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REVIEW

Epigenetics of Alzheimer's Disease and Frontotemporal Dementia

Chendhore S. Veerappan · Sama Sleiman · Giovanni Coppola

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Abstract This article will review the recent advances in the understanding of the role of epigenetic modifications and the promise of future epigenetic therapy in neurodegenerative dementias, including Alzheimer's disease and frontotemporal dementia.

Keywords Neurodegeneration · Epigenetics · Alzheimer's disease · Frontotemporal dementia · Epigenetic drugs · Therapy

Background

Alzheimer's disease and frontotemporal dementia

Alzheimer's disease (AD) and frontotemporal dementia (FTD) are two of the most common neurodegenerative disorders and are the leading causes of neurodegenerative dementia [1–3]. Current therapeutics designed to treat AD have not been successful in effectively treating the progressive nature of cognitive decline observed in patients. Cholinesterase inhibitors donepezil, rivastigmine and galantamine, huperzine-A, and *N*-methyl-D-aspartate antagonist memantine are approved drugs available for AD; however, these drugs fail to treat the underlying cause of neurodegeneration and only provide modest short-term symptomatic relief [4]. Clinical trials to test drugs designed to reduce levels of abnormal protein accumulation and other pathophysiological mechanisms of AD have failed. Food and Drug Administration (FDA)-approved drugs designed to treat the causes of FTD are currently unavailable [5]. One of the underlying reasons for the failure of treatment measures is the lack of knowledge pertaining to the epigenetic, environmental, and mechanistic drivers of neurodegeneration.

Many studies have focused on determining the genetic contributions to AD and FTD. AD pathology is typically characterized by the presence of intracellular neurofibrillary tangles, including phosphorylated microtubule associated protein tau (MAPT) and extracellular plaques, including aggregated amyloid beta (Aβ) [6–8]. In familial forms of AD, autosomal dominant mutations in *APP*, *PSEN1*, and *PSEN2* (all genes involved in the production of Aβ [9, 10]) are mainly responsible for the early onset (younger than 65 years) form of the disease. Recently, *TREM2* was designated as another rare monogenetic candidate for early onset of disease risk [11]. However, these mutations represent a very small percentage of cases, and 90–95 % of cases are nonfamilial and late onset (>65 years old) [12]. Multiple studies conducted to determine disease-causative loci have revealed that AD is highly complex and heterogeneous in nature; susceptibility loci vary according to gene penetrance, ethnicity, geography, environment, and sample size of various studies; therefore, identifying genes responsible for late onset of disease is highly challenging [13–15]. Linkage and genome-wide association studies have mapped regions in chromosomes 9, 10, and 12 that are associated with AD risk; several genes, such as *APOE*, *BACE1*, and *BACE2*, for example, are thought to be prime candidates to confer risk because of their role in pathways associated with Aβ biosynthesis and deposition [16]. However, approximately 300 genes have been implicated without strong causative evidence to increase risk for AD [14]. Therefore, nongenetic factors, such as epigenetic modifications, may also be causative and are currently the subject of intense research.

C. S. Veerappan (✉) · G. Coppola
Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA
e-mail: cveerappan@ucla.edu

S. Sleiman
Burke Research Center, Weill Medical College of Cornell University, White Plains, NY, USA

G. Coppola
Program in Neurogenetics, Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

FTD is a leading cause of dementia after AD and is more common among those below the age of 65 years. FTD shares common susceptibility genes and potentially similar molecular pathways with other neurodegenerative disorders, such as amyotrophic lateral sclerosis, corticobasal degeneration, and progressive supranuclear palsy. Based on the clinical spectrum, FTD is divided into 3 syndromes: behavioral, semantic, and nonfluent variants [17]. Similar to AD, FTD patients present abnormal accumulation of proteins in the brain [18]. FTD is classified under an umbrella condition known as frontotemporal lobar degeneration (FTLD). Based on the pathology and type of protein inclusions involved, FTLD is classified into FTLD-Tau, FTLD-TDP43, and FTLD-FUS (reviewed in [5]). Several causal mutations have been identified in FTD. Mutations in *MAPT* and the growth factor progranulin (*GRN*) account for nearly 50 % of familial FTLD cases. Mutations in *C9ORF72* account for nearly 25 % of familial FTD [19]. Other rare mutations have been found in DNA and RNA binding proteins (e.g., TDP-43, FUS), charged multivesicular body protein 2B (CHMP2B) and vesicle-transport protein; these mutations account for less than 5 % of familial cases [18]. It must be noted that CHMP2B is also known as chromatin modifying protein 2B, which may suggest an epigenetic contribution to disease. However, current studies point to the abnormal protein trafficking and degradation functions associated with CHMP2B that may contribute to neurodegeneration in FTD [20, 21].

The majority of FTD cases are sporadic and the molecular causative factor in most patients is unknown. Like for AD, other nongenetic factors may also contribute to the pathogenicity of the disease. Large-scale genome-wide association studies have identified a number of risk-associated variants in AD and, to a lesser extent, in FTD (reviewed in [22, 23]). Also, interestingly, with respect to this review, functional screens for modifiers of *MAPT* have revealed several chromatin binding proteins and a histone variant [24], some of which may play a role in disease further raising the potentially critical role of epigenetics in AD and FTD.

Neuroepigenetics

Background and Motivation

Epigenetics is the study of changes in gene expression and/or chromatin structure and cell function, caused by mechanisms other than changes in the underlying DNA sequence [25]. This field is an important area of investigation because epigenetic modifications may explain differential regulation of AD and FTD risk genes and genomic regions, without changes to their DNA sequence and therefore undetected in genetic studies. These modifications can occur on DNA molecules (mainly on cytosine bases at citosine-guanine (CpG) sites) or on histone proteins, which make up the fundamental structure of chromatin [26, 27]. Modifications to histones include methylation, acetylation, phosphorylation, ubiquitination, sumoylation, etc., and more than 100 different modification residues have been characterized [28]. Recently, several additional new histone medications and histone amino acid target residues have been described in the brain, adding to the repertoire and complexity of histone modifications; often, histone and DNA modifications occur in a multitude of various combinations to control gene transcription and chromatin architecture resulting in a highly complex, context-dependent, and specific regulation of the genome [28–30]. DNA methylation and histone modifications together regulate chromatin structure, which, in turn, regulates gene expression by facilitating access to DNA regulatory elements. Recently, noncoding RNAs (ncRNAs), such as long noncoding RNAs (lncRNAs) and microRNAs (miRs), among other regulatory RNA molecules, have been shown to play an epigenetic role in the regulation of genes by various mechanisms, including recruiting DNA methyltransferases and chromatin modifiers to their targets, inhibiting translation of mRNA, and in the degradation or stability of mRNA by sequence complementarity with their targets [31]. Epigenetic modifications are therefore central facilitators of the nexus between genes and the environment. The specific roles of DNA methylation, histone modifications, and ncRNAs in AD and FTD will be discussed in later sections.

The role of epigenetic modifications has been studied in various fields of biology, especially in developmental and cancer biology; erroneous regulation of epigenetic modifications has been linked to many developmental deficiencies, including neurogenesis, and in the formation and progression of cancer [32, 33].

Unlike mutations and other genetic abnormalities, which are largely stable in the genome throughout life, epigenetic modifications are dynamic and potentially reversible with the use of drugs and therapeutic approaches [34]. Therefore, with the understanding of the epigenetic contribution to neurological diseases, new therapeutic approaches can be potentially designed to reverse aberrant epigenomes—an active area of research in oncology and other fields.

Until recently, epigenetic regulation of neuronal processes was not considered a critical area of study because dynamic changes in the "neuro-epigenome" were not expected to occur in postmitotic neuronal cells. However, several key observations have indicated epigenetic modifications and their regulation play a critical role in the development of the nervous system, as well as in aging and the decline of cognitive processes [35–37]. The dynamic nature of epigenetic marks lend themselves mechanistically to the regulation of neuronal processes during stimulation and maintenance of synaptic plasticity during learning and memory formation, which occur within relatively short time spans [38–40].

During development, neuronal genes expressed during neurogenesis are repressed in other lineages by epigenetic mechanisms. Neuronal genes contain a repressor element in their promoters, which are then recognized by proteins complexes containing histone deacetylases (HDACs) [41]; deacetylation of histones in the promoter region subsequently results in promoter DNA methylation leading to gene repression. Trimethylation of lysine 27 on histone H3, H3K27me3, and other epigenetic modifications plays an important role in neuronal development during embryogenesis by orchestrating repression and/or expression of genes required for the neuronal lineage and subsequent differentiation [42]. Several studies have shown that epigenetic modifications are dynamic in postnatal brains and throughout the aging process [43, 44]. 5-methylcytosine (5-mc) and 5-hydroxymethylcytosine (5-hmc) levels in the brain increase with age at promoters associated with neurodegenerative diseases [45]. Several post-translational modifications of histones, mainly histone methylation and acetylation, drift with age and are associated with age-related decline in cognitive and memory related process [46, 47].

The roles of epigenetic readers, writers, and erasers in neurological disease are also becoming clearer: mutations in DNA methylation writers and their regulators result in a number of neurological disorders, including Rett syndrome and autism (*MECP2*) [48, 49], hereditary sensory and autonomic neuropathy 1 with adult-onset dementia [*DNA methyltransferase 1* (*DNMT1*)] [50], and immunodeficiency, centromeric instability, and facial anomaly (ICF1/2; *DNMT2B* and *ZBTB24*) [51, 52]. Similarly, mutations in histone-modifying enzymes have been implicated in neurological disorders. Mutations in epigenetic writers (e.g., histone lysine methyltransferases *MLL1*, *KMT1C* and *KMT6A*) have been associated with loss of memory and learning, schizophrenia, and cognitive and neurodevelopmental defects [53–55]. Similarly, mutations in epigenetic erasers (e.g., lysine demethylases *KDM5C*, *JARID1C*, *SMCX*, and *JMJD3*) result in disorders such as mental retardation, autism, and abnormal neurogenesis [56–58]. Addiction and other external environmental agents also cause chromatin modification differences in the brain [47]. Along with the aforementioned defects in epigenetic readers and writers, histone acetylation regulation [catalyzed by histone acetyltransferases (HATs)] and its interaction with other epigenetic marks are critical components in the maintenance of neuronal plasticity and memory [59]. Histone acetylation regulation is an important avenue for epigenetic therapy because of its fundamental role in cognition and memory, and the promise of HDAC inhibitors (HDACi) as general neuroprotective agents.

More recently, ncRNAs have been associated with neuronal development, differentiation, and disease [60]. miR–processing proteins, like Dicer, and several miR transcripts play an important role in the differentiation of neuronal stem cells by targeting transcription factors and other proteins responsible for programmed differentiation and maintaining cellular identity. lncRNAs also play a vital role in neurogenesis [61]. One study found more than 1300 lncRNAs associated with brain development and region-specific expression, many of which are associated with recruitment of chromatin remodeling complexes [62]. The interaction of ncRNA with epigenetic remodelers is another potential avenue for therapeutic intervention for neurological disorders. In the context of memory maintenance and synaptic plasticity, ncRNA molecules and their processing and regulatory mechanisms are important in maintaining homeostasis of cognitive processes [63]. Importantly, defective ncRNA pathways may lead to neurodegenerative diseases, psychiatric disorders, and brain cancer. The regulation of *brain-derived neurotrophic factor* (*BDNF*) by *BDNF-antisense* (*BDNF-AS*) transcript, lncRNA *SCAANT1* transcribed from the mutated expansion locus in spinocerebellar ataxia 7, *FMR1* locus associated lncRNA in fragile X syndrome, and dendritic plasticity factor *DPP1* regulating ncRNA are some select examples of ncRNA-mediated regulation of neurological function and disease; detailed reviews on the role of ncRNAs in neurological function and disease have been published recently [64–66].

Overall, epigenetic modifications play a major role in both neurogenesis and maintaining long-term activity and the homeostasis of cognitive processes in the adult brain, and may result in neurological disease when dysregulated. Epigenetic therapy holds great promise in that several small molecules and environmental modulation have been shown to successfully reverse several epigenetic marks and disease symptoms in both laboratory and clinical settings. Several epigenetic drugs (DNMT and HDAC inhibitors [DNMTi, HDACi]) have been approved by the FDA for use in cancer and others are currently in clinical trials [67, 68]. However, given the central role epigenetic modifications play in neuronal cells, the potential use of these approved drugs and future drugs to treat neurodegenerative disorders is very promising.

Mechanistically, epigenetic therapeutics must address the complex and intricate cross-talk between various epigenetic modifications, while minimizing the risk of altering other biological processes and pathways. In the next section, we will address potential targets of therapy specific to AD and FTD, and the promise of epigenetic medicine in treating faulty epigenetic processes that lead to neurodegeneration.

Avenues of Epigenetic Therapy in AD and FTD

DNA Methylation-based Therapy

Several groups have investigated the role of DNA methylation at specific AD risk loci and also the genome-wide DNA methylation profile differences between AD patients and controls. Owing to the relative lack of postmortem human tissues, many studies have used cell lines, patient samples, and animal

models to determine changes in DNA methylation. Environmental and extra-cellular factors, and the deregulation of epigenetic readers, writers, and readers are primary causes of aberrant DNA methylation patters in the genome. Several epigenetic therapeutic strategies have been proposed based on the DNA methylation profile changes that typically occur at risk loci.

Genes associated with Mendelian forms of dementia, such as *APP*, *PSEN1*, and *MAPT*, showed no clear differences in DNA methylation between AD patients and controls in multiple studies [44, 69, 70], and high-throughput studies have failed to detect large differences in methylation profiles between cases and controls [71]. However, small differences in DNA methylation along with age-related epigenetic drift may play a role in AD risk over time. A study conducted to determine the DNA methylation state of repetitive elements in AD patients compared with healthy controls found elevated LINE-1 element DNA methylation, 83.9 % *vs* 83.1 % respectively ($p=0.05$) [72].

In cerebral endothelial cells, under high Aβ conditions, the promoter region of discoidin domain receptor 1 (DDR1) is hypermethylated. *DDR1* is involved in the degradation of Aβ [73]. Age-related decreases in *DDR1* expression, explained partly by promoter DNA methylation increases, may play a contributing role in the pathogenicity of AD by reduced degradation of Aβ [74]. Lung cancer associated gene *S100A2*, related to the neurotrophic factor *S100B*, showed increased DNA methylation in AD cases compared with normal patients. In the same study, cell adhesion protein *SORBS3* showed hypermethylation in AD [44].

In FTD, data for global epigenetic differences between patients and controls from large sample sizes are currently unavailable. However, several studies have focused on individual risk genes to determine disease-related DNA methylation differences. No significant differences were detected in methylation levels of *MAPT*, *APP*, and *PSEN1* in postmortem brain from AD and FTLD-spectrum cases [69]; however, significant differences in *GRN* methylation levels were detected, with the *GRN* promoter hypermethylated in FTD *vs* controls (61.5 % *vs* 46.3 %) [75]. The G_4C_2 repeat expansion in the *C9ORF72* gene is a common cause of ALS and FTLD [19]. A recent study found a proximal region of the repeat expansion to be hypermethylated in patients compared with controls, and associated with the presence of the repeat expansion [76].

Overall, DNA methylation appears to play a role in differentiating AD and FTD samples from control at a few risk loci and LINE-1 repeat elements. Additionally, several experiments have further demonstrated that changing the environmental conditions that affect the DNA methylation pathways may induce dynamic epigenetic and expression changes at genes associated with AD and FTD risk.

In mammalian and cell line models, modulating the bioavailability of methionine synthesis factors resulted in the differential methylation and expression of the AD risk genes, *PSEN1* and *APP*. Reducing the uptake of vitamin B12 and folate caused hypomethylation of the *PSEN1* promoter and increased its expression along with reduced DNA *de novo* methylation; reducing the S-adenosylmethionine (SAM)/ S-adenosylhomocysteine (SAH) ratio also resulted in the hypomethylation of *PSEN1* and *APP* while inhibiting *DNMT1* activity [77–81]. Interestingly, the environmental toxin lead caused similar differential expression and hypomethylation at risk loci [82, 83]. In neuroblastoma cells, activation of mitogen-activated protein kinase pathways by cellular stress (by anisomycin) caused Aβ overproduction and *APP*, *PSEN1*, and *BACE1* hypomethylation accompanied by histone H3 hyperacetylation and lower expression of HDACs [84]. In human brains, hypermethylation of neurotrophic factors BDNF and cyclic adenosine monophosphate response element-binding protein, and hypomethylation of pro-inflammatory regulator nuclear factor kappa b were observed and provided evidence for the involvement of epigenetic modifications in maintaining synaptic plasticity [85]. Ten-eleven tanslocation (TET) proteins are responsible for converting 5-mc to 5-hmc and belong to a family of proteins that include oxidative stress-responsive genes [86]. It is possible that TET proteins might play a role in hypomethylation of AD risk genes during aging and cellular stress. Further evidence for the environmental influence for AD pathogenicity comes from monozygotic twin studies, where the AD twin showed reduced DNA methylation in the temporal neocortex compared with the non-AD twin [87]. Therefore, minor epigenetic drift caused by environmental toxins and cellular stress at genes such as *APP* and Aβ overproduction may induce hypomethylation at other AD risk loci and heighten the epigenetic disposition to AD in a positive feedback loop. Therefore, future DNA methylation targeted epigenetic therapy strategies must address the contributing factors that may cause age-related drifts in the DNA methylation profiles.

In AD, the hypomethylation of *APP*, *PSEN1*, and *MAPT* promoters could be reversed by modulating the bioavailability of methionine by increasing the levels of B12, folate, and other methionine sources in the diet. The increased level of methyl donor SAM (high SAM/SAH ratio) has been shown to decrease the levels of *PSEN1* expression, possibly by promoter hypermethylation, and reverse the hypomethylation-driven higher expression of *APP* [77–81]. More studies are required to determine the role of TET proteins and the conversion of 5-mc to 5-hmc during the hypomethylation of AD gene promoters. In the future, specific DNMT and TET inhibitors, along with controlled methionine nutritional uptake, could be used to modulate methylation of AD risk loci and in genes involved in maintaining neural plasticity, especially during episodes of cellular stress in the brain during injury or disease.

DNMT inhibitors (DNMTi) include azacitidine, decitabine, and zebularine. Azacitidine and decitabine have been FDA approved for use in leukemia [68]. These molecules are

analogs of cytosine and are incorporated during cell division and then function to sequester and inhibit DNMTs, therefore reducing levels of DNA methylation in rapidly dividing cancer cells. In FTD and AD, genes such as GRN, BDNF, cyclic adenosine monophosphate response element-binding protein, and C9ORF72, are hypermethylated and repressed, possibly contributing to the pathogenicity of the disease, and are potential targets for DNMTi-based therapies. A study in Friedreich ataxia, an autosomal recessive disease, used DNMTi to reverse the hypermethylation associated with a trinucleotide repeat expansion at the *FXN* locus; the study revealed a modest effect in mouse cells, but the treatment was ineffective in human Friedreich ataxia cells (reviewed in [88]). However, cell lines derived from fragile X patients showed beneficial effects of 5-azadeoxycytidine treatment [89]. Importantly, the same group also demonstrated that combined administration of DNMTi and other chromatin modifier inhibitors acted synergistically in the reactivation of the *FMR1* gene, which is hypermethylated in patients [90].

Histone Modification Targeted Therapy

Epigenetic therapeutics targeting histone methylation and acetylation is a promising strategy to treat loss of synaptic plasticity and neurodegeneration. Histone acetylation plays a dynamic role during synaptic stimulation and the maintenance of synaptic plasticity [59]. Histone methylation, as described in the previous sections, is associated with multiple neurological disorders. Histone acetylation and methylation are better candidates for targeted epigenetic therapy compared to DNMTi because multiple protein families and complexes target specific histone modifications to specific locations in the genome [28, 46, 91]. Similarly, multiple proteins are involved in the removal of certain marks from histones [27, 68, 92–94]. A recent study in pancreatic and liver cells demonstrated that histone methylation acts in a tissue- and gene-specific manner compared with histone acetylation. For example, G9a/GLP is a histone H3 lysine 9 tri-methyltransferase (repressive mark) and the inhibition of the complex by a small molecular inhibitor selectively upregulated cholesterol synthesis genes in pancreas, but not liver, cells [95]. In contrast, HDACi deregulated hundreds of genes irrespective of tissue type. More studies to investigate the role of specific chromatin modifiers and complexes in neurodegeneration may allow future drug designs to target specific proteins involved in inducing neurodegeneration. For example, a recent study identified deletions of *KANSL1*, regulator of histone H4 lysine 16 HAT *KAT8*, as responsible for the 17q21.31 microdeletion syndrome, characterized by mental retardation and delayed motor development [96]. Therefore, the identification of other specific epigenetic regulators involved in neurodegeneration will aid in the development of novel chromatin mark modifying compounds. Recently, it was shown that histone methylation plays a dynamic role in long-term memory formation. Mice lacking the histone H3 lysine 4 trimethyltransferase *MLL2* in the forebrain excitatory neurons had impaired memory function in the hippocampus [97].

HATs play an important role in the maintenance of synaptic plasticity and expression of neurotrophic factors. In mice, fear-based contextual learning results in large increases in the acetylation of histone H3; blocking the histone H3 acetylation pathway resulted in learning deficits; long-term potentiation by stimulation resulted in increases of histones H3 and H4 acetylation—in part by releasing HDAC2 from chromatin and the activation in the promoter regions of neurotrophic factors such as *BDNF* by the de-repression and release of *MECP2* (reviewed by [59, 92]). Loss of the HATs *P300* and *CBP* in mice models resulted in cognitive defects following fear conditioning and reduced histone acetylation was observed [38, 98].

HDACs fall into 4 main classes. Class I, II (a and b) and IV are zinc-dependent, and class III is nicotinamide adenine dinucleotide-dependent. In the memory-associated regions of the brain, class I HDACs (HDACs 1, 2, 3, and 8), especially HDAC2 and HDAC3, are more highly expressed than the other HDACs [99]. Consequently, HDAC2 and HDAC3 have been extensively studied for their role in memory formation and loss. Knockout of HDAC2/3 resulted in better spatial memory [100, 101]. Therefore, inhibiting the role of HDACs in memory and cognitive impairments is a potential avenue of epigenetic therapy. Several studies have been conducted to characterize the effects of HDACi in AD and FTD models, and have demonstrated improvements in long-term potentiation and memory. In the cognitive decline observed in AD mouse models, HDAC2 was expressed at higher levels in the hippocampus and prefrontal cortex, even in the earliest stages of disease, along with decreases in histone acetylation; downregulation of HDAC2 restored plasticity and memory formation, albeit during continued degeneration [102, 103]. HDAC2 was also found to be elevated during stress and injury in the brain, and resulted in the downregulation of genes involved in memory and cognition [104].

More recent work has probed the roles of class II HDACs. Class II HDACs are subdivided into class IIa, which includes HDAC4, HDAC5, HDAC7, and HDAC9, which are characterized by one catalytic site; class IIb proteins HDAC6 and HDAC10 are characterized by two catalytic sites [105]. HDAC6, a cytoplasmic protein that interacts with MAPT, was found to be elevated in AD patients [106]. Govindarajan et al. [107] observed that a reduction of HDAC6 levels in the APPPS1-21AD mouse model restored learning and memory, as well as acetyl tubulin levels. They also observed that HDAC6 reduction ameliorated mitochondrial trafficking in this AD model, although these data did not clearly demonstrate whether tubulin acetylation is actually a direct effect of HDAC6-mediated neurotoxicity. Nevertheless, these data warrant the need to investigate whether HDAC6 inhibitors,

such as tubastatin A, can ameliorate the deficiencies observed in AD mouse models. Kim et al. [108] probed the role of HDAC4 and HDAC5, and observed that selective loss of HDAC4, but not HDAC5, in the brain is detrimental to learning and memory.

Several HDACi have been characterized. HDACi such as carboxylic acids sodium butyrate, phenylbutyrate, and valproic acid target class I and IIa HDACs with the most efficacy; bacterial- and fungal-derived class 4 cyclic tetrapeptides selectively inhibit class I HDACs; hydroxamic acid trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA) (FDA-approved in cancer) and its derivatives generally target class I and II [109]. However, it must be noted that although SAHA (along with most other HDACs) is considered to be a pan-HDACi, it does not inhibit class IIa HDACs at pharmacologically acceptable concentration ranges [110]. As opposed to the aforementioned HDACi, which do not selectively target specific HDAC proteins, HDACi that are members of the benzamide group, MS-275 and CI-994, specifically target HDAC1 and, to a lesser extent, HDAC3 [92]. Studies characterizing the roles of HDAC inhibition in synaptic plasticity in neurodegenerative models first emerged from the laboratories of Tsai and colleagues. They demonstrated that both an enriched environment and HDACi induce histone tail acetylation, restore learning, and re-establish long-term memory in a mouse model of neurodegeneration dependent on the inducible neuronal expression of p25, a cell cycle molecule [111]. In more recent studies, the role of HDAC2 in plasticity and memory was probed. HDAC2 negatively regulates memory formation and synaptic plasticity [102]. Neuron-specific overexpression of HDAC2, but not HDAC1, lead to decreased neuronal plasticity and impaired memory formation. Conversely, HDAC2 knockout mice displayed enhanced memory formation and exhibited improvement in associative learning tasks [112]. Indeed, HDAC2 binds to promoters of memory-related genes, such as *BDNF* and *FOS*. SAHA administration improved associative learning and ameliorated the deficiencies observed in the HDAC2-overexpressing mice. In *in vitro* cellular models, mouse models of AD, as well as in AD patients, HDAC2 mediates an epigenetic blockade by binding and deacetylating the promoters of genes important for learning and memory. This blockade was reversed by HDAC2 knockdown [104]. The studies implicating HDAC2 in AD pathology and the observation that it is possible to reverse the effects mediated by HDAC2 through knockdown strategies advocate for the development of HDAC2 selective inhibitors. The need for HDAC2 selective inhibitors is critical, especially because the data may explain the toxicities associated with pan-HDAC inhibition by attributing the toxicity to the inhibition of some HDACs, such as HDAC1, which may promote survival of neurons. Indeed, the same group showed that p25-mediated neuronal death involves sequestration of HDAC1 and inhibition of its activity leads to double-stranded DNA breaks and aberrant cell cycle re-entry [113].The exact mechanism and specific targets regulated by HDAC1 remain undefined.

The use of HDACi in FTD is not as extensively studied as AD, however the data available to date suggest that they may be valuable therapeutic agents. In FTD, SAHA administration in *GRN* haplo-insufficient patient cell lines restored GRN expression to normal levels [114]. In this study, Cenik et al. [114] attempted to identify which isoform is relevant for the effectiveness of SAHA. They observed that class I HDAC inhibitors such as MS-275 could induce GRN levels; however, the high concentrations required for such an effect did not allow them to rule out cross reactivity with other HDACs. HDAC6 inhibitors, such as tubastatin A and tubacin, however, were not able to induce GRN levels. This suggests that it is possible that inhibition of more than one isoform may be required to restore GRN levels. A thorough molecular knockdown approach may reveal the responsible HDACs.

Together, HDACi could potentially be used as potent and selective inhibitors of HDACs involved in the progression of memory decline and regulation of genes involved in AD and FTD. These small molecules could also be used synergistically in combination with DNMTi to improve specificity and enhance the reversal of the decline in neurological functions. In fragile X, for example, the combination of DNMTi and HDACi synergistically enhanced the reactivation of *FMR1* [90].

Even though the majority of the focus on HDAC inhibition has been on changes in gene expression through histone acetylation, both the ability of multiple HDACs to shuttle between cellular compartments and the huge number of cytosolic, mitochondrial, and nuclear proteins targeted by acetylation suggest that acetylation of multiple proteins other than histones may be relevant for disease progression. For example, acetylation of *MAPT* inhibits the degradation of its phosphorylated form and contributes to tauopathies. Indeed, *MAPT* acetylation is elevated in patients at early and moderate stages of tauopathies [115].

The potential for HDAC inhibition as a therapeutic strategy for AD and FTD is promising. However, there is an urgent need for the development of isoform-selective inhibitors because the data available to date suggest an intricate interplay between the different HDAC isoforms with only a subset promoting toxicity. This alone may explain the toxicities observed with pan-HDAC inhibition. For therapeutics in the brain, the challenge of designing isoform-selective inhibitors is compounded by the need for compounds that will readily cross the blood–brain barrier (BBB). Moreover, it will also be important to develop methods to test the selectivity of the inhibitors other than determining the inhibition constant (Ki) in test tubes. This has been problematic because the concentrations needed to see any effect in cell culture or *in vivo* exceeds the measured Ki, complicating the interpretation of the roles of the relevant HDACs and raising the possibility of

off-target effects. The disconnect between the Ki measured in test tubes and the concentrations used *in vivo* may be explained by the cellular permeability of the compound, as well as the competition with other HDACs in a cell, whereas no such competition is available when the Ki is measured in the test tube. One way to facilitate the interpretation of the results obtained with HDAC inhibitors lies in possibly designing compounds that have similar structures, but cannot inhibit the specific HDACs targeted by the HDAC inhibitor.

ncRNA Therapy Strategies

miRs are complementary short (20–23) nucleotide fragments that are involved in the downregulation of the genes they target. miR processing proteins are indispensible for neurogenesis and have been implicated in AD and FTD pathogenesis [50, 116, 117]. Studies in human patients and cell lines have led to the identification of miRs that target genes involved in various pathways involved in neurodegeneration [118]. Conditional knockout of miR processing protein Dicer resulted in hyperphosphorylation of MAPT, a key pathophysiological feature of AD [119]. In AD models and patient studies, the expression of miRs in different tissues and fluids were found to be heterogeneous [120]. These miR expression pattern changes were observed in different tissues of the brain and suggested that the effects may be local and specific. Several miRs are associated with regions of the brain affected in AD. miRs also target kinase and acetylase pathways associated with AD [119, 121]. Several miRs are differentially regulated in different molecular pathways affecting AD pathogenesis. Reduced expression of miR targeting genes such as *APP*, *BACE1*, and *MAPT* were detected (miRs 29,15,107,101,106, etc.), and miR that regulate neurotrophic factors and immune system-related proteins were upregulated (miRs 125b, 146a, 206, 181, 146, let-7b, etc.); comprehensive reviews of particular miR differential expression in neurodegeneration have been published recently [118, 122, 123, 124].

Recently it was shown that addition of Aβ to neural cultures elicited differential expression of miR. In AD model mice, reduced expression of miRs 103 and 107, which target actin binding protein cofilin, resulted in the formation of rod-like actin structures, typically found in AD patients [125]. However, it is unclear if differentially regulated miRs drive AD pathogenesis or if they are a consequence of AD pathology. In one study, overexpression of miR-29a and miR-29b-1 resulted in the reduced expression of BACE1 and Aβ production [126]. miRs 107, 298, and 328 also target BACE1 and are downregulated in AD [126, 127]. Similarly multiple miRs interact with the Aβ precursor, APP [128, 129]. lncRNA and small interfering RNA are other important class of ncRNAs that may also be associated with AD. The overexpression of the pathological isoform of Aβ, Aβ-42, increased *BACE1* antisense transcript lncRNA was detected in AD and prevented miR-485-5p mediated repression of *BACE1* by masking the target sequence [130]. lncRNA also function in recruiting epigenetic factors to their targets. Therefore, altered lncRNA expression may play a role affecting the epigenetic landscape at different parts of the genome. *XIST* is a classic example of a lncRNA that promotes X chromosome inactivation by recruiting repressive chromatin marks [131].

In the context of neurodegeneration, further studies are required to determine differential expression of ncRNA in AD and FTD brains, and their role in altering epigenetic modifications. Together, pathways altering expression of ncRNAs may affect the regulation of AD and FTD risk genes and play a contributing role in the progression of disease. Inflammatory, apoptotic, and RNA sequestration pathways have been hypothesized to alter AD-associated ncRNA expression in addition to mRNA expression [122, 132–134]. Abnormal RNA sequestration may play a greater role in FTLD because two types of FTD protein inclusions (FTLD-TDP43 and FTLD-FUS) play a role in binding and dendritic transport of mRNA and ncRNA, as well as in post-transcriptional and translational regulation in the cell [122, 135]; increased cytoplasmic TDP-43 and FUS relocation due to stress or mutations and resulting inclusions in FTD pathology may therefore play a role in neurodegeneration, in part owing to erroneous processing of associated RNA transcripts. Identification of RNA transcripts associated with TDP-43 and FUS may serve as targets for exogenous RNA therapy. In addition, TDP-43 interacts with miR processing Dicer complex and regulates a subset of miR and is required for neuronal outgrowth [136].

ncRNAs play an important role in neurological functions and a subset of these transcripts are differentially regulated in AD and FTD. It is unclear if these transcripts drive disease or act downstream during neurodegeneration. However, ncRNA may provide useful information as biomarkers for early AD detection in peripheral tissues and blood. Diseased or degenerating neurons may shed extra membrane vesicles containing differentially-expressed RNA and DNA into the circulatory systems that maybe used as biomarkers. In therapeutics, RNA therapy using these vesicles as delivery systems may provide highly specific outcomes in affecting particular genes and pathways deregulated in AD and FTD [137]. For example, anti-ncRNA oligonucleotides could be administered to increase expression of genes downregulated in disease due to higher expression of the ncRNAs that target them. For example, *BDNF-AS* normally downregulates the neurotrophic factor *BDNF* by recruiting chromatin-modifying enzymes to its locus; recently, Modarresi et al. [138] restored expression of *BDNF* by targeting *BDNF-AS* using modified oligonucleotides called antagoNATs. Similarly, lncRNAs may increase expression of AD and FTD risk-associated proteins by masking transcripts normally targeted by miRs. Therefore,

anti-ncRNA could be used to decrease expression of risk genes. For example, antisense BACE1 antagoNATs could be designed to counteract ncRNA-mediated mRNA stability of the BACE1 transcript and target it for degradation.

Potential and Challenges of Epigenetic Therapy

In the previous section, we highlighted the 3 major epigenetic pathways that are erroneously regulated in AD and FTD, and possible avenues for intervention using epigenetic pharmacological agents (Fig. 1). One of the major challenges of biomedical neuroscience is the limitation of kind of molecules that can pass through the BBB. In general, molecules <500 daltons and with fewer than 8 pairs of hydrogen bonds can pass through the barrier. Other modes of delivery that bypass the BBB are BBB disruption and intracerebral implantation, and intracerebroventricular infusion convection enhances diffusion and transnasal delivery; however, the diffusion of drugs throughout the tissue remains poor [139]. DNMTi and HDACi molecules have been shown to cross the BBB and effectively alter epigenetic modifications in the brain [140–142]. However, the risk–benefit balance has to be considered in terms of efficacy, toxicity, delivery, and patient quality. DNMTi nucleoside analogs that insert in the genome are extensively used in the advanced treatment of cancer. However, owing to the cyto- and genotoxicity and low stability of DNMTi, these molecules may not be appropriate for continuous treatment for progressive degenerative diseases like AD and FTD. Therefore, to address adverse side effects several non-nucleoside allosteric inhibitors of DNMT are currently under preclinical development [143, 144]. HDACi are comparatively tolerated better in both human and mice models with milder side effects in the treatment of different diseases, despite their broad target range in the genome. The clinical side effects of HDACi have been well documented [92, 145]. However, the risk–benefit of long-term usage of HDACi for nonadvanced stages AD and FTD needs further

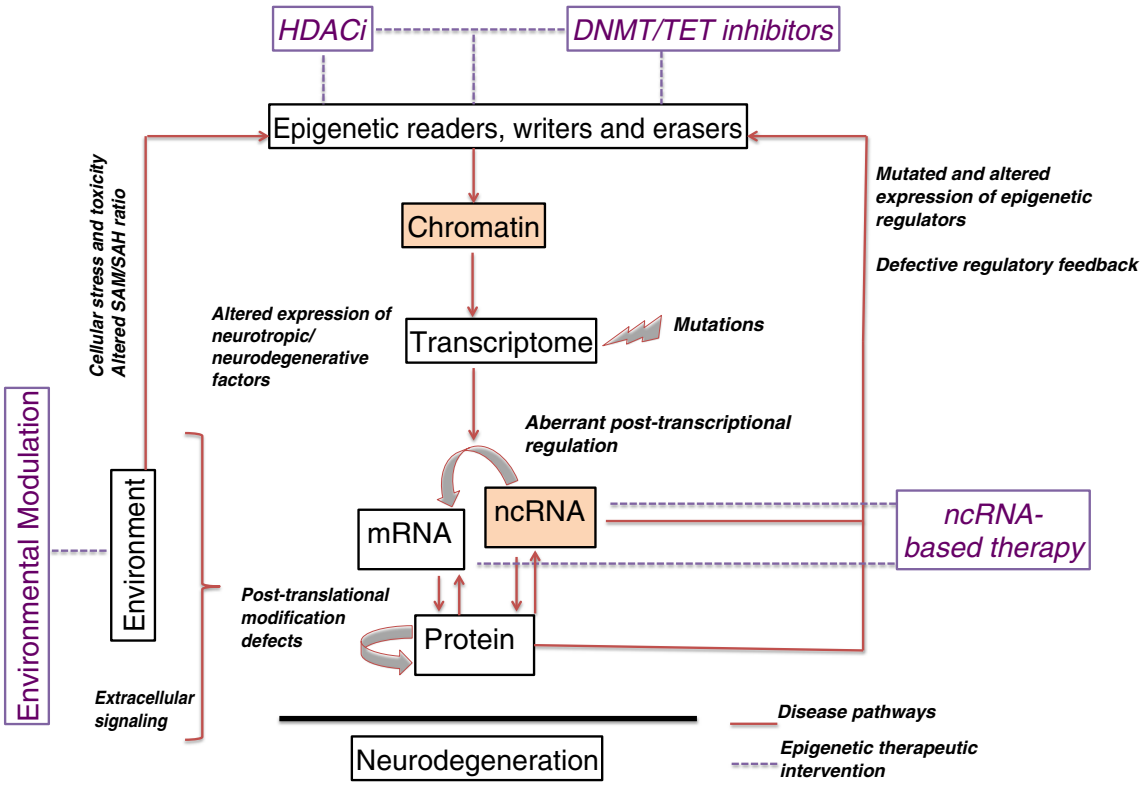

Fig. 1 The general overview of neurodegeneration and possible avenues for epigenetic therapy. Histone methylation/acetylation levels along with 5-methylcytosine and 5-hydroxymethylcystosine levels undergo age-related epigenetic drift and potentially deregulate genes associated with neurodegeneration. Mutations in epigenetic readers, writers and erasers have been implicated in multiple neurological disorders including cognitive decline. Cellular stress, toxicity and altered SAM levels are associated with altered promoter DNA methylation in risk-associated genes. Noncoding RNAs (ncRNAs) are associated with the regulation of neurodegeneration and neurotropic genes and were found to be differentially regulated in disease models. Together, an altered epigenetic landscape due to deregulation or mutations in epigenetic readers, writers and erasers is being portrayed in AD and FTD. Studies have shown several possible epigenetic therapy intervention avenues. Specific HDACi have been shown to be beneficial in restoring cognitive decline and memory formation in disease models due to important the role of histone acetylation in maintaining neuronal plasticity. DNMTi (and potentially TET inhibitors), may epigenetically restore expression of specific genes dysregulated in neurodegeneration. Similarly, the anti-mRNA and/or anti-lncRNA could be used to target deregulated ncRNAs that alter expression of epigenetic and neurodegenerative factors

investigation; for example, SAHA administration causes reactive oxygen species-induced genotoxicity [146]. Therefore, the use of SAHA may increase risk of cancer. However, a very recent study showed that the antioxidant Tempol prevents genotoxicity induced by SAHA and may, potentially, alleviate the long-term risks of the drug [147]. Hence, further detailed studies are required to develop safe and effective treatment protocols using DNMTi and HDACi.

Several carrier molecules capable of transporting small interfering RNA therapy and cross the BBB have been studied and developed [139, 148–150]. However, nanoparticle carriers designed to cross the BBB have raised several issues regarding systemic toxicity and neurotoxicity arising from the carriers molecules and the oligonucleotides themselves; further studies are required to reduce the immunogenicity and neurotoxicity of potential ncRNA treatment of brain-related disorders [151]. In addition, several chemically-modified anti-ncRNA and oligonucleotides have been developed to improve the therapeutic efficacy of ncRNA-based therapy [151]. Owing to the low uptake of therapeutic molecules through the BBB, several strategies to directly administer oligonucleotides directly to the brain have also been proposed and some are in advanced clinical validation and clinical trials [152]. Several promising studies to regulate levels of mutated BACE1 proteins and altering BDNF expression levels by direct injection of oligonucleotides in the brain have been reported.

Little is known about the off-target effects of epigenetic therapeutics for neurodegeneration. DNMTi and HDACi may target many genes and genomic regions and reverse epigenetic marks not associated with disease. ncRNA-based therapy is more specific compared with other approaches, but off-target effects must be assessed prior to development. Combination therapy may improve the mal-effects associated with target specificity and some combination strategies are currently undergoing clinical trials for cancer therapy [153]. More importantly, the role of epigenetic drift during aging and associated drivers of disease needs to be further explored by chronological studies. Early therapeutic interventions and biomarkers could be developed based on the specific epigenetic deviations detected early in disease. An often-neglected area of epigenetics and its role in disease is transgenerational inheritance. Several new studies have shown that some DNA methylation and histone modifications (up to 10 %), along with other small RNA molecules, escape re-programming during gametogenesis and fertilization, and can be passed both maternally or paternally to the next generation [154, 155]. Importantly, diet, stress and other environmental factors do play a role in transgenerational inheritance of neurological disorders in mainly mouse models [154]. Further studies are required to determine if AD or FTD risk factors are also transgenerationally inherited and increase risk of disease.

Unlike genetic changes that drive disease, a large number of epigenetic variations are readily reversible with the use of drugs. Recent studies have tied the role of epigenetic modifications directly to AD and FTD and opened up the possibility of applying epigenetic pharmacology to neurodegenerative diseases and other brain-related disorders.

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