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ALS and FTD: an epigenetic perspective

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Abstract

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are two fatal neurodegenerative diseases seen in comorbidity in up to 50% of cases. Despite tremendous efforts over the last two decades, no biomarkers or effective therapeutics have been identified to prevent, decelerate or stop neuronal death in patients. While the identification of multiple mutations in more than two dozen genes elucidated the involvement of several mechanisms in the pathogenesis of both diseases, identifying the hexanuceotide repeat expansion in *C9orf72,* the most common genetic abnormality in ALS and FTD, opened the door to the discovery of several novel pathogenic biological routes, including chromatin remodeling and transcriptome alteration. Epigenetic processes regulate DNA replication and repair, RNA transcription, and chromatin conformation, which in turn further dictate transcriptional regulation and protein translation. Transcriptional and post-transcriptional epigenetic regulation is mediated by enzymes and chromatin-modifying complexes that control DNA methylation, histone modifications, and RNA editing. While alteration of DNA methylation and histone modification have recently been reported in ALS and FTD, assessment of epigenetic involvement in both diseases is still at an early stage, and the involvement of multiple epigenetic players still needs to be evaluated. As the epigenome serves as a way to alter genetic information not only during aging, but also following environmental signals, epigenetic mechanisms might play a central role in initiating ALS and FTD, especially for sporadic cases. Here, we provide a review of what is currently known about altered epigenetic processes in both ALS and FTD, and discuss potential therapeutic strategies targeting epigenetic mechanisms. As approximately 85% of ALS and FTD cases are still genetically unexplained, epigenetic therapeutics explored for other diseases might represent a profitable direction for the field.

Keywords

Amyotrophic lateral sclerosis; chromatin remodeling; epigenetic processes; frontotemporal dementia; RNA-mediated regulation; transcription regulation

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Introduction

Degeneration of motor neurons results in progressive loss of motor skills, a condition first described by Charcot and Joffroy in 1869 [29] and commonly known as Lou Gherig's disease in honor of the baseball Hall of Famer who gave a memorable farewell speech in 1939. Also referred to as amyotrophic lateral sclerosis (ALS), the disease is characterized by degeneration of upper motor neurons of the motor cortex and corticospinal tract, and lower motor neurons of the brain stem and spinal cord, progressively causing muscle weakness, spasticity, atrophy, and finally lethal respiratory failure within two to five years of disease onset [20]. Only 5–8% of overall ALS cases report a family history of the disease, where there is much heterogeneity in clinical presentation across affected relatives [2,24,25,63]. The most common alternative deficit observed in ALS family members is cognitive impairment, which is also comorbid to ALS in about 50% of patients. In fact, while deficits in executive functioning, visual and immediate verbal memory, language and fluency, as well as psychomotor speed are commonly present in ALS patients, these symptoms are mostly not acute enough to receive a diagnosis of dementia [144]. As such, only 15–20% of ALS patients receive concomitant diagnosis of frontotemporal dementia (FTD) [23,65,67,106,153]. While ALS is the most common motor neuron disease, FTD is the second-most common cause of early onset dementia after Alzheimer's Disease (AD) [120], and comprises three clinically distinct syndromes: behavioral variant FTD, progressive nonfluent aphasia, and semantic dementia [136,163]. Briefly, FTD is characterized by neuronal degeneration in the frontal and temporal lobes causing progressive deterioration of language, personality, and behavior [68]. Up to 50% of FTD cases report a positive family history, with members affected with either FTD or other neurodegenerative diseases [68].

The link between ALS and FTD was strengthened after the finding that a hexanucleotide repeat expansion (HRE) in the *C9orf72* gene explains disease in multiple family pedigrees counting members diagnosed with either one or both diseases [45,150]. Multiple genetic assessments now predict this HRE to be carried by approximately 34% of familial and 6% of sporadic ALS cases, as well as 26% of familial and 5% of sporadic FTD patients [145,177]. Although higher and lower frequencies have been reported depending on the population studied [107], the HRE in *C9orf72* is considered the most common genetic cause of ALS and FTD identified thus far [8,149].

Causative genetic mutations identified in more than two dozen genes currently explain ~68% of familial and ~11% of sporadic ALS cases [149], leaving about 86% of overall cases, mostly sporadic, unexplained. Similarly, genetic mutations explain about 25% of familial and 10% of sporadic FTD, leaving about 83% of overall FTD cases genetically unexplained [77]. The fact that genes associated with familial ALS remain typically unaltered in sporadic ALS (sALS) patients, and genome-wide association studies have identified variants with only moderate risk, points to the likelihood of other disease culprits [34,40,99,149,179]. Specifically, increasing evidence supports altered RNA processing as a central pathological mechanism in ALS [71,140,142]. Epigenetic processes are known to regulate RNA transcription, which can in turn dictate protein translation or further regulate downstream transcription [127]. Thanks to the discovery of a HRE in *C9orf72*, numerous studies using blood, brain tissues and induced pluripotent stem cells from *C9orf72* repeat expansion

carriers demonstrated the involvement of epigenetic and transcriptional dysfunction in ALS and FTD [15,14,50,142,187,191,190]. How epigenetic and transcriptomic mechanisms interact with one another, and whether these interactions can be exploited as potential therapeutic targets for ALS and FTD remain unanswered questions. Here, we provide a review of what is currently known about the involvement of altered epigenetic processes in these two devastating diseases, and discuss potential strategies for targeting these alterations therapeutically.

Epigenetic regulatory mechanisms

Since Crick's 1958 central dogma suggesting a flow from genetic information to RNA transcription and protein translation [39], much effort has been devoted to better understand RNA regulation and its role in human diseases. It has been recognized for decades that the genetic material is under epigenetic control through modification of the DNA and chromatin-associated proteins dictating RNA transcription, the template for protein synthesis, as well as regulating DNA replication and repair. The ability of the RNA to also act as an intermediate in gene regulation was only contemplated in 1969 [22], a proposition refined in 2001 suggesting a direct role for regulatory RNA networks to control epigenetic processes [111]. It is now recognized that RNA not only functions as a messenger between DNA and protein, but also regulates the organization of the genome, as well as gene expression [127]. Regulatory RNAs play central roles in transcriptional and post-transcriptional epigenetic processes, while their own expression is also under epigenetic control [113,127]. While most epigenetic changes responsible for developmental processes result from anticipated internal processes rooted within the genome, communication between the environment and the genome is reflected through RNA editing, and these changes can further be transmitted from cell to cell to enhance proper physiological adaptation during development [112]. Specifically, RNA editing serves as a way to alter genetic information following environmental signals, especially in the brain, highlighting a dynamic RNA-mediated interaction between the environment, the epigenome and the transcriptome [113]. Over the last decade, there has been emergent interest to better understand the interaction between the epigenome and the transcriptome, especially in the contexts of cancer and neurodegenerative diseases. A general overview of the major epigenetic processes controlling transcription and chromatin conformation is provided in this section (Figure 1).

Modification of DNA and chromatin-associated proteins

During the last few decades, the role of transcriptional and post-transcriptional epigenetic modifications in gene activation and repression has been intensely studied, especially in the cancer field, and neuroscientists are increasingly more interested in assessing its role in neurodegeneration. Epigenetic modifications constitute codes that regulate chromatin organization as well as DNA transcription and repair, balancing stability and reversibility of the genetic material to maintain cell identity and/or enable appropriate cellular responses to internal and external stimuli. Epigenetic responses are initiated by chemical modifications of eukaryotic DNA and histone octamers around which the DNA is wrapped. Each histone octamer is composed of four different pairs of histones (H2A, H2B, H3 and H4), and each

have N-terminal tails that can be post-transcriptionally modified. DNA cytosine residues, especially at CpG dinucleotides, can also be chemically adjusted, mostly in CpG-rich regions commonly referred to as CpG islands. CpG methylation has been known for a long time to act as an epigenetic repressive modulator in vertebrates [167,180–182], and only recent evidence demonstrated that DNA methylation is actually highly interconnected to post-transcriptional changes at histone lysine residues; each system mechanistically relying on the other for normal regulation of chromatin conformation [155]. As such, histone modification can direct DNA methylation patterns, and DNA methylation can serve as a template for histone modifications.

DNA methylation and histone modification pathways can act independently or be mutually dependent of one another through mediation of different biochemical interactions. Such interactions are mediated by a limited number of enzymes and chromatin-modifying complexes that broadly influence the transcription of the genome, with only a few of these having affinity for specific DNA sequences. These enzymes and chromatin-modifying complexes facilitate transcriptional regulation by acting as ‘writers’ or ‘erasers’, adding or removing chemicals to DNA and histone protein [105]. Specifically, epigenetic writers lay down epigenetic marks on DNA or histones by either covalently modifying the amino-terminal tails of histone proteins, or by altering the DNA itself. The covalent modification generated by epigenetic writers can be reversed by epigenetic erasers and recognized by epigenetic readers [53]. DNA methyltransferases (Dnmts), such as Dnmt3a, Dnmt3b, and Dnmt1, are epigenetic writers responsible for establishing and maintaining DNA methylation patterns at different genomic sites [31]. Other epigenetic writers, such as histone acetyltransferases (HATs), histone methyltransferases (HMTs), protein arginine methyltransferases (PRMTs) and kinases are responsible for modulating epigenetic histone marks by modifying amino acid residues on histone tails. Epigenetic readers recognize specific epigenetic marks through their protein-containing domains and recruit other chromatin modifiers and remodeling proteins, all together regulating DNA-dependent processes [53]. Proteins containing DNA methyl-binding domains, chromodomains, bromodomains, and Tudor domains are all considered epigenetic readers. Finally, some enzymes act as erasers after catalyzing the removal of epigenetic marks [53]. Examples of erasers are histone deacetylases (HDACs), lysine demethylases (KDMs), phosphatases, and deubiquitylases [53].

While histone modification leading to chromatin remodeling is readily reversible, changes in DNA methylation are perceived as stable, long-term changes. Specifically, Dnmt1 is often considered as a ‘maintenance’ methyltransferase after recognizing hemimethylated CpG sites following semi-conservative DNA replication by reinstating original methylation patterns [180]. On the other hand, Dnmt3a and Dnmt3b are seen as *de novo* methyltransferases, both catalyzing methylation of originally unmethylated CpG sites [155,162]. Dnmts thus work in an interconnected fashion, with Dnmt3a and Dnmt3b recognizing and methylating specific genomic regions, and with Dnmt1 faithfully maintaining such *de novo* methylation. Recent reports demonstrated that *de novo* methylation through Dnmt3a and Dnmt3b action rely partly on pre-existing histone lysine methylation and enzymes catalyzing lysine post-transcriptional modifications[155]. In contrast, a recent report suggested that non-methylated sites in CpG islands influence

histone lysine methylation at gene encoding regulatory elements [155]. There is also an emerging belief that histone lysine methylation protects DNA from active demethylation [155].

The process by which demethylation can take place was first considered in the early 1970's, when Penn et al. suggested that methylated cytosines, or 5-methylcytosines (5mCs), can be oxidized to become 5-hydroxymethylcytosines (5hmC), an observation finally demonstrated in 2009 [98,134]. Growing evidence now show that 5hmCs, initially thought to represent an intermediate state between methylated DNA and unmethylated DNA, also act as a stable epigenetic marker that might contribute to neurological disease development [164,166]. Of interest, studies using human and mouse tissues have shown that the number of 5hmC sites increase with age and levels vary across organs [30,66,170]. In fact, the highest levels of 5hmC are found in the central nervous system [30,66,170]. Enzymes Tet1, Tet2, and Tet3 are Tet family 5mC hydrolases that convert 5mC to 5hmC [95,98,171] to potentially restore gene expression. While not essential for 5mC to 5hmC conversion, recent evidence demonstrated that oxidative stress can also trigger this oxidation event [94,141]. Finally, it was recently reported that Tet enzymes can also catalyze the establishment of 5hmC in RNA [58], which promotes RNA translation [46].

Enzymes and chromatin-modifying complexes must be purposefully directed to specific genomic positions in different types of cells to elicit DNA and histone tail modification. One important source of guidance for these proteins is RNA species which, as opposed to enzymes and chromatin-modifying complexes, are highly sequence and locus specific. The role of RNAs in mediating epigenetic processes is explained in the next section.

RNA-mediated epigenetic regulation

There is now compelling evidence that RNA signaling and editing play a crucial role in chromatin remodeling and nuclear architecture [5,113]. Specifically, coding and non-coding RNAs (ncRNAs) are involved in epigenetic regulation by recruiting chromatin modifying complexes and Dnmts to particular genomic loci [112]. ncRNAs, which mostly operate through repressive control while still having the potential to act as gene activators [160,161], comprise small RNAs (sRNAs) of less than 200 nucleotides and long non-coding RNAs (lncRNAs) of more than 200 nucleotides. sRNAs are further subcategorized as microRNAs (miRNAs), short interfering RNAs (siRNAs) and PIWI-associated RNAs (piRNAs), and lncRNAs are classified according to their position and direction of their transcription (e.g. antisense, intergenic, overlapping, intronic, bidirectional, processed) [114,137]. Several miRNAs originate from introns of protein-coding genes either by canonical Drosha pathway or splicing (which generates mirtrons) [17,132,156], whereas lncRNAs often overlap with or are interspersed between several coding and non-coding transcript variants [28,90]. In this way, lncRNAs regulate the expression of neighboring protein-coding genes [6].

Different sRNAs and lncRNAs are classified into groups depending on their genomic origin, but also according to their mechanism of action [5,137]. In fact, sRNAs and lncRNAs modify chromatin structure and silence transcription though distinct but unifying mechanisms. One of these is sRNA-guided gene regulation, which has emerged as a central mechanism that guides Argonaute (AGO) containing complexes to complementary nascent

RNA scaffolds [118]. AGO proteins are highly specialized direct binding partners of miRNAs, siRNAs and piRNAs, and interact with other proteins to coordinate downstream gene-silencing and RNA splicing [118]. sRNAs also perform as mediators of chromatin structure and transcription repression by facilitating the recruitment of histone and DNA methyltransferases. Besides playing a central role in RNA degradation and translational repression, sRNAs also modulate chromatin and gene expression via RNA interference (RNAi) pathways [85], which in turn modulate histone or DNA methylation to repress transcription [154]. sRNAs such as miRNAs can also act oppositely: they can stimulate gene expression under stress conditions as a result of new miRNA-ARGO complexes interacting with RNA-binding proteins which relocate during cellular stress [102]. Transcriptional silencing under sRNA control is also 'memorized' through self-reinforcing epigenetic loops, a process by which sRNA amplification loops are fused to histone modification or DNA methylation and form positive feedback systems to maintain epigenetic conditions. These self-reinforcing epigenetic loops are key players in epigenetic inheritance of histone and DNA methylation patterns [78]. Specifically, such association of sRNAs with positive feedback loops in the germ line acts as a fingerprint for internal or environmentally induced alterations, and can be transmitted from parents to their offspring [60,146].

On the other hand, several lncRNAs and some messenger RNAs (mRNAs) mediate the recruitment of chromatin-modifying complexes independently of sRNAs and RNAi pathways [154]. Specifically, lncRNAs can recruit chromatin-modifying enzymes to specific loci to activate or silence gene-specific transcription [19,78,154]. One example are exonized Alu elements, the most common transposable elements in humans, which are mostly located in lncRNAs and untranslated regions of mRNA [93]. Alu RNAs act as transacting transcriptional repressors after binding RNA polymerase II [109], and are also involved in the regulation of alternative splicing, modulation of translation and monitoring of mRNA stability [74]. Also, several studies attempted to establish whether lncRNAs recruit Polycomb proteins, which are epigenetic regulators of transcription, but the data remain inconclusive [78]. Current evidence does support a role for lncRNAs transcribed from enhancers in transcription regulation. These particular enhancer sequences are different from enhancer sequences that bind transcription factors as they activate specific target genes [101]. However, as the exact function of lncRNAs in genome regulation is still largely unknown, much will likely be learned in the near future.

Transcriptional silencing mediated by sRNAs and lncRNAs is an efficient RNA surveillance system responsible for the detection and silencing of aberrant transcript variants. sRNAs and lncRNAs, while having distinct functions, act together to regulate gene transcription. A good example is the piRNA-induced silencing complex, which protects the integrity of the genome by silencing transposable elements that can in turn act as transcriptional repressors when expressed [165]. As such, along with enzymes such as DNA and histone methyltransferases, or acetylases/deacetylases, and repressive and permissive chromatin-modifying complexes such as Polycomb and Trithorax groups, RNA-directed processes assist in orchestrating chromatin architecture, gene transcription, and epigenetic memory [6,18]. Moreover, RNA-mediated regulation has the highest affinity for specific DNA sequences, and thus, sheds light on interesting therapeutic targets for diseases such as ALS and FTD.

Finally, another way to regulate epigenetic processes is through RNA editing. Environmental information can be transmitted and reflected on the hardwired genetic information after post-transcriptional editing of the RNA base sequence, which in turn affects the regulation of downstream targeted RNAs. Two classes of enzymes are responsible for editing the RNA: the adenosine deaminases acting on RNA (ADARs), which catalyse adenosine deamination to inosine [26], and the apolipoprotein B mRNA editing enzymes (APOBECs), which catalyse cytidine deamination to uracil [129]. While RNA editing has been shown to take place in most tissues, it is particularly abundant and important in the brain [13], and has been shown in some cases to alter the amino acid sequence and splicing patterns of neurotransmitter receptors, thereby altering the electrophysiological properties of synapses [53]. Consequently, these RNA alterations can be transmitted across cells and offspring, a phenomenon that was first demonstrated in plants prior to animals [48,75,185].

RNA editing highlights the dynamic interplay mediated by RNA between the environment, the epigenome, and the transcriptome. These post-transcriptional changes in RNA lead to alteration of epigenetic information, which is memorized, and then transmitted between cells, across organ systems, and through different generations. Future studies will have to determine how extensively RNA editing may modulate epigenetic processes and assess how plastic the epigenome may be. This is particularly important for germline and *de novo* RNA editing occurring in the brain considering the possibility that edited RNAs may eventually cause disease, including neurodegeneration.

The role of epigenetic regulation in ALS and FTD

Very few epigenetic studies related to ALS were published before the identification of *C9orf72* HRE in September 2011 [45,150]. As alteration of epigenetic processes have been observed in a number of repeat expansion disorders [16], the finding of an HRE in *C9orf72* unveiled the possibility that epigenetic modifications and chromatin remodeling might also play a role in ALS and FTD. Since the HRE discovery, more than twenty studies have been reported, half of which are *C9orf72* locus-related. This sudden increase in ALS/FTD epigenetic reports reflects the enthusiasm of the field to explore new territories in terms of disease mechanism, as the young field of epigenomics might provide novel explanations for these two lethal diseases for which no treatment to prevent, decelerate or stop neuronal degeneration currently exists. The assessment of epigenetic modifications for ALS and FTD is still at an early stage and much remains to be evaluated. For example, it is not known whether unique epigenetic changes contributing to ALS and FTD can be found in all cells or subgroup of cells more susceptible or vulnerable to specific epigenetic changes. However, coupled with evidence modifications in the epigenome contribute to ALS and FTD pathogenesis, is the dynamic nature of epigenetic writer, eraser, and reader enzymes. Thus, developing therapeutic strategies that target the enzymes regulating epigenetic dynamics in order to reverse pathogenic epigenetic changes that lead to neurodegeneration offers an attractive approach to combat these diseases.

The following sections provide an overview of what we currently know about epigenetic modifications in ALS and FTD (Table 1), including the therapeutic implications of these

findings, environmental factors that may lead to epigenetic changes, and suggest avenues that should be explored in future studies.

DNA methylation in ALS and FTD

While earlier studies found the promoters of *SOD1*, *VEGF*, and *GLT1*, genes implicated in the pathogenesis of ALS, largely unmethylated in ALS patients [131,192], several studies indicate that DNA methylation plays a role in neurodegeneration pathophysiology. DNA methylation was reported altered in ALS post-mortem brains after methylation levels were compared between sALS and control subjects using Affymetrix GeneChip Human Tiling 2.0R Arrays [124]. The authors reported 38 differentially methylated regions (DMRs), and their pathway analysis suggested that the genes with DMRs were involved in calcium homeostasis, neurotransmission and oxidative stress. Another study designed to identify epigenetic modifications associated with sporadic ALS reported global changes in both 5mC and 5hmC levels in postmortem spinal cord, but not in blood samples [54]. The authors saw hyper- or hypo-5mC with corresponding under or over expression changes in 112 genes highly associated with immune and inflammation responses. Furthermore, whole blood was analyzed to determine whether DNA methylation is a modifier of ALS age of onset [174]. Here it was found that DNA methylation may be a marker of epigenetic dysfunction in ALS, as levels of methylation are increased independently from age of onset. Moreover, two studies analyzing the progranulin-encoding gene (*GRN*) reported that *GRN* promoter methylation regulates progranulin expression [11,59]. Both reports found increased *GRN* promoter methylation in FTD subjects negatively correlating with *GRN* mRNA levels [11,59], an interesting finding considering that GRN haploinsufficiency is a major cause of FTD [56]. A recent study analyzing genome-wide DNA methylation patterns in the peripheral blood of tau-related PSP and FTD subjects relative to unaffected controls identified a specific methylation signature associated pathologically with tauopathy, indicating the signature serves as a risk factor for neurodegeneration [103].

The most extensively studied epigenetic change in ALS and FTD thus far is the methylation of *C9orf72*; different studies aimed to determine whether this modification may play a role in mechanisms possibly leading to C9ORF72 loss of function. The loss of function theory has been supported by several reports demonstrating decreased expression of one or multiple *C9orf72* transcript variants in frontal cortex, motor cortex, cerebellum and cervical spinal cord of FTD or ALS *C9orf72* HRE carriers (c9FTD/ALS) [15,36,57,50,64,126,178], as well as in lymphoblastoid cell lines generated from c9FTD/ALS patient blood [36] and neuronal cell lines differentiated from c9FTD/ALS induced pluripotent stem cells (iPSCs) [4,50]. Hypermethylation of the 5′ CpG island located in the *C9orf72* promoter region has been shown by different groups to be present in about 10–30% of c9FTD/ALS subjects [14,104,187,191], possibly leading to reduced *C9orf72* expression levels in these cases. However, the cause of reduced *C9orf72* expression in the remaining 70% of c9FTD/ALS cases that are not hypermethylated was still obscure. A subsequent study demonstrated that the repeat expansion itself is methylated in all HRE carriers [190], suggesting that methylation of the HRE region might be the cause of the reduced expression for most, if not all, c9FTD/ALS patients. The consequence of *C9orf72* down regulation has been evaluated in several model systems, including by knocking-down the *C9orf72* orthologue in zebrafish.

Knock-down of the zebrafish orthologue led to both altered morphology of motor neuron axons and locomotor deficits, a phenotype rescued by overexpression of human *C9orf72* [36]. Depleting the *C9orf72* orthologue in the nematode also lead to motor neuron deficits [172]. Of note, the fact that the *C9orf72* mouse orthologue is enriched in brain regions susceptible to degenerate in ALS and FTD [168] suggests that sufficient *C9orf72* expression is critical for neuronal survival. However, since conditional deletion from mouse neuronal and glial cells was not associated with neurodegeneration [96], reduced *C9orf72* levels alone may not be sufficient to trigger motor neuron degeneration in higher organisms.

One report suggested that the length of the repeat might influence the level of DNA methylation at the *C9orf72* promoter. Specifically, the process of anticipation was demonstrated in a Canadian family with a father carrying an intermediate length allele (70 repeats) with an unmethylated *C9orf72* promoter, which expanded to approximately 1,750-repeats at the time of transmission to four of his children [188]. The expanded allele carried by the four children, two of whom having developed ALS symptoms thus far, was characterized by *C9orf72* promoter hypermethylation and associated with reduced *C9orf72* expression [188]. The timing associated with hypermethylation of the *C9orf72* promoter and the reason why it happens in only ~30% of c9FTD/ALS cases is still under investigation. However, in an attempt to explore this phenomenon, one group used iPSCs generated from a hypermethylated c9ALS patient and observed that 5mC levels at the *C9orf72* promoter were reduced during reprogramming but restored upon neuronal differentiation. On the contrary, 5hmC levels in the same region were increased during the reprogramming process, and were even higher after neuronal differentiation. The abundance of 5hmC at the *C9orf72* promoter was also confirmed in the brain of hypermethylated c9FTD patients [52]. Several groups attempted to assess whether DNA methylation can be a clinical modifier of disease. So far, very few significant correlations have been identified. Among these, however, hypermethylation of the CpG island upstream of the HRE has been shown to correlate with shorter disease duration [191], which may serve as a prognostic tool for *C9orf72*-associated disease.

The role that methylation at the *C9orf72* locus plays in ALS and FTD pathogenesis is yet to be fully determined, as contradictory results have arisen. For instance, while epigenetic modification of *C9orf72* through hypermethylation has been significantly correlated with shorter disease duration, it also has been shown to be neuroprotective in patients [15,116,104,157,191,190]. Specifically, it was shown that methylation of the HRE reduces the pathogenic effects of the HRE, as determined by quantification of dipeptide protein poly(GP) levels, one product of non-traditional repeat associated non-ATG (RAN) translation of the HRE, and of RNA foci formation, when the HRE was expressed in cells [12]. As such, simultaneously promoting methylation of the mutant allele to reduce its expression and overexpressing the normal allele might avoid both the haploinsufficiency and the toxic gain of function observed in c9FTD/ALS. Consequently, using epigenetic modifiers to independently regulate expression of the normal and mutant alleles might be a novel strategy to explore in the near future. In fact, the mechanism of *de novo* gene methylation was first demonstrated in plants in 1994, and for the first time embraced the possibility of artificially modulating gene expression through epigenetic modulation [186]. Strategies to therapeutically reverse pathogenic changes in DNA methylation have been

intensely studied since then to treat many diseases, including cancer and neurodegeneration [76,184]. Interestingly, to combat the potential toxicity associated with *C9orf72* haploinsufficiency, small molecules targeting bromodomain proteins, proteins that recognize acetylated lysine residues on chromatin, have been shown to specifically enhance *C9orf72* RNA expression without affecting the epigenetic regulation of this gene [193].

Other therapeutic strategies targeting DNA methylation include developing drugs that alter the enzymatic activity of the hydroxymethylase TET to normalize 5mC or 5hmC levels, as well as altered activity of Dnmts to treat diseases where DNA methylation levels are perturbed [44,81]. While these strategies are being explored in diseases such as cancer, where deregulated TET enzymes have both tumor suppressing and promoting capabilities [86,183], their potential to treat neurodegenerative diseases is even less known. DNA methylation studies characterizing changes in 5hmC levels in many neurodegenerative diseases aim to identify whether these changes may serve as potential biomarkers or therapeutic targets for those diseases [3]. Interestingly, involvement of 5hmC level changes and regulation of transcription factors have been reported in neurodevelopment, neurodevelopmental diseases, aging, and neurodegenerative diseases [164,166], suggesting these DNA marks are important for neuronal cell development and maintenance.

Integrative analysis of DNA methylation findings from ALS subject spinal cords with transcriptome analyses revealed a potential to use DNA methylation changes to identify suitable targets to develop as biomarkers or for therapy [54]. Experimentally, Dnmts were reported to be pro-apoptotic and increase 5hmC levels in motor neurons [32]. Interestingly, pharmacologically treating a mouse model for motor neuron neurodegeneration and apoptosis with Dnmt inhibitors abrogated both increased 5mC levels and apoptosis of the motor neurons. Furthermore, in human sporadic ALS, Dnmt1 and Dnmt3a levels were found elevated in motor cortex and spinal cord motor neurons, as were 5mC levels in motor cortical pyramidal neurons. Dnmt3a expression is also upregulated in FTD patients and the methyltransferase was shown to regulate *GRN* promoter activity [11]. Taken together, targeting Dnmts may be an important therapeutic strategy to treat ALS.

Histone modification in ALS and FTD

Repressive histone marks at the *C9orf72* locus were found to reduce the expression of the gene in both ALS and FTD patients with the HRE, but not in control ALS patients without expanded repeats [15]. Interestingly, treating fibroblasts derived from patients with expanded repeats with the demethylating agent 5-aza-2-deoxycytidine increased *C9orf72* mRNA expression. These data demonstrated that a potentially pathogenic histone modification event regulating *C9orf72* expression can be reversed. Therapeutic strategies targeting histone modification have been intensely studied and developed as anti-cancer agents where multi-faceted HDAC inhibitors have successfully reversed the effects of cancer-induced aberrant epigenetic changes [100]. Among other diseases, HDAC inhibitors have also been explored to treat progressive neurodegenerative diseases such as Parkinson's disease (PD) where an imbalance between histone acetylation and deacetylation is known [73]. Because of the pathogenic potential for excessive histone deacetylation in PD, which leads to altered expression of neuronal genes including those essential for survival, HDAC inhibitors were

shown to provide neuroprotection in PD *in vitro* and *in vivo* models. However, the detailed molecular mechanisms for neuroprotection, and whether HDAC inhibitors will prove clinically successful in PD remain to be determined. HDAC inhibitors have also been tested for the epigenetic therapy of ALS in *in vitro* and animal models, with some proceeding to clinical trials. For example, a phase 2 study of sodium phenylbutyrate (NaPB) in ALS, a histone deacetylase inhibitor that was neuroprotective and prolonged the survival of SOD1-Gly93Ala mice [158], was found safe and well-tolerated by study participants, and importantly, significantly increased histone acetylation in blood buffy-coat specimens [42]. These data demonstrate the ability for a compound to alter the epigenomic architecture in patients.

miRNAs in ALS and FTD

Disrupting miRNA biogenesis has the potential to have many downstream consequences affecting many cellular pathways. Postmortem human spinal cord tissues from ALS subjects were assessed to identify aberrantly regulated microRNAs [55]. Expression and systems biology analyses revealed that mature miRNAs are globally reduced and miRNA processing is altered. Furthermore, the same study found that cellular redistribution and cytoplasmic aggregation of TDP-43 regulates ALS-associated miRNA expression. Interplay between different cell types is also being explored for pathogenic roles in neurodegeneration and evidence suggests that alterations in neighboring skeletal muscle may enhance damage to motor neurons in ALS [128]. Selectively expressing mutant *SOD1*(G39A), a known mutation in ALS, in mouse muscles lead to altered expression of miRNAs and mRNAs associated with myelin homeostasis in the spinal cords of the mice, therefore revealing interplay between cell types affects epigenetic regulation [49].

Since altered miRNA regulation could aberrantly regulate many cellular pathways, reversing pathogenic miRNA changes could provide therapeutic benefit. Both miRNA antagonists, to inhibit pathogenic gain-of-function mechanisms, and miRNA mimics, to replace downregulated miRNAs, have been intensely explored to treat cancer [7,135]. In ALS mouse models, specific oligonucleuotide miRNA inhibitors known as anti-miRs, and miRNA agonists, have been used to demonstrate anti-miR delivery and function in the brain and spinal cord and to support targeting miRNAs to treat ALS. For example, anti-miRs to miR-155 or miR-29a extended the lifespans of *SOD1*-Gly93Ala mice [97,130]. Injecting miR-124a oligonucleotides into *SOD1*-Gly93Ala mice prevented the pathological loss of the rodent excitatory amino acid transporter 2 (EAAT2/GLT1) [125], an astroglial glutamate transporter implicated in astroglial dysfunction in ALS. Similarly, in a mouse model expressing FTD-associated mutant *CHMP2B*, miR-124 levels were found decreased; re-expressing miR-124 in those mice decreased the levels of the miR-124 target AMPA receptor (AMPAR) and partially rescued behavioral deficits [62]. Moreover, the authors found correlative levels of miR-124 and AMPAR in induced pluripotent stem cell-derived neurons from subjects with behavioral variant FTD, supporting investigation of targeting this miRNA for FTD therapy. Several more studies have identified additional alternatively expressed miRNAs in ALS and FTD that could be developed as drug targets or as circulatory biomarkers for ALS [37,69,87,108,133,173,194]. For example, miR-206 was consistently altered during the course disease in *SOD1*-Gly93Ala mice and increased in the

circulation of a small cohort of ALS patients [173]. Furthermore, exploring therapeutic strategies targeting pathogenic miRNAs in ALS is further supported by the recent report on aberrantly regulated miRNAS in sporadic ALS discussed above [55]. Manipulating miRNAs has the advantage to alter multiple gene targets simultaneously using a single drug, but the disadvantage of non-specific binding to other miRNAs resulting in deleterious off-target effects. Therefore, designing approaches to target pathogenic miRNA alterations requires great specificity.

Environmental signals and epigenetic modifications in ALS and FTD

Communication between the environment and the genome is reflected through epigenetic alteration of the genetic information, and these changes can further be transmitted from cell to cell [139]. The dynamic interaction between the environment, the epigenome and the transcriptome can be initiated by different factors, including age, exercise, diet, and toxic environmental exposure, to name a few. The first association between environmental factors and ALS was observed with the Chamorro indigenous people of Guam, who showed an extremely high incidence of ALS. Disease was linked to accumulation of cycad neurotoxins, including beta-N-methylamino-L-alanine (BMAA) produced across the cyanobacterial order, from consuming flying fox [10,21,35]. It is well know that diet can induce epigenetic changes and cause various diseases [148], and the high incidence of ALS and other neurodegenerative diseases in Guam might represent the first example reported for the field [79]. Association between BMAA, reactive oxigene species (ROS), and ALS has also been reported by others [27,35,91,43,139,143].

Precisely, environmental signals can induce the liberation of free radicals, leading to oxidative stress and alteration of epigenetic mechanisms including histone remodeling, RNA editing, as well as DNA methylation and hydroxymethylation, and consequently alter gene expression [70,83,117,151]. For instance, stress after social defeat has been shown to cause both histone methylation and acetylation changes in rodents [175], and histone modifications after acute and chronic stress was demonstrated to cause gene activation or repression associated with memory processes [152]. Acute stress has a repressive effect on retrotransposable elements (RTE), as well as on coding and non-coding RNA of the hippocampus after trimethylation of H3K9 and H3K27. Such repression was lost after repeated stress, suggesting that expressional activation of RTEs after prolonged stress may impair genomic stability and give rise to cognitive impairments [51,82,84,89,92,115,147]. Interestingly, two recent reports of twins highlight the potential contribution by environmental factors to ALS onset. One study focused on monozygotic twins discordant for ALS, where no SNPs or genome-wide structural differences were found to explain the discordance, and the second study of a pair of *C9orf72* HRE-positive identical twins discordant for ALS [119,189].

Many other studies suggest connections between environmental influences and ALS. For example, accumulating evidence indicates heavy metals induce cellular stress and toxicity by catalyzing ROS formation, thereby mediating protein denaturation and aggregation, and leading to the inability of the ubiquitin/proteasome system to eliminate dysfunctional proteins [121]. One study used a mixed isomer fluorescent indicator (5-(and-6)-carboxy-2′,

7′-dichlorofluorescein diacetate or carboxy-DCFDA) to assess ROS generation within human neuronal cells [138] after generating stress using different metal sulfates. Of note, aluminum sulfate demonstrated the greatest ability to induce ROS. They found that carboxy-DCFDA is a highly sensitive and long-lasting tracer enabling ROS quantification, which can also be useful to evaluate epigenetic changes initiated by metal sulfate to ROS generation in neurodegeneration [138]. Furthermore, regular exposure to electromagnetic fields may trigger DNA methylation and histone modification, as was suggested by a study of a large cohort of workers, especially resistance welders regularly exposed to extremely low frequency magnetic fields who had an increased risk for AD and ALS [72]. While no robust association has been reported between ALS and other environmental factors, some studies suggested connections with heavy metal exposures such as lead, mercury, and selenium, as well as agricultural and household pesticides- and herbicides-containing organophosphate (OP) exposure [9,88,38,169,123,41,47,110,159,176].

Finally, a common subject of discussion is the increased ALS frequency among soccer and football players [33,1], as well as in war veterans [80,122] further supporting that neurological symptoms of ALS arise from environmental exposures. While different factors such as physical activity, drug consumption, and ischemia caused by head injuries have been proposed to increase the production of ROS in ALS, the exact molecular mechanisms and which each of these exposures lead to epigenetic changes and neurodegeneration remains to be determined.

Concluding remarks

While much of the epigenome was initially believed to be inherited and mostly stable, that it is in fact dynamic, and that it is altered in ALS and FTD makes the epigenome an attractive target for therapeutic development. Much progress has been made characterizing the status of different epigenetic mechanisms in neurodegenerative diseases, but whether epigenetic altered regulation is a consequence of neurodegeneration or pathogenic remains a matter of debate [61]. For example, a recent study observed distinct transcriptome alterations in c9ALS and sALS brain [142], but whether these unique signatures are the result of aberrant epigenetic regulation has not yet been demonstrated. If epigenetic mechanisms are indeed found to mediate transcriptome alterations, these unique changes would be useful to monitor the effectiveness of epigenetic targeting therapeutics in restoring transcriptome defects. In laboratory and clinical settings, strategies targeting epigenetic writers, readers, and erasers have shown some support to treat neurodegeneration and cancer, suggesting that therapeutic agents that reverse pathogenic epigenetic alterations have the potential to treat ALS and FTD. Because RNAs mediate epigenetic regulation by recruiting important chromatin remodeling factors, RNAs such as miRNAs may be interesting therapeutics targets to develop based on their ability to recognize specific sequences. While research identifying epigenetic pathogenic mechanisms is still in its infancy for ALS and FTD, lessons learned from other diseases, especially cancer, have the potential to fast-track the development of epigenetic targeting strategies from bench to bedside to treat ALS and FTD. Drugs already approved to target epigenetic mechanisms may turn out to be efficacious and restore altered cellular pathways in ALS and FTD; already FDA approved to treat cancer, Dnmt and HDAC inhibitors [76,53] may be able to reverse aberrant epigenetic changes in the central nervous

system [184]. Thus, the emerging field of epigenetics provides new hope for patients with lethal ALS and FTD, and exciting studies exploring new territories should be expected in the near future.

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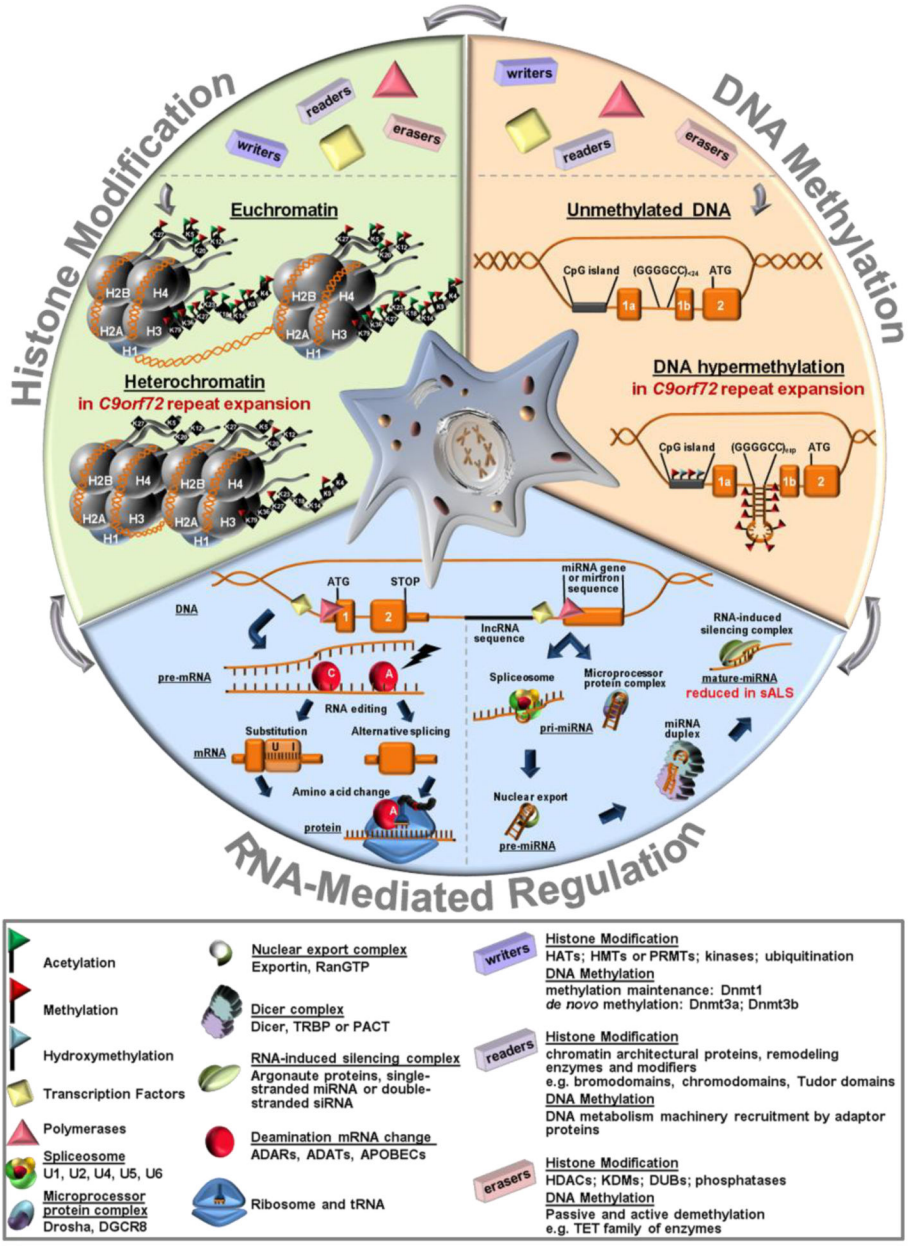

Figure 1.

Major epigenetic regulatory mechanisms. Schematic representation of the major cellular epigenetic mechanisms: histone modification, DNA methylation, and RNA-mediated regulation, as described in the review. It is suggested that interplay between these mechanisms exists in cells, as depicted by the arrows from one pie slice to the next. For each epigenetic mechanism, one example of aberrant regulation demonstrated in ALS and/or FTD is provided (font in red).

Table 1

Epigenetic Modifications in ALS and FTD.

Epigenetic Modification	Disease Findings	Disease Implications	References
DNA Methylation	DNA methylation of the *C9orf72* promoter and HRE regions in c9FTD/ALS.	Decreased expression of *C9orf72* possibly contributing to C9ORF72 loss of function. Evidence for neuroprotective effects and reduced RAN translation of poly(GP) protein.	[14,104,187, 191,190]
	38 differentially methylated regions (DMRs) found in sporadic ALS subjects.	DMRs in genes associated with calcium homeostasis, neurotransmission and oxidative stress, suggesting a role for these mechanisms in ALS pathogenesis.	[124]
	Global changes in 5mC and 5hmC levels in ALS postmortem spinal cord.	Expression changes in 112 genes associated with immune and inflammatory responses.	[54]
	Increased *GRN* promoter methylation negatively correlates with *GRN* mRNA levels in FTD subjects.	May contribute to *GRN* haploinsufficiency.	[11,59]
	Specific DNA methylation signatures in patient peripheral blood were pathologically associated with tauopathy in PSP and FTD subjects.	Risk factor for neurodegeneration.	[103]
Histone Modification	Repressive histone marks at the *C9orf72* locus in c9FTD/ALS.	Reduced expression of *C9orf72*.	[15]
Altered miRNA Regulation	miRNAs are aberrantly regulated in ALS.	Mature miRNAs are globally reduced and miRNA processing is altered.	[55]
	Expressing *SOD1* (G39A) in mouse muscles alters expression of both miRNA and genes associated with myelin homeostasis in spinal cords.	Suggests an epigenetic regulation interplay between muscle cells and neighboring neurons.	[49]
	Altered expression of specific miRNAs in ALS and FTD subject samples and patient-derived cell lines.	miRNAs and/or their targets could potentially serve as biomarkers or therapeutic targets.	[62,37,69,87, 108,133,173, 194]
Environmental Contribution	Increased incidence of ALS in Chamorro indigenous people of Guam.	Dietary consumption of neurotoxins can induce epigenetic changes possibly through ROS.	[79,10,21,35]
	Monozygotic twins discordant for ALS.	Supports evidence for environmental contribution to disease onset.	[119,189]
	C9orf72 HRE-positive identical twins discordant for ALS.		[119,189]
	Increased risk for AD and ALS in workers exposed to low frequency magnetic fields.	Electromagnetic fields may cause epigenetic changes leading to neurodegeneration.	[72]