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Epigenetics in Amyotrophic Lateral Sclerosis: A Role for Histone Post Translational Modifications in Neurodegenerative Disease

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is the third most common adult onset neurodegenerative disorder worldwide. It is generally characterized by progressive paralysis starting at the limbs ultimately leading to death caused by respiratory failure. There is no cure and current treatments fail to slow the progression of the disease. As such, new treatment options are desperately needed. Epigenetic targets are an attractive possibility because they are reversible. Epigenetics refers to heritable changes in gene expression unrelated to changes in DNA sequence. Three main epigenetic mechanisms include the methylation of DNA, micro-RNAs and the post-translational modification of histone proteins. Histone modifications occur in many amino acid residues and include phosphorylation, acetylation, methylation as well as other chemical moieties. Recent evidence points to a possible role for epigenetic mechanisms in the etiology of ALS. Here we review recent advances linking ALS and epigenetics, with a strong focus on histone modifications. Both local and global changes in histone modification profiles are associated with ALS drawing attention to potential targets for future diagnostic and treatment approaches.

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VII. Conflicts of Interests

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I. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the selective loss of both upper and lower motor neurons. (1) As motor neurons in the spinal cord, brain, and brainstem weaken, skeletal muscular atrophy spreads through the patient.(2) Depending on the type of motor neurons affected, ALS can present itself clinically as either limb onset-manifesting as muscle weakness- or bulbar onset manifesting as speech impediments. (1) Prognosis is poor and quality of life is significantly reduced as most patients succumb to the disease within three years of diagnosis.(3) There is no cure for ALS and the only two FDA approved drugs, Rilutek® (riluzole) and Radicava® (edaravone), fail to stop progression of the disease.(4-6)

ALS is classified into two categories: familial and sporadic. Familial ALS represents about 10% of all cases, where the disease can be attributed to a particular gene mutation running in families.(7) Sporadic cases, on the other hand, represent the remaining 90% for which there is no family history of the disease. Numerous genes have been associated to ALS.(8) Some of these include *superoxide dismutase 1* (*SOD1*), *chromosome 9 open reading frame* 72 (*C9orf72*), *Fused in Sarcoma (FUS),* and *TAR DNA binding protein 43 (TDP-43).*(9) Both familial and sporadic cases share similar pathology; the overwhelming majority of cases present neuronal TDP-43 protein aggregates.(10) Interestingly, not only neuronal cells are affected by these mutations. Glial cells harboring *SOD1* mutations have been shown to drive motor neuron degeneration in experimental models.(11-14) More specifically, microglia bearing a *SOD1* mutation caused motor neuron degeneration in otherwise healthy mice,(15) and human derived motor neurons co-cultured with these microglia showed signs of motor degeneration as well.(16) Nevertheless, the true origin of ALS remains obscure. Therefore, there is an urgent need to understand the pathogenesis of ALS in order to develop new treatment options. Aberrant epigenetic mechanisms linked to ALS are beginning to be discovered. These are attractive therapeutic targets as they are pharmaceutically accessible and largely reversible.(17)

Epigenetics refers to heritable alterations in gene expression without modification to the genome.(18) Three main epigenetic mechanisms include DNA methylation, micro RNAs (miRNA), and histone post-translational modifications (PTMs). DNA methylation takes place on the 5’ carbon on cytosine bases and is involved in transcription regulation.(19) DNA methylation at enhancers is key in determining cell line fate.(20) Hypermethylation at gene promoters is generally found to silence gene expression, while methylation in the coding region can increase transcription. DNA methylation is a crucial rate-controlling step that occurs in genomic regulatory regions during transcription, making it detectable and possibly even reversible for treatment purposes.(21) miRNAs are key regulators of gene expression.(22) miRNAs are non-coding short pieces of RNA, containing approximately 22 nucleotides, that generally bind to the 3’-untranslated region (3’-UTR) of mRNA, causing degradation of the mRNA and translational silencing.

Histones are proteins which package and organize cellular DNA.(23) 146 bases of DNA coil around two H2A/H2B dimers and one H3/H4 tetramer. The histone N-terminal tails are heavily modified with a multitude of chemical moieties, including mono-, di- and tri-

methylation, acetylation, phosphorylation, SUMOylation and ubiquitination occurring in a variety of residues.(24) Histone post-translational modifications (PTMs) play an important role in gene regulation by controlling the accessibility of DNA to the transcriptional machinery. Initially, histone PTMs were thought to only impact gene transcription by controlling how tightly DNA wraps around the histones. For example, histone acetylation on lysine residues lowers the positive charge on histones and the strength of interaction with the negatively charged DNA backbone favoring gene transcription. Conversely, hypoacetylation is associated with transcriptional silencing.(25-28) More recently, it has been established that these modifications actually comprise a "histone code" that other proteins can 'write,' 'erase' and 'read.'(29, 30) Histone PTMs can also affect one another through 'cross talk.' (31) For example, the phosphorylation of Serine 10 on Histone H3 (H3S10ph) promotes acetylation on Lysine 16 on Histone H4 (H4K16ac) and also inhibits tri-methylation on Lysine 9 on Histone H3 (H3K9me3).(32, 33)

While a thorough understanding of the underlying mechanisms resulting in ALS have yet to be reached, recent evidence shows that alterations in the epigenetic landscape might contribute to disease pathology. Here, we review recent evidence showing a link between ALS and epigenetics. While we incorporate exciting findings featuring DNA methylation and miRNA mechanisms, we mostly focus on recent advances linking histone PTMs to ALS.

II. DNA methylation in ALS

DNA methylation on cytosine bases is one the most studied epigenetic factors in neurodegenerative diseases and ALS.(17) In post-mortem spinal tissue from sporadic ALS patients, there are global alterations in DNA methylation and hydroxymethylation.(34) Not surprisingly, many of the genes that were hypo- or hypermethylated showed corresponding changes in decreasing or increasing gene expression. Interestingly, these genes were largely involved with the immune and inflammatory responses. Other reports link Dnmt3a, a *de novo* DNA methyltransferase, to ALS phenotypes.(20, 35-37) Mice lacking Dnmt3a are hypoactive, underperformed on tests of neuromuscular function and motor coordination and had decreased numbers of motor neurons akin to *SOD1* mouse models of ALS.(35) Interestingly, Dnmt3a is required for the development of motor neurons *in vitro*.(20) Moreover, apoptosis observed in NSC34 cells treated with camptothecin and in wild-type mice with unilateral nerve avulsion was driven by increased activity of Dnmt3a, Dnmt1 – a maintenance DNA mehtyltranserfase – and increased levels of 5-methyltransferase.(36) Remarkably, Dnmt inhibition with RG108, a DNA methyltransferase inhibitor, blocked apoptosis in both cultured neurons and mice. In agreement, levels of Dnmt1, Dnmt3a and 5-methylcytosine are upregulated in the brain and spinal cords of ALS patients. (36) Furthermore, Dnmt3a was found in the mitochondria of the CNS and skeletal muscle of adult wild-type mice, but was significantly reduced in the mitochondria of ALS *SOD1* mice. (37) Counter intuitively, there was also an increase in mitochondrial DNA methylation in the SOD1 mice, including at the 16S ribosomal RNA gene, which encodes for the mitochondrial 16 S rRNA subunit. The SOD1 mice also displayed increased mitophagy- the degradation of the mitochondria by way of autophagy- which contributed to neuronal degeneration.

Recently, genome-wide association studies discovered differentially methylated genes involved in pathways important to ALS and frontotemporal dementia(FTD)-ALS.(38) In the FTD-ALS subgroup, pathway analysis revealed three gene sets displaying enriched DNA methylation; among these is the Meissner Brain HCP with H3K4me3 and H3K27me3 gene set. This gene set contains genes with high-CpG-density promoters (HCP) bearing the bivalent histone H3 trimethylation mark at K4 and K27 (H3K4me3 and H3K27me3),(39) suggesting that both DNA methylation and histone PTMs are important in the progression of FTD-ALS. Interestingly, H3K4me3 and H3K27me3 are associated with neurological function.(40) For an in-depth examination of the links between DNA methylation and ALS, we direct the reader to a thorough review by Martin & Wong.(41)

III. miRNA and ALS

miRNAs are an epigenetic mechanism that reduce gene expression by binding Argonaute 2 and forming the RNA-induced silencing complex (RISC).(42, 43) The complex then binds the 3'-UTR of a specific mRNA, and degrades it if there is an extensive match between the mRNA and miRNA or, if there is a less extensive match, just binds the mRNA repressing expression of the bound transcript.(44-46) miRNAs are associated with neurodegenerative diseases such as Alzheimer's Disease, (47) Parkinson's Disease,(48) and Huntington's Disease. (49) Several lines of evidence link ALS to miRNA dysregulation.(17, 50) For instance, there is a global decrease in miRNA levels in the spinal cords of ALS patients.(51) The levels of miRNAs were compared to healthy controls and 90 miRNAs were found to be dysregulated. These miRNAs had mRNA targets involved in cell death, immune response and brain development that may possibly contribute to ALS etiology. Some of these included upregulation of miR-155 and miR-142. These miRNA target ubiquilin 2 (*UBQLN2*), the RNA binding protein Fox-1 (*RBFOX1*) and reelin (*RELN*), a protein secreted by certain neurons to guide neuronal migration.(52) All of these genes have been associated with neurodegeneration.(51) Interestingly, genes involved with immune response were also found to be dysregulated in sALS patients with aberrant DNA methylation patterns.(34) This suggests a role for epigenetics contributing to cellular demise caused by inflammation in ALS. Furthermore, TDP-43 overexpression in AinV15 mouse embryonic stem cells inhibited the endogenous activity of miRNAs regulating the genes *EIF2C4/AGO4*.(51) These genes are members of the RNA-induced silencing complex- the ribonucleoprotein complex that is responsible for translational silencing by cleaving miRNA and complementary mRNAs- and have been found to be dysregulated in ALS.(53, 54) Moreover, a large number of miRNAs were differentially expressed in the spinal cord motor neurons of sporadic ALS patients.(55) Functional analysis revealed the some of the upregulated miRNAs could bind to the 3'-UTR of low molecular weight neurofilament (NFL),(55) an important cytoskeleton protein involved in mitochondrial transport in motor neurons,(56) leading to a decrease in NFL mRNA levels. Interestingly, protein levels of NFL are found to lowered in ALS.(57-59) Additionally, FUS disrupts the circuitry between miR-409 and miR-495 in motor neurons derived from embryonic mouse cells with a FUS knock-in mutation.(60) miR-409 and miR-495 regulate the expression of *Gria2,* which encodes for a subunit of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor. The upregulation of these miRNAs led to a decrease in *Gria2* mRNA. The authors

validated that miR-409 and miR-495 bind the 3'-UTR of *Gria2.* Furthermore, FUS stabilizes the interactions between the miRNA and their target, leading to decreased *Gria2* expression.(60) Gria2 alteration has been previously implicated in motor neuron degeneration via alterations in Ca^{2+} homeostasis leading to excitotoxicity.(61-63)

In light of all these alterations, miRNA profiling has been proposed as a potential biomarker panel for neurodegeneration and ALS (Table 1).(50) For example, microarray analysis of leukocytes from sporadic ALS patients compared with healthy controls revealed a eight miRNAs that were dysregulated.(64) Of these miRNA, only miR-338-3p was upregulated, and interestingly it has been previously found to be dysregulated in the brains of ALS patients.(65) A study of skeletal tissue from *SOD1* G93A mice revealed that miR-206 was upregulated, and confirmed to also be upregulated in the plasma of ALS patients.(66) Similarly, comparison of circulating miRNAs in plasma form sporadic ALS patients and healthy controls revealed nine dysregulated miRNAs, three of which were upregulated.(67) Two of these miRNAs, has-miR-46469-5p and has-miR4299, were confirmed to be respectively up- and down-regulated in a larger ALS patient cohort. Interestingly, both of these miRNAs target *EPHA4,* a gene that is has been associated with ALS in animal models.(68) *EPHA4* contributes to brain development and neuronal migration, much like *RELN* discussed above.(51) These results suggest epigenetic mechanisms may be contributing to ALS pathology through alterations in development. Furthermore, a number of miRNAs have been found to be dysregulated in the leukocytes of ALS patients.(69) Specifically, *AAKT,* which encodes for miR-338, is up-regulated, while *DNM2,* which encodes for miR-638, is down-regulated. Both of these miRNAs have been found to be involved in other neurodegenerative diseases, such as FTD and hereditary spastic paraplegia. (70, 71) Overall, miRNAs appear to play an important role in the pathology of ALS and show promise as robust diagnostic biomarkers.

IV. Histone Modifications and Chromatin Remodeling Enzymes in ALS

Compared to other diseases, the study of epigenetic mechanisms involved in ALS is just in its beginning stages and relatively few studies examining the association between epigenetics and the disease have been carried out. While most investigations have focused in DNA methylation, recent evidence has linked aberrant changes in histone PTMs levels to neurodegenerative disease and ALS.(7, 17, 72) Remarkably, many enzymes responsible for installing or removing histone modifications have also been associated with ALS (Table 2). For instance, histone acetyltransferases (HATs) and histone deacetylases (HDACs) are responsible for the addition and removal of acetyl groups on histones, respectively. There are two classes of HDACs that are Zn^{2+} dependent including HDACs 1-11. A third class, Sirtuins (SIRT) 1-7, are NAD^{+} dependent.(73) HDACs are drug targets for the treatment of many diseases, including cancer, inflammatory disease and pulmonary disease.(74-76) Correspondingly, there are a variety of kinases responsible for phosphorylating histones, including Aurora B kinase and AMP kinase.(77) Lastly, many histone methyltransferases are responsible for the deposition and removal of methyl groups on lysine and arginine residues on histones.(78) These enzymes can be specific to mono-, di- and tri-methylation, as well as symmetric and asymmetric methylation.(79)

IV.A. Histone Acetylation, HATs and HDACs

Histone acetylation has been repeatedly associated with ALS. In a FUS overexpression model in *HeLa* cells, FUS binds to and inhibits CBP/p300 HAT at a specific gene promoter and causes hypoacetylation near the *CCND1* gene.(80) This causes reduced expression of *CCND1,* which encodes for cyclin D1, a protein required for progression through the cell cycle.(81) HeLa cell models have been repeatedly used in ALS research.(82-84) Evidencing another link between histone acetylation and ALS, ELP3 – a protein with HAT activity- was linked to motor neuron degeneration in ALS in a microsatellite-based genetic association study.(85) In zebra fish embryos, ELP3 knock down with anti-sense RNA leads to motor neuron degeneration in a dose dependent manner.(85) ELP3 acetylates Lysine 14 on Histone H3 (H3K14) and Lysine 8 on Histone H4 (H4K8).(86) Interestingly, mutagenesis screening in *Drosophila* revealed that ELP3 is critical for neuronal communication and survival.(85) These results support a role for histone hypoacetylation in ALS pathology. In fact, ELP3 directly regulates heat shock protein 70 (HSP70) expression by acetylation of histones H3 and H4 in yeast;(87) hence, ELP3 defects could result in motor neuron degeneration through a decrease in the transcription of HSP70.(81)

Recently, we characterized global histone acetylation levels in yeast ALS proteinopathy models.(72) Many cellular pathways are conserved from yeast to humans.(88, 89) Furthermore, yeast recapitulate the cellular toxicity and cytoplasmic foci of TDP-43 and FUS seen in human pathology.(90, 91) In fact, yeast models have enabled identification of common ALS genetic risk factors.(92) Yeast overexpressing human FUS showed significantly decreased levels of acetylation on Lysine 14 and Lysine 56 on Histone H3 (H3K14 and H3K56).(72) These histone PTM are conserved in humans. H3K14ac and H3K56ac are both involved in the DNA damage checkpoint activation.(93-95) Furthermore, H3K14ac is also found at the promoter of actively transcribed genes.(96) Interestingly, yeast overexpressing FUS had overall decreased RNA levels, suggesting that histone hypoacetylation leads to reduced transcription.(72) Surprisingly, an analogous TDP-43 yeast proteinopathy model did not display the same decreases in histone acetylation, but instead revealed hyperacetylation on Lysines 12 and 16 on Histone 4 (H4K12 and H4K16). H4K12ac is a modification localized on gene promoters and is associated with gene activation.(97) H4K16ac is a particularly interesting modification because it is associated with both gene expression and repression.(98, 99) Remarkably, each proteinopathy displayed its own distinct histone modification landscape. Puzzlingly, while both of these models share protein aggregation and cytotoxicity features, FUS and TDP-43 overexpression resulted in histone hypo- and hyperacetylation, respectively. This suggests that each proteinopathy and corresponding histone PTM profile may be leading to ALS in unique ways.

In addition to changes on histone acetylation, HDACs have been thoroughly implicated in ALS.(100) For instance, deletion of Set3- a member of a histone deacetylase complex, homolog to the human protein ASH1- was found to suppress the toxicity of TDP-43 inclusions in a yeast model.(101) Moreover, post-mortem analysis of brains and spinal cord tissue derived from ALS patients showed a decrease in HDAC 11 mRNA and an increase of HDAC 2 mRNA.(102) Furthermore, HDAC 1 has been found to mislocalize to the

cytoplasm in a FUS knock-in mouse model.(103) Curiously, post-translational modification on the histone modifiers themselves appears to be important. Phosphorylation of serine residues in HDAC1 controls its subcellular localization, and HDAC1 accumulation in the nucleus was neuroprotective in a mouse model.(104) Further evidence for HDAC perturbations in ALS comes from *SOD1* mouse models. SIRT1 levels are decreased in neurons and increased in muscles of mice expressing mutant SOD1, while SIRT2 mRNA levels decrease in motor neurons in the same model.(105) In NSC34 and HEK293 cells as well as mice expressing wild type and mutant $SOD1^{G93A}$, HDAC6 knock-down induced SOD1 aggregation resulting in increased motor neuron loss.(106) In the same mice model, HDAC6 levels drop as ALS symptoms appear and then plummet as the disease progresses. (107) Interestingly, in this mouse model HDAC6 overexpression prolongs life span and delays motor neuron decay by inducing fusion of autophagosomes to lysosomes and promoting autophagy.(107)

HDAC cofactors also appear to play a role in disease.(108) For example, loss of NAD^+, a SIRT cofactor, contributes to neurodegeneration.(109) Furthermore, the loss of intracellular nicotinamide phosphoribosyltranferase- the rate limiting enzyme in NAD^+ synthesis- leads to motor neuron degeneration in mice where the gene was knocked out.(110) Increased activity of PARP1 has been observed to deplete NAD^+ pools, and contributes neurotoxicity. (111) Interestingly, silencing of *Parp1* is neuroprotective in a mouse model of cerebellar ataxia,(111) and it is a possible therapeutic target for neurodegeneration.

HDAC inhibition has arisen as a promising therapeutic in various ALS models. Treatment with trichostatin A, an HDAC inhibitor, ameliorated motor neuron degeneration in a SOD1 mouse model.(112) In motor neurons derived from ALS patients, pharmacological inhibition and genetic silencing of HDAC6 reverses axonal transport defects caused by mutant FUS. (113) Furthermore, HDAC inhibition with 4-PB increased motor function and neuroprotection in transgenic ALS mice.(114) Interestingly, treatment with sodium phenylbutryate, a general HDAC inhibitor, extended survival in $SOD1^{G93A}$ ALS mouse model,(115) and its effect is increased when combined with an antioxidant or Riluzole.(116, 117) Phenylbutyrate has shown to be safe and increase histone acetylation levels in ALS patients.(118) Perplexingly, loss of HDAC function and is related to disease in some models, (112-115) while HDAC inhibition is neuroprotective in others.(103, 105-107) Future studies will potentially reconcile these seemingly opposite landscapes and elucidate their contribution to ALS pathways.

IV.B Histone Methylation and Methyltransferases

Lysine and arginine methylation have varying effects on gene expression. Generally, mono-methylation is associated with transcription activation, while tri-methylation is associated with transcription repression.(119) Recent evidence has linked tri-methylation of lysine residues on H3 and H4 with loss-of-function toxicity in ALS patients with dipeptide repeat expansions (DRE) in *C9orf72*.(120) There is an increase in H3K9me3, H3K27me3 and H4K20me3 levels around the DREs sequence in brain tissue from ALS patients compared to healthy controls. These histone PTMs are strongly associated with gene silencing.(119) Decreased levels of *C9orf72* mRNA in patients support a loss-of-function toxicity model.

(120) Interestingly, treating fibroblasts derived from patients bearing *C9orf72* mutations with a histone demethylating agent reduced tri-methylation levels near DREs and restored *C9orf72* mRNA levels.(120)

In yeast models of ALS, we observed distinct histone methylation profiles for TDP-43 and FUS proteinopathies.(72) Specifically, FUS overexpression is associated with decreased levels of asymmetric di-methylation on Arginine 3 on Histone H4 (H4R3me2asym), while TDP-43 overexpression is associated with decreased levels of tri-methylation on Lysine 36 on Histone H3 (H3K36me3). H34Rme2asym is associated with increased gene expression,(121) whereas H3K36me3 is linked to transcriptional repression by serving as a docking site for HDACs and promoting deacetylation.(122, 123) As for acetylation, these results highlight that different proteinopathies can have unique effects on epigenetic mechanisms. H4Rme2 is linked to H3K14ac,(124) which also decreased in this FUS model, underscoring cross talk between these two modifications.

Protein arginine N-methyltranserfase 1(PRMT1) is a methyltransferase that has been positively implicated in ALS. PRMT1 is responsible H4R3me2asym, which promotes histone acetylation and gene transcription.(125) In a FUS^{R521C} mouse model of ALS, overexpression of PRMT1 was found to rescue neurite growth after oxidative stress.(126) The same study showed that PRMT1 activity is inhibited by interaction with FUS as a stable complex of FUS/PRMT1/Nd1-L mRNA is formed. Nd1-L is an actin stabilizing protein and is under-expressed in this model. Furthermore, in agreement with our FUS yeast model results,(72) loss of PRMT1 function -due to FUS mislocalization-led to the reduction of asymmetric di-methylation of Arginine 3 on Histone H4 (H4R3me2asym) causing a drop in the acetylation of Histone H3 on Lysine 9 and 14, ultimately leading to transcriptional silencing.(127)

IV.C Histone Phosphorylation and Ubiquitylation

Phosphorylation on serine, threonine and tyrosine histone residues plays an important role in gene expression, transition through the cell cycle and DNA damage repair.(77) Histone phosphorylation and many enzymes responsible for it have been implicated in ALS and other neurodegenerative diseases.(128) For example, loss of FUS through RNAi leads to decreased cell proliferation and an increase in H3 phosphorylation in NSC-34 and HEK-293T cells.(129) This coincides with altered expression of genes involved in cell cycle regulation, cytoskeletal organization, oxidative stress and energy homeostasis, and may point to a loss-of-function mechanism for FUS mutants related to ALS.

In a FUS overexpression model in yeast, we discovered a reduction in phosphorylation levels on Threonine 129 on Histone H2B (H2BT129ph).(72) In yeast, reduced H2BT129ph is associated with decreased gene expression.(130) In the same model, we identified a profound decrease in the levels of phosphorylation on Serine 10 on Histone H3 (H3S10ph). H3S10ph is associated with active gene expression.(77) Furthermore, H3S10ph promotes acetylation of Histone H3 on Lysine 14 (H3K14ac) in yeast,(131) suggesting histone cross-talk may play an important role in disease processes. Interestingly, Ilp1, the yeast homologue of human Aurora B kinase, can phosphorylate both H3S10 and H2BT129. These results suggest Aurora B kinase might be involved in ALS pathology.

Increased R-Loops (DNA-RNA triple helixes) and DNA double strand breaks were observed *in vitro* and in the spinal tissue of ALS patients with mutations in *C9orf72*.(132) This damage was associated with dipeptide repeats in C9orf72 causing an accumulation of P62 and impaired H2A ubiquitylation at lysine 119 (H2AK119ub1). P62 is an autophagy protein related to ALS, and its accumulation inhibits RNF168, the enzyme responsible for ubiquitylation on H2A.(133) Reduced ubiquitylation impaired ATM signaling, an important pathway involved in DNA damage repair,(134) and perturbed DNA double strand break repair.(132) Figure 1 presents all histone modifications linked to ALS to date.

One issue that arises whenever discussing histone modification is causality. (135) Are histone modifications a consequence of neurodegenerative proteinopathies or do changes in modifications lead to disease? Further research into how ALS-associated proteins interact with histone ‘writers’, ‘erasers’ and ‘readers’, and perhaps even the histone PTMs themselves is necessary to definitively answer this question. This may still be an emerging field with a number of questions yet to be answered, but as discussed above for HDACs inhibitors, drugs targeting histone modifiers are effective treatments in ALS models. (112-118) Thus, causality might ultimately be inconsequential, as pharmaceutical intervention targeting epigenetic features of ALS would alleviate disease outcomes. A number of histone modifications are associated with ALS, and each enzyme responsible for adding, removing or reading these modifications is a potential drugable target. Aside from HATs and HDACs, further research into chemical modulation of histone kinases, phosphorylases, methyltransferases and demethylases is needed. For example, inhibitors of protein phosphatase 1 and 2, responsible for removal of H3S10ph, (136, 137) as well as inhibitors of JMJD6, a Jumonji-domain-containing protein reported to demethylate H4R3me2(138), may be useful therapeutic targets for ALS.

IV.D Chromatin Remodeling Enzymes

Eukaryotic DNA is packed into chromatin. DNA wraps around histones to form nucleosomes, the basic units of chromatin. Chromatin structure affects gene expression by controlling the accessibility to DNA.(139) Transcriptionally active chromatin is termed euchromatin and while transcriptionally silent chromatin is referred to as heterochromatin. (24, 140) Chromatin plays a key role in nearly all eukaryotic DNA-templated processes such as mitosis, DNA repair, and transcription. Some histone PTMs directly contribute to chromatin structure. For instance, H4K16ac inhibits the formation of heterochromatin,(141) while H3K9me3 binds Heterochromatin Protein 1 promoting chromatin compaction.(33) Additionally, enzymes that target histone PTMs can also play a role in chromatin compaction. For example, the HDAC SIRT1, which deacetylates H4K16, also has the ability to dephosphorylate the active site of the methyltransferase suppressor of variegation 3-9 homologue 1 (SUV39H1), increasing its activity and consequently increasing H3K27me3 levels and promoting chromatin compaction.(142) Aside from enzymes that directly affect histone PTMs, there a number of ATP-dependent chromatin remodeling enzymes that move, eject or otherwise restructure histones to control chromatin structure.(143, 144)Some of these have been associated to ALS and neurodegenerative disease. For example, in a TDP-43 overexpression *Drosophila* model, the chromatin-helicase-DNA binding protein Chd1 was inhibited by TDP-43, which in turn inhibited the stress response needed for neuronal

survival.(145) Chd1 alters gene accessibility by modifying chromatin structure. (146) This loss of Chd1 function led to decreased expression of protective genes, such as the proteins involved in the REST and Hsp70 pathway. Correspondingly, up-regulation of Chd1 was found to be neuroprotective. The human orthologue of Chd1, CHD2, physically interacted with TDP-43 and was significantly reduced in the temporal cortex of patients with ALS. (145) Therefore, at least some of toxicity associated with TDP-43 seems to be caused by the reduced expression of protective genes caused by chromatin rearrangement.

POLR2A, a subunit of the carboxy-terminal domain of RNA Polymerase II, reads modifications specifying the recruitment of factors that regulate transcription, mRNA processing and chromatin remodeling.(147) Arginine 1810 of POLR2A is symmetrically di-methylated by protein arginine methyltransferase 5 (PRMT5) and this modification recruits the Tudor domain of survival of motor neuron (SMN). SMN interacts with senataxin, which is sometimes mutated in ALS.(148) Perturbations in this pathway lead to the formation of R-loops, genomic instability and pre-mature transcription termination causing neurodegeneration.(147)

Furthermore, RNA Polymerase II, as well as TDP-43 and FUS, colocalize with γH2AX (a histone H2A isoform phosphorylated on serine 139).(149) γH2AX is a sign of DNA double strand breaks.(150) γH2AX co-localization with TDP-43 and FUS suggests these proteins may have a role in double strand break repair. DNA double strand breaks may be harder to resolve when FUS or TDP-43 mislocalize from the nucleus, promoting neurodegeneration and suggesting a loss-of-function toxicity model for these two ALS-associated proteins. A summary of the histone and chromatin modifying enzymes implicated in ALS is presented in Table 2.

V. Conclusions

Mounting evidence highlights the role of epigenetic mechanisms in ALS pathology. DNA methylation, miRNAs and histone PTMs have distinct contributions to neurotoxicity. The evidence reviewed here reveals distinct DNA methylation patterns and dysregulation of miRNAs are associated with ALS. Although understudied, perturbations in the levels of histones modifications lead to alterations of gene expression and can contribute to the neurodegeneration. Remarkably, these alterations seem to be distinctly connected to different proteinopathies. Chromatin remodeling enzymes, which do not specifically impact histone modifications, also contribute to ALS pathology by reducing expression of survival genes and impairing DNA break repair. Though exact knowledge of how the different epigenetic mechanisms, in particular histone PTMs, affect ALS development and progression is still lacking, we are beginning to characterize them and realizing their potential importance in understanding ALS. Although much work remains to elucidate causal relationships and mechanisms linking histone PTMs and neurodegeneration, these findings highlight the critical need for the inclusion of epigenetics in neurodegenerative disease research. Remarkably, some of these altered epigenetic profiles can be detected in blood, and may become useful biomarkers for diagnosis and assessment of disease or treatment progress. We expect discoveries to come in the next decade will take us beyond establishing the links between ALS and epigenetics and move towards elucidating the

precise epigenetic mechanisms associated with disease processes and specific symptoms. Pinpointing how epigenetic changes relate to disease can potentially lead to novel diagnostic and therapeutic tools for ALS and other neurodegenerative diseases.

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List of Abbreviations:

ALS	Amyotrophic Lateral Sclerosis
FTD	Frontotemporal Dementia
PTM	Post-Translational Modification
HAT	Histone Acetyltransferase
HDAC	Histone Deacetylase
SIRT	Sirtuin
PRMT	Protein Arginine N-methyltransferase
SOD1	Superoxide Dismutase 1
C9orf72	Chromosome 9 open reading frame 72
FUS	Fused In Sarcoma
TDP-43	TAR DNA Binding protein 43
DRE	Dipeptide Repeat Expansion
miRNA	micro RNA
3’-UTR	3’-Untranslated Region
NFL	Low Molecular Weight Neurofilament
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole Propionic Acid
SMN	Survival of Motor Neuron
HCP	High-CpG-density promoter
RISC	RNA-induced silencing complex
SUV39H	Suppressor of variegation 3-9 homologue 1

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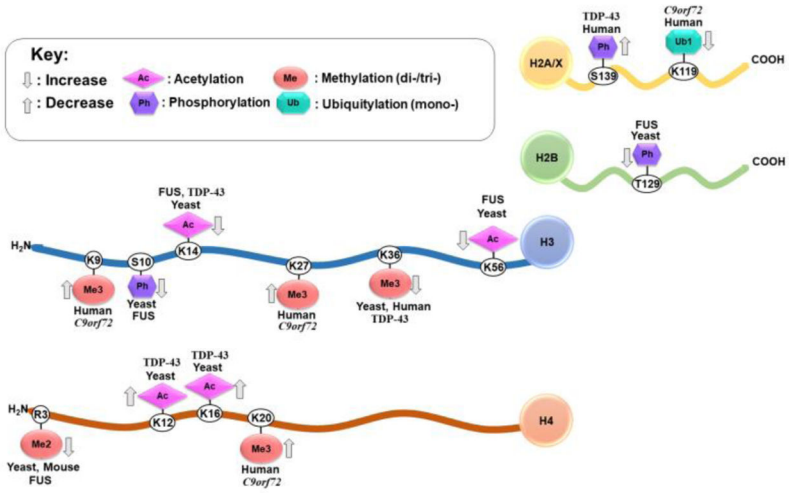

Figure 1.

Histone Post-Translational Modifications Linked to Different Proteinopathies and Genes in Amyotropic Lateral Sclerosis. Arrows denote an increase or a decrease for a given modification in the context of ALS.

Table 1.

List of potential miRNAs biomarkers for Amyotrophic Lateral Sclerosis.

miRNA	Dysregulation	Tissue	Reference
miR-338-3p	Upregulated	Leukocytes of sporadic ALS patients	45
miR-206	Upregulated	Plasma of sporadic ALS patients	47
has-miR-46469-5p	Upregulated	Plasma of sporadic ALS patients	48
has-miR-4299	Downregulated	Plasmas of sporadic ALS patients	48
miR-338	Upregulated	Leukocytes of ALS patients	50
miR-638	Downregulated	Leukocytes of ALS patients	50

Table 2.

List of Epigenetic Enzymes Involved in Amyotrophic Lateral Sclerosis.

Class	Enzyme	Activity in ALS	Reference
Histone Acetyltransferases	CBP/p300	Reduced activity when interacting with FUS	61
	ELP3	Required for neuronal communication and survival in *Drosophila*	63
Histone Deacetylases	HDAC1	Mislocalizes to cytoplasm in FUS ALS model	73
		Accumulation in nucleus is neuroprotective	74
	HDAC2	Levels decrease in spinal tissue of ALS patients	72
	HDAC6	Promotes SOD1 aggregation	76
		Overexpression is neuroprotective in mouse model	77
	HDAC11	Levels increase in the spinal tissue of ALS patients	72
	SIRT1	Levels increase in the muscles of a mutated *SOD1* mouse model	75
	SIRT2	Levels decrease in motor neurons of a mutated *SOD1* mouse model	75
	NAD^+ *	Depletion leads to motor neuron degeneration	79
Histone Methyltransferases	PRMT1	Overexpression rescues neurite growth in FUS model	93
		Reduced methylation of H4R3, ultimately leading to gene silencing	94
	PRMT5	Genomic instability and R-loop formation	110
Chromatin Modifying	CHD2/Chd1	Inhibited by TDP-43, inhibited stress response required for neuronal survival	108
	POLR2A	Genomic instability and R-loop formation	110

*Sirtuin cofactor involved in ALS pathology.