whereas methylation of histone H3 on lysines 9 and 27 (H3K9 and H3K27) is generally associated with a "closed" heterochromatin structure and gene silencing [20, 22]. Methylation of histones is carried out by histone methyltransferases and demethylation by histone demethylases, such as the jumonji protein family [23].

Potential Targets for Epigenetic Therapeutic Interventions

DNA Methylation and DNMT Inhibitors

DNA methylation is a conserved epigenetic mechanism that is used to transduce environmental influences into enduring changes in neuronal function and circuitry [24] [25]. An effective epigenetic pharmacological strategy for selectively reducing the expression of genes may involve methylating cytosine bases in promoter regions of DNA by increasing endogenous levels of the methyl donor S-adenosylmethionine (SAM) that is used in DNA methylation reactions via exogenous administration of methionine, choline, folates, and vitamin B12 [25, 26]. The selectivity of the latter epigenetic therapeutic strategy depends on increasing DNA methylation, thereby interfering with the binding of transcription factors to promoter regions that contain a high guanine-cytosine content of islands of CpG-enriched dinucleotides. Increasing levels of SAM can also lead to binding of proteins that recognize methylated cytosine bases in enriched CpG islands in promoters and recruit enzymes with HDAC activity, leading to chromatin compaction as an alternative mechanism of gene repression [27].

DNMT inhibitors, also referred to as demethylating agents, have been under preclinical and clinical investigation for over 30 years. The most widely studied of these have been the nucleoside analogs 5-azacitidine (AZA) and decitabine (DAC). Because they are cytidine analogs, both agents are incorporated into DNA after activation to a triphosphate moiety. After formation of an irreversible complex with DNMT1, degradation of the enzyme occurs [28]. This prevents methylation of daughter DNA in CpG islands during DNA replication. In addition, AZA (but not DAC) is converted into a ribonucleoside moiety and is incorporated into RNA, interfering with protein translation. A Phase III randomized trial in patients with high-risk myelodysplastic syndrome (MDS) indicated a significant improvement in median overall survival with AZA versus conventional care regimens, including best supportive care or standard chemotherapy (24.5 months versus 15 months) [29]. Impressive disease responses were also seen with the use of DAC in a similar patient population [29].

Other DNMT inhibitors in an earlier phase of development include DAC analogs, such as SGI-110 and zebularine. When administered directly into the brain tissue of mice and rats, these and other DNMT inhibitors disrupt synaptic plasticity and hippocampal learning and memory, and they are powerful modulators of reward and addiction behaviors [30–33]; however, nucleoside analogs are thought to act primarily at sites of DNA synthesis and replication during the cell cycle, making them seem at first glance to be of little relevance to postmitotic neurons and glia. Notably, N-phthalyl-L-tryptophan (RG 108) and other drugs that interfere with sites at which DNMT is active independent of DNA replication still cause a robust impairment of hippocampal learning and memory [34, 35]. The potential of drugs that interfere with DNMT activity may go beyond these examples of synaptic and behavioral plasticity. In mice, for example, treatment with DNMT inhibitors can confer stroke protection after mild ischemia; furthermore, haploinsufficiency for Dnmt1 in mice is associated with smaller infarction volumes after acute ischemia and stroke [36, 37]. For neurological diseases, the few DNA methylation markers that have been identified so far require further validation in large-scale multicenter studies.

Histone Acetylation and HDAC Inhibitors

Histone acetylation is of great interest in the nervous system, due in part to our knowledge of the enzymatic machinery and signal transduction mechanisms that regulate this post-translational modification. Acetylation of core histones is catalyzed by transcriptional co-activators, such as CREB-binding protein (CBP), which possess histone acetyltransferase (HAT) activity [20, 21]. Histone acetylation remodels chromatin structure, thereby

modulating transcription. Specificity of gene regulation is achieved via the recruitment of HATs by transcription factors to specific genetic loci, where they locally modify histones. Importantly, HATs interact with a large number of transcription factors and thus serve as crucial hubs, integrating the activity of multiple signaling cascades. Deacetylation of histone proteins shifts the balance toward chromatin condensation and thereby silences gene expression. Unlike HATs, HDACs have a rich structural diversity, which confers diversity of function and makes HDACs promising targets for drug discovery and therapeutic intervention.

HDAC inhibitors can be classified into four main chemical families: the short-chain fatty acids (e.g. sodium butyrate, phenylbutyrate, and valproic acid); the hydroxamic acids (e.g. trichostatin A and suberoylanilide hydroxamic acid (SAHA)); the epoxyketones (e.g. trapoxin); and the benzamides. Of these, the most widely studied are sodium butyrate, phenylbutyrate, trichostatin A, and SAHA; the butyrates are known to cross the blood-brain barrier [38, 39]. In the nervous system, the anticonvulsant and mood-stabilizing drug valproic acid was identified as an inhibitor of HDAC1, thereby linking its antiepileptic effects to changes in histone acetylation. As described below, more recent work has revealed that inhibitors of class 1 and 2 HDACs represent novel therapeutic approaches to treat neurodegenerative disorders, depression and anxiety, and the cognitive deficits that go hand in hand with many neurodevelopmental disorders.

Deacetylation of histone tails leads to the condensation of chromatin and suppression of transcription, whereas acetylation weakens the binding of histone to DNA, facilitating the accessibility of transcription factors and their complexing with RNA polymerase II. The extent of histone acetylation is a dynamic process that is influenced by the antagonistic enzyme activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). The dynamic nature of acetylation of histone proteins is reflected in the short turnover time for acetyl groups in the core histones [40]. Histone acetylation also influences the interaction of nucleosomes with each other, and thus the structure of chromatin itself. In summary, histone acetylation destabilizes chromatin structure and promotes transcription, whereas deacetylation promotes chromatin condensation and the repression of gene expression. The acetyl groups are donated by acetyl coenzyme A in a reaction catalyzed by a family of HATs. Proteins from one of these families of HAT, referred to as ''PCAF,'' associate with the complex of p300 and cyclic adenosine monophosphate (cAMP) response element binding (CREB) protein binding protein (CBP); the latter complex is an important global transcriptional co-activator in essentially every cell type and is referred to as p300/CBP [40]. In addition to acetylation of histones, another mechanism of transcriptional regulation by PCAF relates to its ability to acetylate nonhistone transcription-related factors. Interestingly, p300/CBP, which stimulates transcription via its interactions with promoter-binding transcription factors, can itself acetylate the amino terminal tails of all the core histone proteins and nonhistone transcription-related proteins [40].

Implications for Treatment in Neurodegenerative Disorders

Alzheimer's Disease

Alzheimer's disease (AD) is a slow, progressive dementia that primarily affects the cortex and hippocampus. AD is characterized by the deposit of abnormal filaments of hyperphosphorylated Tau protein in neuronal cytoplasm, known as neurofibrillary tangles, accompanied by extracellular aggregates of large amyloid β protein (Aβ), known as senile plaques [30]. Decreased amounts of methylcytosine within the APP promoter in the DNA from the parietal cortex of individuals without dementia are associated with increasing age [32]. It was also found that the components of the methylation co-repressor complex were markedly decreased in AD brains [31•]. Elevated levels of homocysteine are seen in patients

with AD and are associated with deficiency of folate and vitamin B12 [33], which are essential cofactors required to regenerate methionine (the precursor of the methyl donor for DNA methylation) from homocysteine.

Since increased histone acetylation is found in the brains of patients with AD, the use of histone acetyltransferase (HAT) inhibitors may hold some potential for treatment of AD [34]. The use of biomarkers to define an individual's epigenome may allow drugs to be tailored to specific epigenomes, so that epigenetic switches could be turned back pharmacologically. So far, the use of HDAC inhibitors in humans has not been successful. A recent clinical trial revealed significant worsening of agitation and aggression in AD patients receiving VPA versus placebo [35]. Moreover, the effectiveness of VPA in treating behavioral symptoms in elderly dementia patients with agitation and aggressive behaviors has also been limited; low doses of VPA fail to reduce agitation in all patients, and high doses in some patients lead to unacceptable adverse effects [36, 37]. While HDAC inhibition may have limited benefits in AD patients and dementia, alternative methods of manipulating the general DNA hypomethylation seen in AD may hold greater therapeutic promise.

Parkinson's Disease

Parkinson's disease (PD) is a progressive neurological disorder characterized by a number of motor and non-motor symptoms [42]. Pathologically, PD is characterized by the loss of dopaminergic neurons in the substantia nigra (SN) pars compacta, and patients frequently have Lewy bodies, eosinophilic intracellular inclusions composed of amyloid-like fibers and α-synuclein (SNCA) [28]. Misfolded -synuclein bound to ubiquitin forms a complex that cannot be transferred to the proteasome and aggregates in cytoplasmic inclusions, or Lewy bodies. These inclusions may be a cause of the midbrain dopaminergic neuron loss in the SN [43].

Recently, DNA methylation of human SNCA intron 1 and demethylation of the SNCA CpG in the brains of PD patients was found to regulate SNCA gene expression [44•, 45]. Alternatively, or in addition, nuclear -synuclein decreases histone H3 acetylation through direct interaction with histones [29]. In vitro cell culture and *Drosophila* studies have shown that familial PD mutations in -synuclein (A30P and A53T) cause increased nuclear targeting of -synuclein in cultured cells. -synuclein is found to bind to histones and HATs and inhibits acetylation in HAT assays [29].

Consistent with these findings, the administration of class I HDAC inhibitors, such as SAHA (Vorinostat) and sodium butyrate, ameliorate -synuclein-induced neurotoxicity; these inhibitors have neuroprotective properties in neurotoxin models of PD-related neurodegeneration [29, 46, 47]. In terms of target genes that are potentially affected by epigenetic dysregulation in PD, brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, is known to play a key role in the growth, survival, synaptic plasticity, and maintenance of neurons. BDNF expression is regulated by histone acetylation as well as DNA methylation [38]. In the substantia nigra pars compacta of PD-affected neurons, the amount of BDNF mRNA expression is decreased. The pathogenic -synuclein mutations A30P and A53T are suspected of being linked to the loss of BDNF [39, 40], whereas HDAC inhibitors may rescue BDNF expression by increasing BDNF expression. Recently, inhibition of the SIRT2 NAD-dependent lysine deacetylase was shown to protect against -synuclein-mediated toxicity in vitro in cellular models and in a *Drosophila* model of PD [41]; however, the mechanism by which inhibition of SIRT2 confers neuroprotection remains poorly understood, although most recent studies suggest it is through a non-nuclear/histone-mediated effect involving regulation of sterol biosynthesis [48••].

Huntington's Disease

Huntington's disease (HD) is a late-onset, autosomal dominant neurodegenerative disorder that presents with prominent motor, cognitive, and psychiatric symptomatology. The disease is associated with expansion of polyglutamine (polyQ) repeats in the amino-terminal portion of huntingtin, a predominantly cytosolic protein of more than 38 repeats; polyglutamine repeats under 35 are not linked to manifest disease [48••]. There is mounting evidence to suggest that transcriptional dysregulation appears to play a significant role in the pathophysiology of HD [24, 25], and may correlate with epigenetic dysregulation.

The therapeutic potential of drugs could be used to manipulate the epigenetic dysregulation seen in HD models and patients. A transgenic *Drosophila* model exhibited marked histone hypoacetylation corresponding with the transcriptional repression resulting from CBP inactivation. Furthermore, HDAC inhibitors prevented polyQ-induced toxicity and neurodegeneration in a *Drosophila* model of HD [26, 27], pointing to a novel target for HD therapy. HD transgenic models expressing exon 1 of the human huntingtin gene generally exhibit decreased histone acetylation, which correlates with patterns of reduced gene expression. For example, the HDAC inhibitor phenyl butyrate could increase histone H3 and H4 acetylation and improved the survival rate of HD mice in a dose-dependent manner [49]. Sodium butyrate treatment induced hyperacetylation and reduced neural and brain atrophy and improved motor performance [50]. These studies reveal great therapeutic promise for HDAC inhibitors in the treatment of HD. Conversely, the relation between histone modifications and gene expression is complex. Treatment with HDAC inhibitors in transgenic HD mice induced histone hyperacetylation, but decreased the expression of specific genes associated with cell death [51]. One explanation for the paradoxical changes in gene expression induced by butyrate may be due to the upregulation of a repressor, which in turn reduces the expression of the genes it regulates.

In human HD brain studies, Anderson et al. [52] uncovered interesting evidence for the potential role of histone hyperacetylation, in contrast to the hypoacetylation observed in transgenic *Drosophila* and rodent models. They saw significant increases in HAT 1 and in histone H3 family 3B mRNA expression in HD brain striatum and cortex, respectively. They also showed gene repression in specific gene clusters, such as Chr1p34, Chr17q21, and ChrXp11.2, all of which encode HDAC genes (HDAC 1, 5, and 6, respectively). The results point to possible species differences among transgenic *Drosophila* models, rodent models, and the human disease state.

Although the various results can be complicated and at times contradictory, there is ample evidence that alterations in epigenetic pathways are involved in the etiology of HD. Most studies, which use either cell lines or transgenic animals expressing polyQ, have found evidence of reduced histone acetylation. HDAC inhibitors generally provide positive outcomes in these models, although thus far their effects in humans with HD have been much less impressive. Some human studies hint at increased histone acetylation; however, this runs counter to the work using cell lines and transgenic animals. It will be vital in future studies to investigate and compare specific histone modifications in the model systems and the human condition to determine which, if any, of the models are valid.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) presents as a familial and sporadic neurodegenerative disorder characterized by progressive muscle wasting that leads to paralysis due to loss of upper and lower motor neurons. About 10 % of patients report a family history, and mutations in SOD1 (which encodes superoxide dismutase-1) are the cause in about 20 % of these cases.

Transgenic rodent models of ALS expressing mutant SOD1 have been created to unravel pathogenic mechanisms and screen and identify potential therapeutic interventions [53]. The transgenic ALS mice show hypoacetylation of H-4 and other histones in spinal cord sections, and treatment of transgenic ALS mice with sodium phenylbutyrate, an HDAC inhibitor, extended their survival and improved body weight and motor performance. Moreover, neuropathologic examination of the lumbar spinal cord showed less gross atrophy and ventral neuron loss, less reactive gliosis, and reduced immunoreactive staining of ubiquitin-positive aggregates in the cytosol.

Two genes have recently been linked to familial forms of ALS: TARDBP (also known as TDP-43; which encodes TAR DNA-binding protein) [54] and FUS (RNA-binding protein fusion) [55], which comprise 3 % and 4 % of familial cases, respectively, and are generally involved in regulating many aspects of RNA metabolism [56]. Sporadic amyotrophic lateral sclerosis, on the other hand, has been linked to another gene, elongator protein 3 (ELP3), which is important for paternal DNA demethylation [57••]. Knockdown of ELP3 impairs paternal DNA demethylation as indicated by reporter binding, immunostaining, and bisulfite sequencing. The demethylation process may be mediated through a reaction that requires an intact radical SAM domain. ELP3 encodes the catalytic subunit of the HAT complex [58] and can regulate the expression of Hsp70 via the modification of histone H3K14 and H4K8 acetylation [59]. Overexpression of Hsp70 helps to clear the aggregates that arise in a SOD1 mouse model [60] and also protects against mutant SOD1-induced death in mammalian neuronal cells [61]. As with most neurodegenerative diseases, amyotrophic lateral sclerosis also features cytoplasmic deposits of misfolded proteins, consisting of SOD1, TARDBP, or FUS aggregates. The best-known pathogenic mechanism in ALS is the toxic action of SOD1, which lies in its tendency to produce aggregates [62]. FUS is able to bind CBP and strongly inhibit its HAT activity [63], and overexpression of FUS induces hypoacetylation of histones H3K9 and H3K14 on the CCND1 promoter.

Conclusion

Epigenetic changes play important roles in the pathogenesis of neurodegenerative disorders, with many experimental studies showing the involvement of epigenetic modulations in these diseases. Research has revealed DNA methylation and histone modification profiles in some of the more common neurodegenerative disorders, and there is rapidly mounting evidence linking epigenetic alterations to their development. Some of the DNA methylations and histone modifications seen might prove useful as early disease biomarkers, while they might also be targeted with epigenetic drugs, such as DNMT inhibitors and HDAC inhibitors, or with new preclinical drugs that target histone demethylases, histone methyltransferases, and sirtuins. Understanding the contribution of epigenetic changes to common neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases, will give us better molecular tools to improve prognosis, diagnosis, and therapeutic intervention for these disorders.

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