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Epigenetic mechanisms of neurodegenerative diseases and acute brain injury

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Abstract

Epigenetic modifications are emerging as major players in the pathogenesis of neurodegenerative disorders and susceptibility to acute brain injury. DNA and histone modifications act together with noncoding RNAs to form a complex gene expression machinery that adapts the brain to environmental stressors and injury response. These modifications influence cell-level operations like neurogenesis and DNA repair to large, intricate processes such as brain patterning, memory formation, motor function and cognition. Thus, epigenetic imbalance has been shown to influence the progression of many neurological disorders independent of aberrations in the genetic code. This review aims to highlight ways in which epigenetics applies to several commonly researched neurodegenerative diseases and forms of acute brain injury as well as shed light on the benefits of epigenetics-based treatments.

Keywords

Alzheimer's disease; Parkinson's disease; Huntington's disease; stroke; cerebral ischemia; traumatic brain injury

INTRODUCTION

Epigenetics are regulatory mechanisms that modulate gene expression without changing the genetic code. Epigenetics represent interactions between genes and the environment providing a connection between nutrition, toxins, medications, stress and cellular physiology.[1–3] The concept of epigenetics was first described by Conrad Waddington in 1940's with DNA methylation and has since been shown to encompass transcriptional regulation by histone modifications and long noncoding RNAs (lncRNAs) as well as post-transcriptional regulation by microRNAs (miRNAs).[4–8] Epigenetic alterations are involved in neurodevelopmental processes such as brain patterning, neural stem cell maintenance and neurogenesis and has been implicated in many diseases of the brain.[9] Epigenetics can

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CONFLICTS OF INTEREST

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significantly increase our understanding of the molecular mechanisms that contribute to brain damage as well as identify targets for efficient therapeutic targeting to promote neuronal survival. This review discusses the epigenetic targets for both chronic and acute conditions that lead to significant neuronal death and neurological dysfunction including Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), epilepsy, stroke and traumatic brain injury (TBI).

EPIGENETIC MECHANISMS

DNA Methylation:

DNA methylation (addition of a methyl group to cytosine to form 5-methylcytosine; 5-mC) is the most studied epigenetic mechanism implicated in gene regulation.[10, 11] This usually occurs in stretches of dense CG dinucleotide repeats known as CpG islands that when methylated often lead to gene silencing by interfering with the ability of transcription factors to bind (Fig. 1).[3, 12, 13] DNA methylation is mediated by a family of DNA methyltransferases (DNMTs). Methyl groups donated by S-adenosyl-methionine (SAM) are added to CpG islands by DNMT3a and DNMT3b and maintained throughout successive cell generations by DNMT1.[6, 14–16] DNMTs are highly expressed in the embryonic nervous system as well as post-mitotic neurons and glia where they facilitate synaptic plasticity, long-term potentiation and DNA repair.[9, 10, 17, 18] In addition, methyl-CpG binding domain proteins (MBD) like MeCP2 can be recruited to 5-mC and play a role in gene regulation by mediating histone modifications and gene silencing.[10, 19–21] The CNS shows the highest prevalence of DNA methylation of all organs which is thought to be involved in neurodevelopment, cognitive processes and aging.[6, 22] In recent years, it has been shown that 5-mC patterning is strongly associated with aging and mortality.[23] Thus, DNA methylation age (DNAm age) may be used as an estimation of biological age, a measure of an individual's physiological health.[24, 25] DNAm age has been proposed as a biomarker for predicting aging-associated brain disorders such as cognitive decline, dementia and AD.[23, 26]

DNA hydroxymethylation:

The family of ten-eleven translocase dioxygenases (TETs) oxidize 5-mC to 5-hydroxymethylcytosine (5-hmC).[27–29] Similar to 5-mC, 5-hmC is also highly enriched in the brain where it is predominantly found in neurons.[30, 31] Contrary to 5-mC, 5-hmC is often concentrated at euchromatin and is associated with transcriptional activation.[32–34] The TET enzymes are recruited to methylated CpGs where they have been shown to inhibit methyltransferase interaction, hinder MeCP2, and promote demethylation by further oxidizing 5-hmC to yield an unmethylated DNA through base excision repair.[35–38] In the CNS, 5-hmC plays a role in DNA repair, synaptic plasticity and neuronal aging.[39]

Histone modifications:

Nucleosomes, the basic units of chromatin, consist of DNA wrapped around histones that are essential for DNA structure. Histone organization can influence gene expression by affecting the architecture of promoters and the availability of DNA to transcription factors.[10, 40, 41] Histones can undergo various epigenetic modifications including methylation,

acetylation, ubiquitination, SUMOylation, citrullination and ADP-ribosylation.[12] Of these, the roles of histone methylation and acetylation in CNS disorders have been studied in detail. Histone methyltransferases (HMTs) catalyze methylation using SAM as a donor on the amino acid side-chains of histones 3 and 4 (H3 and H4).[6, 42] The degree, symmetry, and location of histone methylation dictates whether a gene is going to be expressed or suppressed (Fig. 2).[43,44] Methylated histones do not change the overall shape of chromatin, but facilitate the recruitment of additional proteins that regulate gene expression.[6, 42] Dysregulation of histone methylation has been linked to brain aging and neurological diseases.[45] Histones are acetylated by histone acetyltransferases (HATs) which results in gene activation due to electrostatic reduction between histones and DNA leading to a relaxed state euchromatin (Fig. 3).[6, 46–49] Histone deacetylation mediated by histone deacetylases (HDACs) and sirtuin deacetylases (SIRTs) lead to tightly wound chromatin and suppression of gene expression.[6, 47, 48] HDACs are implicated in axon growth, oxidative stress, synaptic plasticity and cognition.[50–57] Overall, epigenetic mechanisms that include DNA methylation and histone modifications, together with other proteins like MBDs, regulate gene expression in a highly dynamic manner in normal physiologic states and pathologic conditions.[9, 16]

Non-Coding RNA:

Non-coding RNAs (ncRNAs) are functional RNA molecules that are not translated into proteins, and instead regulate the expression of genes at the transcriptional or post-transcriptional level. The epigenetic-related ncRNAs include micro, circular, short-interfering, PIWI-interacting, and long non-coding RNA, among others.[51] Of these ncRNAs, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are the most studied in relation to their epigenetic roles in diseases of the brain.

MicroRNA (miRNA) act post-transcriptionally on messenger RNA (mRNA), binding to their 3’ untranslated region (3’ UTR) and regulating gene expression by degradation or silencing of transcripts.[7, 52–55] These 20–25 nucleotide long species, of which over 2000 have been classified, undergo splicing by Drosha and Dicer[56] before individually acting on as many as 1000 target genes.[9, 53] The ability of a single miRNA to act upon multiple genes produces an incredibly complex epigenetic environment, providing many therapeutic opportunities for human disease. In the CNS, miRNAs are important for neuronal signaling, synaptic plasticity and neurorepair mechanisms.[57–59]

Long non-coding RNA (lncRNA), RNA transcripts containing more than 200 nucleotides, are highly expressed in the human brain.[60] While the biological function of most lncRNAs remains to be elucidated, lncRNAs have been shown to play a role within chromatin remodeling, often guiding other modifying proteins to specific histones or gene sites and thereby influencing gene expression.[8, 45, 61, 62] In addition, lncRNA may come in the form of antisense transcripts, functionally masking genes and preventing degradation of their sequences by miRNA.[61, 63] LncRNAs are important in normal brain development and function, while aberrant lncRNA expression has been implicated in neurological disorders.[64–69]

EPIGENETICS AND NEURODEGENERATIVE DISEASES

Alzheimer's disease

Alzheimer's disease (AD), the most common cause of dementia is a progressive neurodegenerative disease marked by the aggregation of proteins amyloid-beta (Aβ42) and phosphorylated tau leading to extracellular plaques and intracellular tangles in the brain.[56, 70, 71] These plaques and tangles are accompanied by neuronal loss, dysregulation of microtubule assembly, apoptosis, and brain atrophy.[56, 72, 73] Interestingly, <5% of AD cases are early onset/familial and can be accounted for by common variants.[56, 70, 74] This indicates the possible mediation of epigenetics in the pathogenesis of AD.

The amyloid-β plaques fundamental to AD pathogenesis are caused by the dysregulation of the amyloid precursor protein gene (APP).[75–77] Post-mortem studies with brain tissue from humans that died of natural causes showed that 13 cytosine residues in the promoter region of APP are differentially methylated with age.[78] Additionally, those patients older than 70 showed ~50% reduction in methylation at these cytosines.[78] Increased methylation of APP in AD subjects has been shown to increase APP expression leading to aggregation of the neurotoxic Aβ42 indicating the importance of differential methylation patterning in AD pathogenesis.[79]

Presilin1 (PS1) and β-secretase (BACE) are integral in the processing of APP and their dysregulation leads to the aberrant Aβ42 plaques observed in AD.[80] PS1 and BACE methylation is highly dependent on SAM as methyl donor and severe decrease in SAM levels correlates with AD.[81] In neuroblastoma cell lines, vitamin B12 and folate deprivation induces PS1 and BACE that are reversed by SAM.[82, 83] In transgenic mice that overexpress human APP and display Aβ plaque deposition, SAM supplementation reduced the activity of β- and γ-secretase, decreased Aβ production and plaques, restored normal levels of tau phosphorylation and improved spatial memory.[84, 85] These studies are supported by a clinical trial where increased plasma levels of SAM were correlated with decreased Aβ−40 and PS1 mRNA levels in newly diagnosed AD patients.[86]

Apolipoprotein E (APOE) regulates Aβ42 clearance and hence it is considered as an important risk factor for late-onset Alzheimer's disease (LOAD).[87] APOE has a non-classical (CpG-poor) promoter and hence its regulation is complex.[88] The APOE haplotypes ε2–4 has been shown to be differentially correlated with LOAD risk.[88] For example, APOE4 confers more risk than APOE3, but not all APOE4 carriers develop LOAD and many LOAD patients are not carriers of APOE4.[87, 89–91] Furthermore, significant hypomethylation of the 2 APOE CpG sub-regions in the frontal lobe of Lewy body dementia and AD patients have been identified in post-mortem brain studies.[92, 93] These studies indicate a role for methylation of the APOE promoter as an epigenetic regulator of LOAD.

Histone acetylation levels were reported to be markedly decreased in both AD transgenic mice and AD human brains.[94, 95] In AD transgenic mice, HDAC2 was shown to be induced and treatment with HDAC2-specific inhibitor suberoylanilide hydroxamic acid (SAHA) improved learning and memory.[96, 97] Treatment with another HDAC inhibitor sodium 4-phenylbutyrate (4-PBA) also decreased the number of phosphorylated tau tangles and

enhanced cognitive function in transgenic AD mice.[98] Furthermore, HDAC6 knockout mice showed improved learning and memory and protection against Aβ42-induced disruption of mitochondrial trafficking, which is related to amyloid pathology.[99, 100]

The majority of identified AD-related miRNAs are involved in regulation of APP. Bioinformatics analyses have revealed several putative APP 3'UTR miRNA binding sites that have been validated *in vitro*. MiR-16 and miR-101 were shown to target APP and reduce Aβ-induced cytotoxicity in both PC12 cells and hippocampal neurons.[101–103] In human cell lines, several miRNAs including miR-106, miR-520c, miR-20a, miR-17–5p, miR-106b, miR-17, miR-153, miR-147, miR-644, miR-655, miR-323–3p and miR-20a have been shown to bind to APP and repress APP expression.[104–106] MiR-195, miR-339–5p and miR-107 are reduced in the brain tissue of AD disease patients and have also been shown to directly target and reduce the APP processor BACE1 in human cell lines and mouse cell culture studies.[107–110] Furthermore, overexpression of miR-195 was shown to reduce Aβ toxicity in neuroblastoma cells.[107] BACE1 is also targeted by miR-485–5p and miR-485–5p overexpression returned BACE1 to its non-pathological levels in HEK293T cells.[61]

Several studies have also identified the role of miRNAs in APP regulation both *in vitro* and *in vivo*. For example, the miR-29 family (miR29a, −29b, −29c) is downregulated in AD brains and has been shown to target the 3'-UTR of the APP processor BACE1 in human and mouse cell lines.[111–113] *In vitro,* suppression of miR-29a and miR-29b in human cells increases production of Aβ.[111] Hippocampal injection of miR-29c mimic in SAMP8 mice decreased Aβ and improved learning and memory compared to untreated control mice.[112] In APP/PS1 mice, reductions in miR-135, miR-200b and miR-429 were observed in the hippocampus. MiR-200b and miR-429 were shown to target APP and reduce APP expression while miR-135 targeted and decreased BACE1.[114] MiR-124 is also a negative regulator of BACE1 and lentiviral overexpression of miR-124 in the dentate gyrus of APP/PS1 mice reduced of apoptotic and autophagy markers and ameliorated cognitive deficits.[115]

The miR-132/212 cluster has been shown to be downregulated in tauopathy-related diseases including AD.[116, 117] Knockout of miR-132/212 in mice led to an increase in tau expression, phosphorylation and aggregation.[118] Another study showed that miR-132/212 knockout mice display significant deficits in cognitive function.[119] MiR-132 was shown to directly target and decrease tau mRNA and treatment with a miR-132 mimic restored tau and improved memory function in 3xTg-AD mice.[118] Downregulation of miR-132 was most significantly observed in neurons showing hyper-phosphorylation of tau in the brains of late stage AD patients.[120, 121] Furthermore miR-132 downregulation has been shown to correlate with cognitive decline in patients with AD.[118] MiR-219 also targets and represses tau synthesis and decreased levels of miR-219 were also observed in the human AD brain.[122] In a *Drosophila* model that produces human tau, reductions in miR-219 were associated with exacerbation of tau toxicity, linking this miRNA to AD-related pathology.[122]

The dysregulation of miRNAs has not only been shown to occur within the brain, but also within bio fluids such as serum, plasma, and CSF. A large push to develop AD detection methods has led to miRNA profiling within serum[123–127], plasma[125, 128–130],

CSF[125, 130–135], exosomes[132, 134–136], extracellular fluid[137], and PBMCs[138] of humans and AD animal models. For example, one study showed that miR-135 was reduced in the blood of patients with mild cognitive impairment and miR-135 and miR-200b levels were decreased in CSF of individuals with dementia of Alzheimer's type (DAT) group.[114] In blood samples obtained from AD patients, both miR-29c and BACE1 expression were increased.[112] Recently, Kumar et al. has developed a biomarker technique allowing AD patients to be distinguished from control patients with 95% specificity by hsa-miR-191–5p and hsa-miR-15b-5p signatures within plasma.[139] Another study developed a 16 miRNA exosomal serum panel that predicts AD with 87% sensitivity and 77% specificity.[137] Table 1 outlines the therapeutic potential of miRNAs and the other epigenetic regulators discussed in AD.

Bioinformatics studies have begun to elucidate the roles of lncRNAs in AD. In postmortem brain samples, the expression of hundreds of lncRNAs are significantly changed in AD patients versus age-matched controls in AD-related regions of the brain such as the hippocampus, middle temporal gyrus, entorhinal cortex and cortex.[140–142] Gene ontological analysis identified significantly altered lncRNAs associated with mRNAS involved in protein ubiquitination, amyloid-β clearance, neural communication, electron transport chain, metabolic processes and cholesterol homeostasis.[140–142] When neurofibrillary tangles were sampled, lncRNAs associated with development and morphogenesis of the neural tube and neural crest were significantly changed.[143] Microarray analyses performed in rodent models of AD have similarly shown extensive changes in lncRNA expression.[144, 145] While these bioinformatics studies revealed that several lncRNAs play roles in AD pathology, recent reports have identified Nuclear Paraspeckle Assembly Transcript 1 (NEAT1) as a key lncRNA in AD progression.[141] Downregulation of NEAT1 in hippocampal tissue of APPswe/PS1dE9 mice was observed in the early stage of disease progression.[146] Reduced levels of NEAT1 prevented clearance of Aβ by inhibiting expression of endocytosis-related genes.[146] Alternatively, *in vitro* models of AD performed with mouse brain tissue or neuroblastoma cells have shown upregulation of NEAT1.[147, 148] Knockdown of NEAT1 reduced Aβ-induced toxicity, apoptosis and promotion of p-Tau. Furthermore, NEAT1 was shown to reduce miR-107 and miR-124, thereby increasing BACE1.[148] Another lncRNA that modulates miRNA efficacy is BACE1-AS, an anti-sense transcript that is upregulated in AD and expressed alongside BACE1. BACE-AS competes with the miR-485–5p binding site and prevents miR-485–5p from degrading the BACE1 transcript.[61, 149] Dysregulated expression of both BACE-AS and miR-485–5p have been observed in RNA samples from the brains of AD patients.[61]

Parkinson's disease

Parkinson's Disease (PD) is the second most common neurodegenerative disease, affecting over 600,000 Americans, a number expected to double by 2040.[150] PD is caused by degeneration of dopaminergic nigrostriatal pathways from the substantia nigra pars compacta (SNpc) to the striatum.[6, 151, 152] The neurodegeneration of PD is marked by aggregates of α-synuclein (α-syn), a synaptic protein leading to dopaminergic neuron failure and resulting in tremors, rigidity, and non-motor symptoms like dementia and depression.[6, 151, 153] Levodopa (L-Dopa), an amino acid precursor to neurotransmitters, provides relief

to the motor-based symptoms of PD; however, L-Dopa can lead to the involuntary movement disorder, tardive dyskinesia, and other drugs like it fail to treat the non-motor symptoms of the disease.[6, 154] Therefore, potential PD treatments in the realm of epigenetics are currently being explored (Table 2).

Oligomerization and aggregation of α-synuclein (α-syn) is thought to be responsible for the onset of PD in humans.[152] While phosphorylation and ubiquitination are known to promote α-syn aggregation, the precise mechanisms that control α-syn are still not known. Hypomethylation of the CpG2 (near intron 1) in the α-syn gene was shown in the blood, substantia nigra and putamen tissue samples of PD patients.[155] This hypomethylation of the α-syn gene is thought to be responsible for increased levels of α-syn and correlate with age of onset of PD.[156, 157] Furthermore, DNMT1 levels were shown to be decreased by ~50% that might be responsible for reduction in α-syn promoter methylation in PD brain samples.[158] There has been evidence showing that α-syn mediates the sequestration of DNMT1 in neuronal cells causing its own hypomethylation in a feed-forward mechanism.[158] Thus, epigenetic control by methylation of the α-syn promoter might be a factor responsible for PD onset as well as progression.

Many studies showed that histone acetylation also plays a significant role in PD pathogenesis. In α-syn overexpressing cells, α-syn binds to H3 leading to hypoacetylation of H3.[159] Treatment with HDAC inhibitors sodium butyrate and SAHA reversed this and rescued cells from α-syn toxicity.[159] Furthermore, H3 deacetylation inhibitors valproic acid (VPA), sodium butyrate, Trichostatin A (TSA) and SAHA protected the neuronal cells following MPTP treatment, a drug that produces a neurotoxin up taken by dopaminergic neurons and causes parkinsonism features.[160, 161] In an MPTP mouse model of PD, H3 acetylation was observed to be upregulated and treatment with Levodopa (L-DOPA) reversed this effect.[162] However, in primate PD models H3 acetylation was observed to be downregulated upon L-DOPA administration.[162] Hence, HDAC inhibitors are promising to understand PD pathology, but the mechanistic role of histone acetylation in PD is still not completely clear. Histone acetylation has also been explored in the pesticide exposure-induced model of PD. In rat mesencephalic dopaminergic neurons, pesticides dieldrin and paraquat that are known to cause PD-like symptoms promoted H3 and/or H4 hyperacetylation.[163] Furthermore, CREB-binding protein mediated histone hyperacetylation led to dopaminergic neuronal apoptosis that was rescued by the HAT inhibitor anacardic acid.[163, 164]

Familial and sporadic PD can be caused by gain-of-function mutations in leucine-rich repeat kinase 2 (LRRK2).[165] It was previously shown that mutant LRRK2 leads to miRNA-induced transcriptional repression by negatively regulating Argonaute-2 of the RISC complex and by antagonizing let-7 and miR-184 in *Drosophila*.[166] In mammalian PD models, LRKK2 has been shown to cause dysregulation of GTPase activity[167], autophagy[168], and actin stabilization.[169] Cho et al. found that despite increased expression of LRRK2 protein in PD patients, LRRK2 mRNA levels are not significantly altered, leading them to investigate post-transcriptional modifications.[170] Screening for miRNAs with target sites near the LRRK2 3'UTR, revealed that miR-205 is disproportionately downregulated in PD frontal cortex. Overexpression of miR-205 suppressed LRRK2 protein expression, and inhibition of

miR-205 increased LRRK2 in primary neurons and dopaminergic MN9D cell lines.[170, 171] Increased miR-205 levels were shown to inhibit defects in neurite outgrowth in hippocampal neurons of mice expressing mutant forms of LRRK2.[170]

SNCA is also post-transcriptionally regulated by several miRNAs. MiR-7 has been shown to reduce levels of α-syn by 30% while miR-153 reduced levels of α-syn by 19% in primary neurons.[172] A synergistic effect was observed with overexpression of both miR-7 and miR-153 which reduced α-syn levels by 46% in primary neurons.[172] In another study, miR-7 and miR-153 overexpression was protective via mTOR and SAPK/JNK pathway preservation in cortical neurons exposed to MPP+.[173] Furthermore, inhibition of miR-7 upregulated α-syn and miR-7 was shown to protect against cellular α-syn-mediated susceptibility to oxidative stress, proteasome impairment, and prevent cell death by targeting RelA in dopaminergic neuroblastoma cells.[174, 175] MiR-155 was shown to play a key role in α-syn-induced inflammation and knockout of miR-155 reduced α-syn neurotoxicity in mice.[176] Finally, eight miRNA, including hsa-miR-21 and hsa-miR-301b were shown to deregulate the chaperone mediated autophagy proteins (CMA), lysosome-associated membrane protein type 2a (LAMP-2A) and heat shock protein 70 (hsc70), each degraders of α-syn, resulting in increased aggregates in neuroblastoma cells.[177]

MiR-34b/c and the previously reported miR-7 have been implicated in mitochondrial function in PD and PD-related models. MiR-34b and miR-34c were downregulated in human brain tissue from PD patients in Braak stages 4 and 5.[178] Correspondingly, decreased levels of miR-34b and miR-34c correlated with mitochondrial dysfunction, reactive oxygen species (ROS) generation and increased α-syn aggregation in human dopaminergic neuroblastoma cells.[178, 179] It has been proposed that miR-34b loss in PD patients leads to the characteristic upregulation of A2AR in the putamen observed in the disease.[179] MiR-7 has also been shown to regulate mitochondrial protein expression, prevent ROS and mitochondrial permeability transition pore opening following MPP+ exposure in neuroblastoma cells.[180] Finally, miR-7 has been shown to target the NLRP3 inflammasome in microglia, and a miR-7 mimic provided neuroprotection in Transgenic-α-syn mice subject to MPTP.[181]

Several other miRNAs involved in modulating PD pathology have been identified. For example, treatment with a miR-221 mimetic was shown to be protective against a 6-OHDA treatment model of PD in PC12 cells.[182] Overexpression of miR-185 or miR-181c prevented MPTP-induced apoptosis in neuroblastoma or PC12 cells, respectively.[183, 184] In a rotenone PD model of neuroblastoma cells, miR-384–5p inhibition reversed ER stress and attenuated apoptosis.[185] Overexpression of miR-124 downregulated apoptotic and autophagic pathways to provide neuroprotection in both MPTP-treated mice models and MPP+-treated neuroblastoma cells.[186] Loss of miR-133b has been observed in the midbrain of PD patients and miR-133 was shown to regulate maturation and function of dopaminergic neurons through a feedback loop with Pitx3.[187] MiR-16–1-mediated downregulation of hsp70 was shown to worsen aggregation of α-syn in transgenic neuroblastoma cells.[188] Finally, hydrogen sulfide treatment was shown to protect MPTP-treated mice by increasing miR-135a- 5p, which represses rho-associated protein kinase 2, an enzyme that promotes neurodegeneration.[189]

Profiles of miRNAs expressed in the prefrontal cortex tissue[190], SNpc[191], exosomes of the CSF[192], and serum[193] of PD patients have revealed extensive dysregulation of miRNAs. CSF miRNA profiling was shown to distinguish PD patients from controls and also correlated with different stages of PD pathology.[194, 195] Overlapping miRNAs identified in serum studies have implicated several miRNAs that may be key to PD pathogenesis including miR-29c, miR-221, and miR-214.[196–199] The role of miR-29c has not been elucidated, but miR-221 has been shown to promote survival in human dopaminergic neuronal cells and loss of miR-214 increased alpha-synuclein expression in human neuroblastoma cells.[200, 201] In plasma, a strategy combining k-Top Scoring Pairs algorithm of differentially expressed miRNA can predict PD with 91% sensitivity and 100% specificity.[202]

Several profiling studies have shown aberrations in lncRNA expression in the human PD brain and mouse models of PD providing a basis for biomarker research.[203–208] The majority of the lncRNAs investigated in PD have been shown to modulate miRNAs. For example, HAGLROS was upregulated in MPTP-treated mice and MPP+-treated neuroblastoma cells.[208] HAGLROS was shown to sponge miR-100 and subsequent inhibition decreased apoptosis and autophagy both *in vitro* and *in vivo* through PI3K/Akt/mTOR regulation.[209] P21 was upregulated in neuroblastoma cells subject to MPP+ and subsequent knockdown decreased ROS generation, neuroinflammation, and apoptosis.[210] It was found that p21 exerts protective function through de-repression of miR-625 and thus upregulation of Transient receptor potential melastatin 2 (TRPM2).[210] In addition, p21 promoted apoptosis in neuroblastoma cells by sponging miR-1277–5p and thereby increasing expression of α-syn.[211] MALAT1 is increased in midbrains of MPTP-treated mice and was shown to suppress miR-205–5p, leading to a subsequent increase of LRRK2.[171] Correspondingly, MALAT1 knockdown prevented apoptosis after MPP+ treatment in MN9D cells.[171] In addition, β-asarone treatment has been shown to be protective in both in vitro and in vivo models of PD by downregulating MALAT1 expression.[212]

The small nucleolar host gene 1 (SNGH1) lncRNA was upregulated in MPP+-treated neuroblastoma cells and exacerbated toxicity by sponging miR-15b-5p.[213] Knockdown of SNGH1 or overexpression of miR-15b-5p abrogated ROS production and cell death in the same model.[213] The protective role of miR-15b-5p was again shown through SNGH1 knockdown leading to less α-syn aggregation in neuroblastoma cells.[214] SNGH1 silencing has been shown to act through other axes like miR-221/222 and CDKN1B/p27/mTOR to enhance autophagy and prevent cell death in MPTP-treated mice and MPP+-treated MN9D cells.[215] Importantly, SNGH1 was also elevated in brains of PD patients and was shown to promote neuroinflammation by suppressing miR-7 and enhancing microglia and inflammasome activation in MPTP-treated mice.[216]

MPTP-treated mice and MPP+-treated neuroblastoma cells were both shown to induce NEAT1 expression.[217] Subsequent knockdown of NEAT1 suppressed autophagy in mice by stabilizing PINK 1.[217] Importantly, NEAT1 was also increased in the substantia nigra of patients with PD and the neuroprotective drugs fenofibrate and simvastatin have been shown to require NEAT1 to prevent paraquat-induced cell death in neuroblastoma cells.[218]

Alternatively, NEAT1 silencing was also shown to be protective by reducing apoptosis and inflammatory signaling in MPP+-treated neuroblastoma cells by derepressing miR-124.[219]

The Urothelial Cancer Associated 1 (UCA1) lncRNA was highly expressed in MPTP-treated mice and MPP+-treated neuroblastoma cells, leading to increased SNCA expression.[220] Knockdown of UCA1 decreased caspase-3 activity and apoptosis in the same cell model.[220] Similarly, downregulation of UCA1 prevented inflammation and oxidative stress in a PD rat model induced by 6-hydroxydopamine injection (6-OHDA).[221] MPTP treatment of neuroblastoma cells downregulated NORAD and subsequent overexpression protected against MPP+-mediated apoptosis, decreased ROS, and decreased lactose dehydrogenase activity.[222] Finally, expression of the lncRNA HOTAIR has been shown to increase in both MPTP models of mice and MPP+ models of neuroblastoma cells along with a corresponding increase in LRRK2.[66] Knockout of HOTAIR in the cellular model attenuated induced neurotoxicity.[66]

Huntington's disease

Huntington's Disease (HD) is a dominant, late-onset genetic disorder affecting 5–10 people of 100,000 globally.[223, 224] In HD, CAG repeats form at exon 1 of the Huntingtin gene (HTT), producing the neurotoxic Huntingtin protein (mHTT) and resulting in neurodegeneration of GABAergic spiny striatal neurons.[224–226] HD manifests in motor impairment and chorea, schizophrenia-like behavior and suicidal tendency, as well as changes in mood and judgement.[224] HD patients undergo differing treatment depending on the course of the disease, and it is hopeful that altering gene expression through combinatorial approaches such as tacrine, moclobemide, and creatine will improve treatment options.[227, 228] Several studies have revealed a role for epigenetic mechanisms in HD pathology, many of which display therapeutic potential (Table 3).

In post-mortem tissue from the frontal and parietal cortex of HD patients, a higher level of global methylation was observed compared to control patients.[229] Cultured mouse striatal cells from knock-in embryos expressing full-length huntingtin (HTT) show methylation of promoters and thus down-regulation of several genes that control developmental processes, neuronal migration and cell signaling genes.[230] A correlation between global cortex hypermethylation and age of disease onset in the cerebral cortex has been observed, although differential methylation at probed sites around HTT was not identified.[231] Genome-wide reduction of 5-hmC has also been seen in a HD mouse model, particularly in the cerebral cortex and striatum.[232] Differentially hydroxymethylated promoter regions in these animals correspond to Wnt/β-catenin/Sox pathway, axon guidance, GABA signaling and dopamine feedback, which are all implicated in HD pathology.[232] Stimulation of the adenosine A2A receptor (A2AR) has been shown to ameliorate neurodegeneration and several major HD symptoms in rodents.[233, 234] However, A2AR levels are significantly reduced in the HD putamen of human brains potentially due to hypermethylation and decreased hydroxymethylation of the adenosine a2a receptor (ADORA2A) gene.[235]

HDAC inhibition is a major mechanism of neuroprotection in HD. Various chemical HDAC inhibitors such as SAHA, sodium butyrate, 4-PBA and TSA have been shown to ameliorate motor dysfunction, cognitive deficits or the neurodegenerative phenotype in transgenic C.

elegans, *Drosophila* and mouse models of HD.[236–242] Treatment with the HDAC inhibitor 4b was shown to reduce hypoacetylation of H3 and H4, and diminish transcriptional abnormalities caused by mutant HTT in the striatum, cortex and cerebellum of HD transgenic mice.[243] The 4b treatment was additionally shown to improve motor function and decrease brain atrophy in HD mice.[243] While chemical HDAC inhibition has proven to be effective in ameliorating HD deficits, studies employing genetic knockdown of various HDACs in HD are not clear. For example, knockout of HDAC4, HDAC6, or HDAC7 were not effective in ameliorating neurodegeneration in transgenic HD mouse models.[244–246] Similarly, while HDAC3 chemical inhibition has been shown to have a therapeutic effect in HD, HDAC3 knockout was not effective in reducing transcriptional dysregulation or HTT aggregation in transgenic HD mice and increased nuclear HTT aggregates in HeLA and 293T cells expressing mutant HTT.[241, 247, 248] Alternatively, RNA interference-mediated HDAC3 knockdown suppressed polyglutamine toxicity in a C. *elegans* model of HD using neuronal expression of mutant HTT with expanded polyglutamine repeats.[239] These opposing results highlight the complexity of HDACs in HD as chemical inhibitors may target multiple HDACs, HDAC isoforms differ in target specificity and efficacy, and chemical and genetic inhibition have been shown to have differential compensatory mechanisms.[249]

Levels of brain-derived neurotrophic factor (BDNF) that is essential for striatal neuronal survival is severely reduced in the brain of HD patients.[250–253] HTT is known to interact and recruit the repressor element-1 transcription factor (REST) complex (REST/coREST/Sin3A/HDAC1/HDAC2) to the cytosol which consequently allows BDNF gene expression.[252, 253] A study assessing REST levels in brain tissues of HD patients found that cytoplasmic REST levels are reduced in neurons of the cortex and caudate of HD patients.[254] Studies in mice have shown that the HTT mutation in HD causes the REST complex to accumulate in the nucleus, thereby silencing BDNF and contributing to neuronal death.[253] In addition to BDNF, loss of several REST-controlled genes involved in neuronal maintenance have been observed in both the mouse and human HD brain.[253] Since REST silencing occurs via HDAC-dependent chromatin remodeling, HDAC inhibitors that may also target REST activity may by therapeutically beneficial.

Differential expression of miRNAs has been observed in the brain and blood of HD patients and animal models of HD.[255–260] MiR-9 was decreased in the cortices of HD patients and was shown to target REST and coREST in neuronal precursor cells.[261] In a transgenic non-human primate model, miR-128 was downregulated from the time of birth and was shown to interact with HTT and huntingtin interacting protein 1 (HIP1).[262] Other studies have implicated the miR-10b family which is upregulated in the serum and brain of HD patients.[255, 263–265] In silico analysis revealed that miR-10b-5p targets BDNF, which displays reduced levels in HD leading to neuronal dysfunction.[264] MiR-10b-5p expression in the prefrontal cortex has been correlated with HD age of onset in HD patients.[263] This indicates that miR-10b-5p could serve as an important biomarker in HD treatment; however, it has not been examined in peripheral fluid.

Evidence of other miRNAs with potential involvement in HD pathology include miR-137, miR-148a and miR-214 which have been shown to directly target HTT and reduce HTT

protein levels in HEK293T cells.[266] In STHdh(Q111)/Hdh(Q111) cells, miR-214 was also responsible for the downregulation of β-catenin often seen in HD.[267] MiR-196a has been identified as significantly upregulated in HD[265] and bioinformatics analyses indicated it may target inflammation and apoptosis-related pathway.[263, 268, 269] MiR-196a overexpression was shown to increase neurite outgrowth in neuroblastoma cells[269] and suppress Ran-binding protein 10 (RANBP10), a protein which is elevated in HD mice.[270] MiR-196a also suppressed apoptosis in neural progenitor cells and differentiated neural cells in HD non-human primates.[271] In STHdh(Q111)/Hdh(Q111) cells, increased levels of p53 led to downregulation of miR-146a.[272] Subsequent overexpression of miR-146a attenuated cell cycle abnormalities and decreased apoptosis in the same cell model.[273] Similarly, in the R6/2 mouse model, miR-34a-5p levels have been shown to decrease with increased p53 expression, although the relationship between p53 and miRNA expression has not been elucidated.[274]

Downregulation of miR-22 was observed in the brains of both YAC128 and R6/2 transgenic mice.[257] In vitro, miR-22 has been shown to provide neuroprotection in multiple primary striatal and cortical cell models of HD including mHTT and 3-NP exposure by reducing caspase activation and apoptosis.[275] MiR-132 overexpression in the striatum of R6/2 mice was neuroprotective and delayed disease progression despite having no effect on mutant HTT.[276] MiR-27a overexpression in R6/2-derived neuronal stem cells decreased mHTT aggregates, potentially by upregulating multidrug resistance protein 1 (MDR-1), a transporter of mHTT.[277] Lastly, overexpression of an artificial miRNA targeting mHTT in sheep expressing human HD CAG repeat decreased HTT levels by 50–80% at 1 and 6 months following treatment.[278] This study supports the therapeutic potential of miRNA modulation in the large animal brain.

One study identified the existence of a natural antisense HTT transcript (HTTAS), which manifests in two splice variants HTTAS_v1, containing exons 1 and 3, and HTTAS_v2, containing exons 2 and 3.[279] Up to 50% loss of HTTAS_v1 has been observed in the human HD frontal cortex and depending upon levels of overexpression and HTTAS_v1 repeat length, HTT can be decreased by 20–90% in HEK293 and SH-SY5Y cells.[279] Multiple mouse models of HD have shown decreased levels of the lncRNA Abhd11os.[280] Lentiviral-mediated overexpression of Abhd11os was neuroprotective, while knockdown of Abhd11os exacerbated mHTT toxicity.[280] Other differentially expressed lncRNAs identified in cell and animal models are maternally expressed 3 (MEG3) and NEAT1.[281–283] NEAT1 levels were increased in the brains of HD patients and R6/2 mice and NEAT1 overexpression in neuroblastoma cells was shown to protect against H_2O_2-induced oxidative stress.[282] Similarly, NEAT1 overexpression protected neuroblastoma cells cotransfected with HTT expression plasmids from cytotoxicity.[284] However, knockdown of NEAT1 or MEG3 was also shown to decrease mHTT aggregation and p53 expression in neuroblastoma cells[281], indicating the roles of these lncRNAs in HD needs to be studied further.

EPIGENETICS AND ACUTE BRAIN INJURY

Ischemic Stroke

Stroke is a major cause of death and disability worldwide.[10, 285] Ischemic stroke (cerebral ischemia) is caused by the blockage of blood flow to the brain and results in energy depletion, mitochondrial dysfunction, excitotoxicity and ultimately cell death. During the reperfusion phase, return of the blood supply introduces inflammatory factors and induces oxidative stress which then cause secondary brain damage.[286–288] Following ischemia/reperfusion injury, the cells within the penumbra (the area surrounding the infarcted core) are destined to die; however, some if not all, have the ability to recover if given therapeutic intervention.[289, 290] At this time, recombinant tissue plasminogen activator (TPA) is the only stroke medication approved for treatment.[291, 292] TPA works to digest clots through the degradation of fibrin[293, 294]; however, no significant decrease in mortality has been shown after treatment and increased incidence of intracerebral hemorrhage is linked to TPA.[295] Recent studies showed that epigenetic changes play a significant role in modulating secondary brain damage and neurological dysfunction following stroke and hence may represent much-needed potential stroke therapeutic targets (Table 4).

The contribution of DNA hypermethylation to poor outcomes after cerebral ischemia has been well characterized. After middle cerebral artery occlusion (MCAO) induced focal ischemia in mice, levels of 5-mC were shown to be elevated in the striatum and cortex of mice.[296] Heterozygous DNMT knockout mice or mice heterozygous for a mutant DNMT allele showed smaller infarcts after mild ischemic damage.[296, 297] Furthermore, treatment with the DNMT inhibitor 5-aza-dC or other demethylating agents protected wild-type rodents after focal ischemia.[296, 298, 299] However, in a severe ischemic mouse model, DNMT expression was not increased nor were mice protected by DNMT gene deletion.[296] Interestingly, genomic methylation has been shown to be better predictor of biological age and stroke outcome than chronological age.[300, 301]

Recent studies also evaluated the role of 5-hmC in post-stroke brain damage. Following MCAO in mice, 5-hmC increased quickly after reperfusion (by 5 min) and remained elevated up to 2 days of reperfusion following focal ischemia.[32, 302] It was observed that the post-stroke induction of 5-hmC was mediated by TET3 in the peri-infarct region or TET2 in the whole brain.[32, 302] Pharmacological or genetic inhibition of 5-hmC exacerbated ischemia/reperfusion injury, while TET activation via ascorbate enhanced the expression of protective genes, prevented degeneration, and improved motor function recovery after focal ischemia.[302] A recent study in mice reported that 5-hmC is increased in the mitochondrial genome after focal ischemia where it may influence mitochondrial gene expression and ATP levels.[303]

Inhibition of histone deacetylation was shown to protect the brain after stroke. VPA administration prevented deacetylation of H3 and H4 and ameliorated hippocampal CA1 neuronal death after global ischemia in adult rats.[304] Treatment with VPA or sodium butyrate or TSA was shown to inhibit microglial activation, downregulate nitric oxide synthase and upregulated heat shock proteins leading to improved behavioral outcomes and reduced infarct volume in a rats following permanent MCAO.[305] Importantly, VPA and

sodium butyrate were shown to be most beneficial when given at 3 to 6 h of reperfusion after focal ischemia in rodents indicating the translational potential of these drugs in stroke therapy.[305] Administration of SAHA following transient MCAO in mice was shown to suppress ischemia-induced H3 deacetylation which led to decreased proinflammatory levels of cytokine IL1β and increased levels of the chaperone HSC70.[306] SAHA treatment also decreased size of the infarction after transient MCAO.[306] Pre- or post-stroke treatment with the HDAC inhibitor 4-PBA was also shown to reduce infarct volume significantly in a mouse model of hypoxia-ischemia.[307] An *in vitro* study using white matter cells isolated from the mouse optic nerve showed that HDAC inhibitor treatment (SAHA or MS-275) before or after oxygen glucose deprivation (OGD) preserved white matter architecture and reduced excitotoxicity.[308]

Several rodent studies have shown that miRNAs are significantly altered within the brain after cerebral ischemia.[309–311] Additional studies have identified a number of miRNAs involved in various aspects of stroke pathophysiology including excitotoxicity (miR-223, miR-107, miR-125b), oxidative stress (miR-23, miR-99), apoptosis (miR-21, miR-25, miR-15, miR-497, miR-29), edema (miR-29, miR-9, miR-375, miR-150, miR-130, miR-320) inflammation (miR-22, miR-203, miR-9, miR-132), neurogenesis (miR-17) and angiogenesis (miR-107, miR-376, miR-140).[312] Several key miRNAs studied within the field of stroke are discussed in more detail below.

Both focal and permanent ischemia have been shown to reduce miR-424 expression in the plasma of stroke patients and within the blood and brain of rodents.[313, 314] Overexpression of miR-424 was shown to reduce focal ischemia-induced oxidative stress and infarct in the mouse brain by increasing Nrf2 and MnSOD.[314] In a mouse model of permanent focal ischemia, miR-424 overexpression reduced edema and inflammatory processes by inhibiting microglial activation.[313] MiR-424 expression was increased in human endothelial cells subjected to hypoxia and promoted angiogenesis by stabilizing HIF-1α. In the plasma of stroke patients, miR-424 levels were upregulated in lymphocytes and neutrophils, which was negatively correlated with TNF-α, IL-10, and IGF-1 expression as well as infarct size.[315] Several studies have shown that miR-124 is increased after stroke and delivery of a miR-124 mimetic confers neuroprotection in both transient MCAO and OGD models.[316–318] MiR-124 was shown to promote angiogenesis and inhibit excitotoxicity, apoptosis, BBB damage, and inflammation through modulation of glutamate receptors[319, 320], Notch signaling[321], DNA repair protein Ku70[322], REST inhibition, calpain reduction[316], PI3K/AKT activation[323], upregulation of antiapoptotic proteins[317], and regulation of and M2-like microglia/macrophage activation[318] in several *in vitro* and *in vivo* models of rodent cerebral ischemia. MiR-155 was shown to upregulate inflammatory cytokines like IL-10, IL-4, and IL-6 in mice[324] and increase apoptosis through the Rheb/mTOR pathway in rats[325] following focal ischemic injury. Inhibition of miR-155 significantly decreased infarction in mice following transient MCAO by increasing nitric oxide (NO) production and the expression of Notch1 and endothelial NO synthase.[326, 327]

While the miRNAs discussed above have shown consistent roles in animal models of cerebral ischemia, the impact of other key miRNAs is more complex. For example, following mouse transient focal ischemia, miR-181a increased within the infarcted region

where it was shown to negatively regulate binding immunoglobulin protein (GRP78/HSPA5), a protein involved in ER function and inhibition of apoptosis.[328, 329] However, within the penumbra, miR-181a expression decreased and positively regulated GRP78, implicating miR-181a in ischemic pathogenesis as well as ischemic recovery.[328] The evidence thus far indicates that miR-181 inhibition is protective as it has been shown to reduce infarct and inflammation by decreasing glutamate transporter 1 (GLT-1), apoptosis and mitochondrial dysfunction in rodent models of cerebral ischemia.[330–332] Similarly, miR-210 has been implicated in both protection and injury following cerebral ischemia. For example, miR-210 overexpression has been shown to upregulate BDNF levels, reduce neuronal apoptosis and improve neurological severity scores following transient focal ischemia in rats and mice.[333, 334] However, both pre- and post-MCAO inhibition of miR-210 improved neurological outcomes by reducing inflammation following mouse transient MCAO.[335]

As with neurodegenerative disorders, a significant effort has been made to develop biomarker procedures that can identify stroke with minimal invasiveness. MiRNA profiles have been established in serum[336–341], plasma[342–346], whole blood[347–349], exosomes[350], and CSF.[341] MiR-145[339, 340, 348] and let-7e[341, 347] were identified as key miRNAs in multiple profiling studies. Based off the miRNA let-7e in serum, Peng et al. was also able to predict acute stroke in patients with 73.4% sensitivity and 82.8% specificity.[341]

Several studies have also been carried out to profile changes in lncRNA expression after stroke.[351, 352] These studies implicate lncRNAs associated with genes involved in lipoprotein production, ABO blood type, prostaglandin synthesis, hematopoietic cell lineage, and glycolysis/gluconeogenesis.[351, 352] Several lncRNAs have been shown to play significant roles in cerebral ischemia pathology. For example, MEG3 was increased following cerebral ischemia in mice where it was shown to bind p53 and promote post-ischemic neuronal death.[353] MEG3 silencing reduced infarct size, improved neurological scoring, and promoted angiogenesis in rats and mice subjected to MCAO.[354, 355] MEG3 has been implicated in apoptosis by targeting the miR-21/programmed cell death 4 pathway.[355] ANRIL (CDKN2BAS) overexpression in diabetes mellitus rats upregulated VEGF, NF-κB, p-IκB/IκB and stimulated angiogenesis following MCAO.[356] FosDT has been shown to increase following focal ischemia and associates with the chromatin modifying proteins sin3a and coREST to induce REST.[357] Knockdown of FosDT and REST have been shown to decrease infarct size and improve functional recovery up to 7 days of reperfusion following focal ischemic injury.[357, 358] Other lncRNAs implicated in ischemic stroke include H19, which provided BV2 cells neuroprotection following OGD when silenced[68], N1LR, which prevented apoptosis in neuroblastoma cells when overexpressed[359], and GAS5, which provided neuroprotection via decreased competition with miR-137 following MCAO in mice or OGD in cortical neurons when overexpressed.[360]

A key lncRNA identified in cerebral ischemia is MALAT1 (a.k.a NEAT2) which has been shown to be upregulated after OGD and MCAO.[67, 361] Knockout of MALAT1 increased pro-apoptotic and pro-inflammatory factors and infarct size, and has been shown to directly associate with Bim and E-selectin following MCAO in mice.[67] MALAT1 was shown to mediate autophagy and protect brain microvascular endothelial cells after OGD treatment.

[362] Conversely, MALAT1 inhibition downregulated autophagy, which induced neuroprotection following MCAO in mice[363] indicating MALAT1 involvement in cerebral ischemia is complex and warrants additional research.

Hemorrhagic Stroke

Subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) are two cerebrovascular events resulting in bleeding of the tissue around the brain and bleeding within the brain tissue, respectively. Hemorrhagic strokes account for only a small portion of strokes, but lead to high rates of disability[364, 365], appear earlier in life than ischemic events[365–367], and are responsible for over 25% of potential years of life lost to stroke.[368, 369] Not only do hemorrhagic strokes often lead to secondary cerebrovascular events like vasospasms, ischemia, and hydrocephalus[365, 370–373], but they also cause non-neurological complications like heart, lung, kidney, and liver injury or failure.[365, 374] Risk factors for SAH and ICH include inflammation[375], malformations and tumors[376], anticoagulation medication[377], and heavy alcohol consumption.[378] Lack of screening technology and the reliance on surgical approaches for treatment are major contributors to the devastating effects of these brain bleeds.[379–381] Epigenetics alterations represent potential mechanisms through which hemorrhagic stroke may not only be detected, but also treated (Table 5).

Research on the role of DNA methylation in hemorrhagic stroke is still in its infancy, but a few studies indicate this epigenetic modification may play a role in hemorrhagic stroke pathology. For example, ITPR3, a gene involved in vasospasms caused by SAH[382], was significantly hypermethylated in patients that experience delayed cerebral ischemia following SAH.[383] In addition, SAH patients with delayed cerebral ischemia had higher levels of DNMT1 as well as lower levels of ITPR3 mRNA and TET1.[383] In an autologous blood injection model of mouse ICH, TET1, TET2, TET3 and 5hmC were downregulated from 24–72 hours following hemorrhage.[384] AKT2, PDPK1, and VEGF genes displayed decreased hydroxymethylation and increased methylation, resulting in a downregulation of AKT2, PDPK1 and VEGF expression.[384]

Histone modifications relating to brain bleeds like SAH and ICH have not been thoroughly explored; however, as with each disorder and injury discussed in this review, HDACi may be a promising therapeutic strategy. SAHA administration after spontaneously induced ICH in mice was shown to not only reverse H3 hypoacetylation but also decrease apoptosis, hemin-induced cytotoxicity, behavior deficits, and microglial and astrocytic activation.[385] Similar to the neuroprotective effects of SAHA, VPA administration in a rat model of ICH inhibited inflammation and caspase activity, upregulated BCL-2 and BCL-XL while downregulating BAX.[386]

Despite the lack of classical epigenetic marker studies in SAH and ICH, several studies have been performed assessing the role of noncoding RNAs. Extensive research into circulating biomarkers for hemorrhagic stroke has been conducted. A serum study evaluating miRNA levels has shown that miR-502–5p, miR-1297 and miR-4320 levels are higher in SAH patients when compared to control groups.[387] Furthermore, miR-502–5p and miR-1297 were even significantly higher in those with severe SAH when compared to non-severe SAH.[387] Another serum study identified 86 differently expressed miRNA, 69 upregulated

and 17 downregulated, between three severities of intracranial aneurysms and the healthy control group.[388] Important gene pathways found in this study included smooth muscle cell proliferation, apoptosis, myosin generation, and actin cytoskeleton organization.[388] Plasma studies have identified miR-16 and miR-25 as dysregulated in intracranial aneurysm patients[389] while inflammatory miRNAs are most pronounced in ICH patients.[390] Studies in intracranial aneurysm tissue showed aberrations in several miRNA in common including miR-23b, miR-24–1, and isoforms of miR-143 and miR-145.[391, 392] These studies both indicate gene networks involved in smooth muscle cell proliferation and movement may be involved.[391, 392] Finally, potential biomarkers in cerebrospinal fluid[393–395] and animal models[396, 397] have also been proposed.

After ICH, plasma and brain tissue levels of miR-124 were increased followed by a slow decrease with patient recovery.[398] This is mirrored in an induced ICH rat model, with miR-124 levels returning to normal by day 60.[398] In an erythrocyte lysate model of ICH, miR-124 was significantly downregulated in microglia.[399] However, when microglia were transduced with miR-124, M1 markers decreased, M2 markers increased, and microglia-induced cytotoxicity of neurons decreased.[399] In vivo, mimics of miR-124 also reduced water content of the mouse brain.[399] This study further showed that miR-124 acts by way of BCL-2, BCL-XL, and C/EBP-α to produce these neuroprotective effects.[399]

In ICH and SAH, let-7a and let-7c also play important roles and have shown to have neuroprotective efficacy. In both thrombin-induced cytotoxicity models and induced ICH rat models, let-7c was significantly upregulated.[400] Administration of a let-7c antagomir reduced numbers of MPO+ neutrophils and OX42+ microglia in the basal ganglia and cortex.[400] In addition, let-7c antagomir treatment improved functional outcome and decreased cell death by restoring IGF1 and p-AKT.[400] In the endovascular perforation SAH mouse model, melatonin improved neurological scores and reduced brain water content through the H19 lncRNA, which associates with let-7a and the let-7a target NGF.[401]

A number of other miRNAs that have shown therapeutic potential by modulating inflammatory responses have also been identified. Administration of miR-126–3p mimic reduced MPO+ neutrophils, OX42+ microglia, and apoptosis in ICH rats.[402] Restoration of miR-126 in ICH rats showed neuroprotection, by VEGF upregulation and caspase-3 inhibition.[403] MiR-144 upregulation in ICH mice was shown to downregulate the mTOR pathway.[404] Inhibition of miR-144 with an antagomir reduced autophagy and inflammation as well as improved function in ICH mice.[404] Augmentation of miR-132 in ICH mice reduced brain edema and restored integrity to the BBB.[405] MiR-233 was shown to directly bind to and downregulate NLRP3 of the inflammasome after ICH in mice[406], providing another mechanism through which inflammation can be prevented. Finally, restoration of miR-27a-3p levels after collagenase-induced ICH in rats improved functional recovery by inhibiting aquaporin-11, increasing BBB integrity, and decreasing edema.[407]

Dysregulation of lncRNA expression has been observed in several models of hemorrhagic stroke. A study in rats found 64 upregulated and 144 downregulated lncRNA in early brain injury after SAH.[408] In mice, SAH led to upregulation of 103 lncRNAs and downregulation of 514 lncRNAs.[409] A preliminary study on ICH in rats found 625 differentially expressed

lncRNA corresponding to 826 mRNA.[410] Within human studies, 2926 differentially expressed lncRNA were identified in intracranial aneurysm tissue and superficial temporal arteries.[411] However, further research is needed to identify the specific roles of lncRNAs in hemorrhagic stroke pathogenesis.

Traumatic Brain Injury (TBI)

Traumatic brain injury (TBI) affects nearly 4 million Americans each year and accounts for a large percentage of injury-related deaths.[412] Diffuse brain injuries, affecting the entire brain, and focal brain injuries, affecting a specific area of the brain, are most commonly caused in the field of battle or motor vehicle accidents.[412–415] TBI presents with a host of neurological symptoms from contusions and hemorrhage to mood changes and memory loss.[412, 413, 416] At the molecular level, homeostasis of excitatory neurotransmitter release is disrupted, axonal stretching and shearing occurs, and neurodegenerative pathology like amyloid plaques may appear.[412, 417–421] Although the epigenetic study of TBI is in its infancy, results pointing towards therapeutic intervention are promising (Table 6).

In a weight drop model of TBI in adult rats, global cellular DNA hypomethylation was observed within 24 hours and up to 48 hour post-injury.[422] Activated microglia/macrophages were identified as the major source of the reduced 5-mC in the peri-lesion area.[422] Within repeated blast-injury model of TBI in rats, significant differential methylation between neurons and glia has been shown in the transforming growth factor β (TGF-β) pathway, which includes genes like MAP2K6, RUNX3, NODAL, and SMAD1 which regulates cell survival.[423] Hypermethylation and decreased expression of the aralkylamine N-acetyltransferase AANAT gene that mediates serotonin-to-melatonin conversion was also observed.[423] In blast-induced TBI in rats, there was a negative correlation between blast severity and global DNA methylation levels in the hippocampus, indicating that the degree of injury may influence methylation imbalance.[424] In a rat blast model of TBI, hippocampal DNMT1, DNMT3b, TET2, TET3 and TDG expression increased while prefrontal cortical DNMT3b expression was decreased and TET2 expression was increased two weeks following injury.[425] In addition, controlled cortical impact (CCI) induced TBI in rats upregulates insulin-like growth factor 1B (IGF-1B) hippocampal and cortical mRNA levels.[426] Three days after injury, when IGF-1B mRNA levels are highest, the P1 promoter region and sites upstream/within exon 5 are hypermethylated while the P2 promotor region is unchanged and sites downstream of exon 5 are hypomethylated with respect to sham animals.[426] IGF-1B has been implicated in neural plasticity and regeneration and is considered as a potential therapeutic target after TBI.[427]

Several epigenetic marks of histone acetylation that activate gene expression including H3k9ac and H3K4me3 at the P1 promoter region, H3K9ac, H3K14ac, H3K36me3, and H3K4me3 at the P2 promoter region, and H3K9ac, H3K36me3, and H3K4me3 at exon 5 of IGF-1B are also increased after CCI injury in rats three days after injury.[426] In the hippocampal CA3 region, both acetylation and methylation were decreased 6–72 hours after CCI injury in another rat study.[428] Following closed head injury TBI in mice, administration of the HDAC inhibitor ITF2357 was shown to be neuroprotective by preventing H3 deacetylation.[429] Several other HDAC inhibitors were also tested after TBI. VPA decreases

lesion volume and improves motor function in rats subjected to CCI TBI.[430, 431] Combined administration of sub-effective VPA and lithium doses had the same influence on mice subject to CCI injury.[432] Fluoxetine induces neurogenesis in CCI injury mice; however, no improvement in gait or spatial learning and memory is seen.[433] Furthermore, sodium butyrate administration to mice subject to CCI injury increases histone acetylation, but does not significantly improve function unless combined with behavioral training.[434]

Several studies have shown that dysregulation of hundreds of miRNAs occurs in the rodent hippocampus and cortex following TBI as early as 1 hour, and up to 7 days post injury.[435–440] Distinctive miRNA expression profiles have been observed in a temporal manner following TBI, indicating the association of various miRNAs with differing stages of TBI progression. Altered miRNAs have been associated with processes that regulate transcriptional regulation, oxidative stress, metabolism, synaptic signaling and signal transduction, inflammation, neurogenesis, angiogenesis and apoptosis.[435, 437, 439] Interestingly, a mouse study using a weight drop model of TBI, showed that differential expression of miRNAs may also be observed depending on the severity of TBI.[441]

A study performed in the rat hippocampus found 10 miRNAs that were consistently altered from 1 hour to 7 days following moderate TBI. Of these, miR-144, miR-153 and miR-340–5p were elevated and their predicted targets calcium/calmodulin-dependent serine protein kinase, nuclear factor erythroid 2-related factor (Nrf2) and alpha-synuclein were downregulated, respectively.[437] Although the roles of miR-144, miR-152 and miR-340–5p in TBI have not been evaluated, their targets have been shown to play important roles in neuroprotection and are implicated in learning and memory following TBI in rats.[437, 442] Other miRNAs with important roles in TBI include miR-23a and miR-27a which have been shown to reduce apoptosis and modulate autophagy in a neuroprotective manner following overexpression or mimetic treatment in rodent models of TBI.[443–445] MiR-124–3p was shown to increase in microglia and microglial exosomes from mouse brain extracts after treatment with repetitive CCI injury.[446] Administration of exosomes derived from microglia overexpressing miR-124–3p improved mice neurological recovery following repetitive CCI by downregulating mTOR and reducing inflammation.[446] Let-7c-5p overexpression was also shown to reduce inflammatory processes by attenuating microglial activation, which led to reduced brain edema improved neurological scores in mice subjected to CCI.[447] Interestingly, miR-155 has been shown to be both neuroprotective[448, 449] and damaging to the brain.[450] The differences in experimental design may have led to these results as the first study tested miR-155 knockout mice with CCI[448], the second used the formononetin drug to modulate miR-155 in rats using weight drop injury[449] and the third tested RNA silencing of miR-155 in mice with CCI.[450]

Other studies have shown that miR-21 expression is consistently upregulated from 6h to 72h in the cortex and from 24h to 72h in the hippocampus following CCI in rodents[436, 440, 451], indicating miR-21 may play a pivotal role in pathology of TBI progression. In a study evaluating age differences, miR-21 was upregulated in adult mice subject to brain injury; however, miR-21 was not altered following injury in elderly mice.[452] Despite increased expression of miR-21 upon TBI, miR-21 mimetic administration has been shown to be neuroprotective against scratch-cell injury in cortical neurons[453] as well as rats subjected to

fluid percussion.[454] Co-culture of scratch-injured neurons with miR-21–5p-overexpressing neurons or administration of miR-21–5p overexpressing exosomes was also neuroprotective.[455] Finally, MiR-21 mimic administration in rats with or without hydrogen gas treatment improved functional outcome following CCI or fluid percussion injury, respectively.[456, 457] In addition to hippocampal tissue, miR-21 expression increased in extracellular vesicles after TBI, suggesting its promise in future biomarker screens.[458]

There have been several attempts to establish miRNA profiles to serve biomarker development. Differential expression has been surveyed in serum[459–462], plasma[463–467], CSF[462, 468–470], saliva[468], and extracellular vesicles[471] of humans and animals. Several therapeutic interventions such as exercise hypothermia have been shown to alter the miRNA profiles and improve cognitive function and recovery following TBI in rodents.[472–474] The let-7 family has been involved in multiple studies[467, 469] and may prove to be a promising pathway in TBI.

Emerging evidence indicates lncRNAs may be implicated in TBI. Microarray studies have revealed significant alterations in lncRNA expression in the brain following rodent models of TBI.[475–477] Administration of MALAT1 deficient exosomes derived from adipose stem cells caused rats to develop larger lesions following CCI.[478] Bioinformatics analysis revealed that MALAT1 might modulate pathways related to inflammation and cell regeneration, indicating potential therapeutic effects of MALAT1 in TBI.[478] In mice subjected to CCI, NEAT1 overexpression inhibited apoptosis and inflammation, while knockdown of NEAT1 downregulated hundreds of genes, many of which are involved in synaptic and axonal health.[479]

Epilepsy

Epilepsy, a group of neurological disorders characterized by recurrent seizures, affects 50 million people globally.[480, 481] Epilepsy encompasses both focal and generalized seizures; however, most common is temporal lobe epilepsy (TLE) which often presents with hippocampal sclerosis.[481–484] Epilepsy can be brought about by trauma, an infection, or improper neurodevelopment leading to neuronal hyperexcitability that can lie latent for years.[481, 485] The disorders are commonly marked by anxiety, cognitive defects, and decreased social interaction.[481, 486, 487] Although antiepileptic drugs are given to reverse excitability, they do not target the root cause of the disorder and over 30% of patients become drug resistant.[483, 485, 488, 489] In addition, surgical intervention has a nearly 50% failure rate.[483, 490] Target genes in epileptogenesis that lead to several pathways of dysfunction have been established, including synaptic plasticity, ion transport, and inflammation, suggesting epigenetic therapies may be possible (Table 7).[483, 491–497]

There have been several attempts to characterize DNA methylation within epilepsy. Global hypermethylation has been observed in epileptic human and mouse hippocampal specimens affecting pathways such as neuron remodeling and maturation.[498, 499] Levels of DNMT1 and DNMT3a were increased in human TLE neocortices specifically in NeuN-positive neurons, but not GFAP-positive astrocytes.[500] Comparisons of brain tissue between drug-refractory epileptic patients and control patients showed differential methylation of 224 genes.[501] A ketogenic, high fat, low carbohydrate diet was shown to reverse global

hypermethylation and ameliorate seizure progression in pilocarpine-induced epileptic rats[499], indicating that aberrant methylation promotes pathology. Interestingly, induction of epilepsy in rats through focal amygdala stimulation, systemic pilocarpine injection, or lateral fluid-percussion induced traumatic brain injury did not result in a similar spatiality or degree of methylation despite global hypermethylation across all three models.[502] This suggests that although global hypermethylation is a general feature of epilepsy, distinct DNA methylation patterns exist depending on etiology.[502]

In humans with focal epilepsy and febrile seizures, the promoter of carboxypeptidase 6 (CPA6), a gene involved in familial and sporadic cases of epilepsy, is highly methylated compared to controls.[503] Patients with TLE were shown to have increased reelin promoter methylation, a gene important to hippocampal development.[504] Subjects with juvenile myoclonic epilepsy have varied methylation of cation-chloride transporters, with lower sodium-potassium-chloride cotransporter 1 methylation and higher potassium-chloride transporter member 5 methylation in the epilepsy group.[505] Increased methylation of ionotropic glutamate receptor 2 (GRIA2) has been observed in hippocampal slices of mice and rats subjected to kainic acid-induced epilepsy, which was reversed with administration of the DNMT inhibitor RG108.[506] TLE patients and pilocarpine-induced epileptic rats display decreased levels of Ras-guanine nucleotide-releasing factor 1 (RASgrf1) in the neocortex and hippocampus, respectively.[507] In mice subject to acute epileptic seizures using kainic acid, the RASgrf1 promoter was methylated, suppressing levels of RASgrf mRNA; however, treatment with the DNMT inhibitor RG108 reversed this trend as well as reduced seizures.[508] During memory consolidation in kainic acid-induced TLE rats, methylation of BDNF was significantly decreased leading to an upregulation of BDNF mRNA and increased memory deficit; however, following administration of methionine, BDNF methylation was increased, BDNF mRNA was decreased, and memory deficits were reversed.[509]

The methylation pattern of noncoding gene promoters has also been studied. In human hippocampus specimens, 12 differentially methylated miRNA were discovered, with half hypomethylated and upregulated and half hypermethylated and downregulated.[498] This same study found hypermethylation of several lncRNAs including UCA1, ADARB2-AS1, LINC324, and MAP3K14-AS1.[498] In a study characterizing epileptic whole blood samples, 87% and 85% of differentially methylated lncRNA and miRNA promoters were hypermethylated, respectively.[510] Differentially methylated lncRNA were related mRNAs involved in ion/gated channel activity, GABA receptor activity, and synaptic transmission while differentially methylated miRNA were related to neuronal projection and differentiation, protein kinase activity, and axonal guidance.[510]

Several studies have attempted to characterize the landscape of histone modifications within epilepsy. Expression of HDAC5 and HDAC9 was shown to increase significantly in mice subject to kainic acid, while expression of HDAC5 and HDAC9 decreased in pilocarpine-induced epileptic mice.[511] In addition, both epileptic groups of mice showed a sharp decrease in HDAC7 expression during the acute seizure period.[511] Kainic acid-induced epileptic mice displayed decreased HDAC1, 2, and 11 expression in the acute phase (2–6h after kainic acid treatment) followed by a subsequent increase of all class I HDACs from 12–

48 hours.[512] Pilocarpine-treated mice model showed similar acute results, but HDAC2, 3, and 8 were decreased during the chronic phase (14 and 28 days following pilocarpine treatment).[512] In rats, pilocarpine exposures led to decreased hippocampal acetylation of H4 at the GRIA2 promoter, downregulating GRIA2 mRNA expression.[513] However, administration of the HDACi TSA reversed deacetylation and prevented GRIA2 mRNA downregulation.[513] Interestingly, this study also found that H4 acetylation increased at the BDNF promoter P2.[513] The findings of this study complement the previously discussed methylation studies and point to both DNA methylation and histone acetylation playing a role in GRIA2 and BDNF levels in epilepsy.

Rodent studies have shown promise for HDACi treatment in epilepsy. Administration of SB or VPA in WAG/Rij rats (a model for absent epilepsy that displays H3 and H4 hypoacetylation) increased brain histone acetylation, decreased HDAC1 and HDAC3 expression, and reduced seizures.[514] Furthermore, the protective effects were intensified by co-administration of SB and VPA.[514] SB was also used in a mouse kindling model of TLE which showed decreased HDAC expression, reduced seizures, and decreased mossy fiber sprouting.[515]

The field of noncoding RNA within the pathogenesis, prediction, and prevention of epilepsy has been extensively explored. MiR-134 has been found to be an important factor in dendritic spine density and morphology in pilocarpine- or kainic acid-induced mouse models of epilepsy.[516, 517] MiR-134 inhibition reduced seizures in multiple rodent models of epilepsy.[516–518] In the pilocarpine mouse model of status epilepticus, dendritic spine volume increased upon administration of a cholesterol-tagged locked nucleotide acid (LNA) miR-134 antagomir in CA3 pyramidal neurons.[516] Pre-treatment with the LNA antagomir and subsequent induction of status epilepticus resulted in increased survival and decreased seizures.[516] Another study showed that miR-134 LNA antagomir reduced dendritic spine density in CA3 pyramidal neurons, but still prevented seizures in kainic acid-treated mice.[517] In the mouse pentylenetetrazol-induced model of epilepsy, LNA miR-134 antagomir treatment reduced the number of spontaneous seizures and convulsive behavior.[518] Similarly, rats subjected to the perforant pathway stimulation model showed reduced spontaneous seizures with LNA miR-134 antagomir treatment.[518]

Status epilepticus induced by kainic acid in mice was shown to increase levels of miR-132 as well as its binding to Argonaute-2.[519] Subsequent inhibition of miR-123 with an LNA antagomir reduced hippocampal neuronal death.[519] MiR-124 was significantly reduced after kainic acid induction in rats and subsequent supplementation with synthetic miR-124 inhibited NSRF, effectively contributing to neuroprotection against epilepsy.[520] However, miR-124 supplementation also promoted inflammation, by enhancing microglia activation, effectively contributing to the epileptic state.[520] Another study showed that intrahippocampal administration of miR-124 reduced the severity and occurrence of seizures in both the pentylenetetrazole- and pilocarpine-induced rat models of epilepsy by repressing of CREB, a key protein in epileptogenesis.[520, 521] Importantly, it has been shown that miR-124 was decreased in the hippocampus of adult patients with TLE[520], while miR-124 was upregulated in the hippocampus of children with mesial TLE[522], revealing dynamic differences of this miRNA with age and etiology.

Pilocarpine-induced temporal lobe epilepsy in mice resulted in the upregulation of 22 lncRNA and downregulation of 83 lncRNA in the hippocampus.[523] Another mouse study identified the dysregulation of 384 lncRNA in the pilocarpine model and 279 in the kainic acid model when analyzing whole brain, olfactory bulb, and cerebellum tissue.[524] The lncRNA UCA1 was shown to increase in tandem with NF-κB after pilocarpine-induced epilepsy in the brain of rats[525] and UCA1 overexpression inhibited apoptosis and suppressed seizures.[526] Finally, the lncRNA H19 is significantly upregulated in the latent period of pilocarpine-induced and kainic acid-induced epilepsy in rats where it was shown to regulate apoptosis through sponging of let-7b.[527] Microarray analysis following knockdown or overexpression of H19 in kainic-acid induced epileptic rats revealed involvement of H19 in a number of epileptogenic processes including demyelination, immune response, and inflammation.[528] Inhibition of H19 was shown to protect against hippocampal neuronal death in kainic acid-treated rats[527], indicating a potential role for H19 as a therapeutic target in epilepsy.

Several studies have been conducted to identify miRNA biomarkers of epilepsy in serum, of which the most accurate predict the disorder with 81.2% sensitivity.[529, 530] Other studies have observed expression profiles that distinctly identify epilepsy in human cerebrospinal fluid[531], rat hippocampus and peripheral blood[532], rat hippocampal granule cells and plasma[533], and rat synaptosomes.[534, 535] Profiling studies have also characterized miRNA from the hippocampus of epilepsy patients with TLE, showed overall failure of mature miRNA processing due to Dicer loss in TLE and identified dysregulation of a number of miRNAs involved in immune response.[536, 537] Mooney et al. has provided a comprehensive database known as EpimiRBase providing a plethora of miRNA-epilepsy associations in both human and animal studies[538] facilitating future work in identifying key miRNAs involved pathophysiology or as biomarkers.

CONCLUSION & FUTURE DIRECTIONS

Advancements in epigenetics have revolutionized our understanding into the mechanisms involved in brain diseases. The evidence thus far from various disease models from cell lines to the post-mortem human brain reveals a critical role for epigenetic dysfunction in neurodegenerative diseases and acute brain injury. These studies demonstrate that epigenetic imbalances in DNA methylation and histone modifications by molecular readers, writers and erasers predispose the brain to disease as well as influence neurological recovery. While the role of epigenetics in diseases of the brain is still emerging, it is clear that restoration of epigenetic imbalances may provide potential treatments that lead to recovery. HDAC inhibitors have emerged as an overlapping therapy among all of the brain diseases discussed. However, despite the protective effects shown in animal studies, some studies have shown certain downsides to HDAC inhibitor therapy including inflammation, oxidative stress and apoptosis.[539–541] Therefore, additional research is needed to further delineate the molecular mechanisms by which HDAC inhibitors function in various CNS disorders. Profiling of blood biomarkers is another promising clinical epigenetic approach that may help diagnosis and therapeutic development for CNS disorders. Biomarker profiling of DNA methylation and miRNA has already been used to develop prognostic and diagnostic indicators in brain disorders, and epigenetic profiles in neurological diseases continue to be developed. More

recently, lncRNA profiling has emerged as an additional potential biomarker tool. Modulation of various epigenetic regulatory mechanisms has been shown to provide therapeutic potential against several pathophysiological mechanisms. However, the current challenge lies in further elucidating the interplay between epigenetic changes and the downstream effects on gene expression and the complex cellular environment of the diseased brain.

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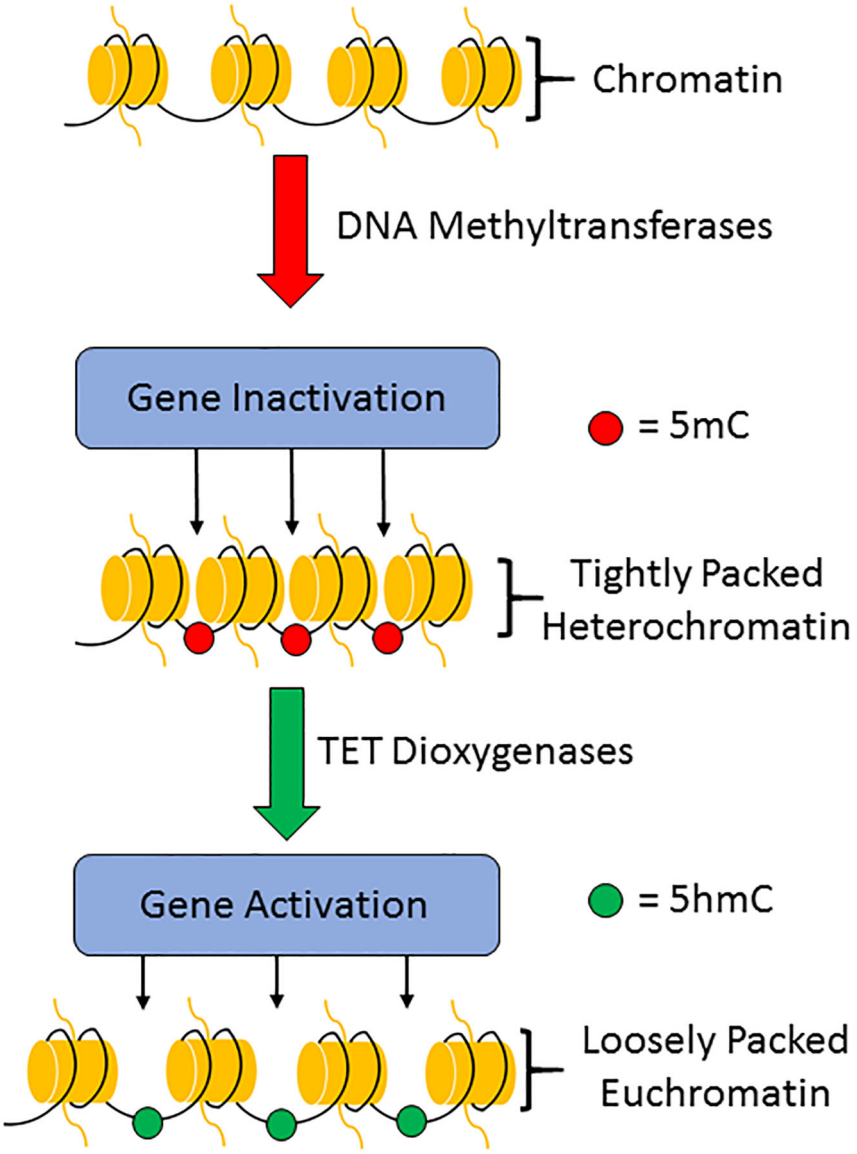

Fig. 1: DNA methylation and hydroxymethylation.

DNA methylation occurs through the addition of a methyl (CH_3) group to the cytosine of DNA by DNA methyltransferases (DNMTs) to produce 5-methylcytosine (5-mC). DNA methylation leads to densely packed heterochromatin that is consistent with gene inactivation. 5-mC can subsequently be converted to 5-hydroxymethylcytosine (5-hmC) by the ten-eleven translocation (TET) dioxygenases. Hydroxymethylation loosens chromatin to promote gene activation.

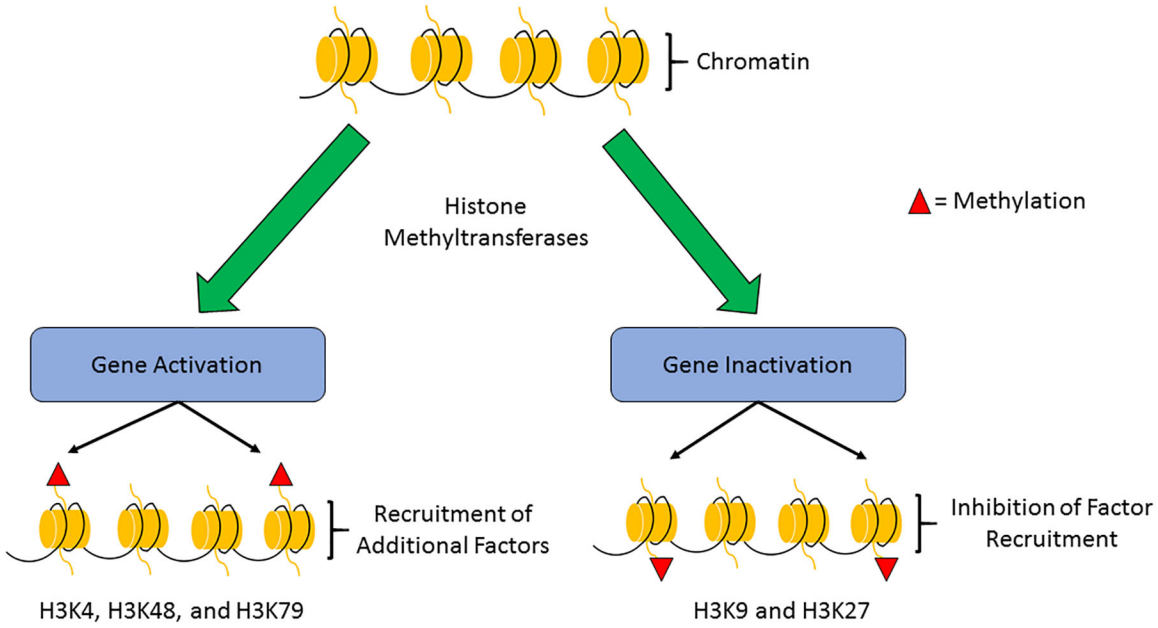

Fig. 2: Histone methylation.

Histone methylation is the addition of methyl (CH_3) groups to arginine and lysine side chains by histone methyltransferases (HMTs). The effect of histone methylation on gene transcription is dependent on the location and degree of methylation. For example, methylation of histone 3, lysine residue 4 (H3K4) is an activating mark whereas H3K9 is a deactivating mark.

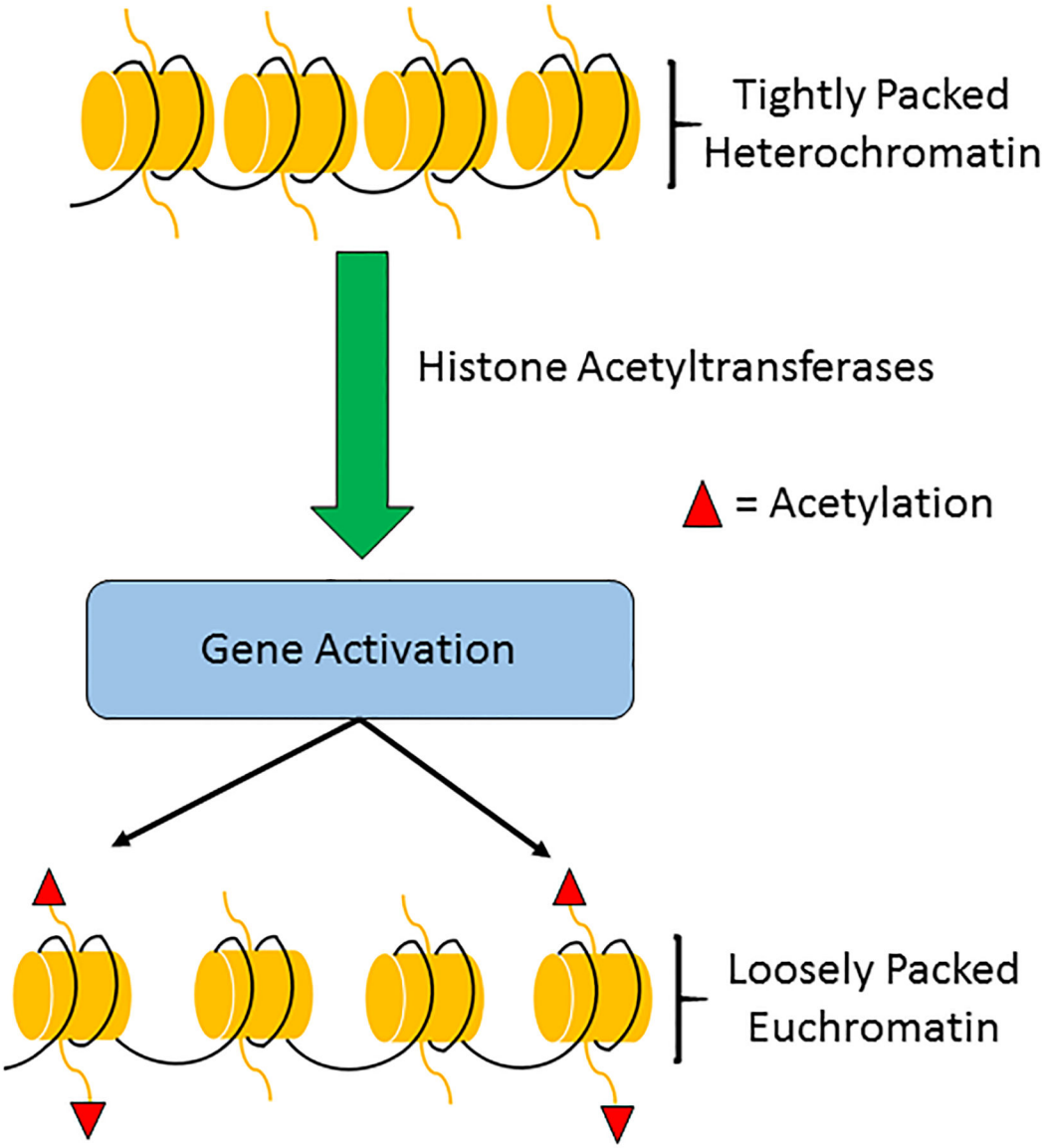

Fig.3: Histone acetylation.

Histone acetylation occurs with the addition of acetyl (CH_3CO) groups to lysine side chains by histone acetyltransferases (HATs). Acetylation reduces the steric clash between histones and DNA, opening up chromatin for gene transcription. Histone deacetylases (HDACs) reverse this modification and repress gene transcription.

Table 1.

Therapeutic Potential of Epigenetic Modulators in Alzheimer's Disease

Model	Therapeutic Potential	Modification	Citation
Neuroblastoma Cells	SAM reduces vitamin B12/folate deficiency-induced overexpression of PS1 and BACE	DNA methylation	Fuso et al., 2005
Neuroblastoma Cells	SAM reduces PS1 expression and Aβ plaques	DNA methylation	Scarpa et al., 2003
TgCRND8 mice	SAM+SOD reduced vitamin B deficiency-induced AD features	DNA methylation	Cavallaro et al., 2017
AD Humans	SAM reduces inflammation in AD patients and improves MMSE	DNA methylation	Chen et al., 2016
CK-p25 mice	shRNA knockdown of HDAC2 reduces memory impairment	Histone acetylation	Graff et al., 2012
Tg2576 mice	4-PBA reverses brain hypoacetylation and reduces phosphorylated tau	Histone acetylation	Ricobaraza et al., 2009
Tg2576 mice	Caloric restriction and NAD+ treatment is neuroprotective via α-secretase	Histone acetylation	Qin et al., 2006
3xTg-AD mice	Nicotinamide reduces phosphor-species of tau (Thr231) and improves memory	Histone acetylation	Green et al., 2008
rTg4510 mice	AK1 is non-toxic and potentially neuroprotective	Histone acetylation	Spires-Jones et al., 2012
APPPS-21 mice	MiR-34c seed inhibitors reverse memory deficit	MiRNA	Zovoilis et al., 2011
Hippocampal Neurons	MiR-34c transfection reduces dendritic length and density	MiRNA	Kao et al., 2018
Neuroblastoma	MiR-195 overexpression reduces Aβ-induced cytotoxicity	MiRNA	Zhu et al., 2012
Hippocampal Neurons	Lentiviral overexpression of miR-101 decreases APP and Aβ	MiRNA	Vilardo et al., 2010
AD PC12 cells and hippocampal neurons	miR-16 mimic targets APP and reduces Aβ-induced cytotoxicity	MiRNA	Zhang et al., 2015
APP/PS1 mice	Lentiviral overexpression of miR-124 improves behavior through BACE1	MiRNA	Du et al., 2017
HEK293T	LNA inhibition of miR-485–5p or overexpression of BACE1-AS increase BACE1 levels	MiRNA, lncRNA	Faghihi et al., 2010
Human plasma	Biomarker technique of 2 miRNAs identify AD with 95% specificity	MiRNA	Kumar et al., 2013
Human serum exosomes	Biomarker panel of 16 miRNAs identify AD with 87% sensitivity	MiRNA	Cheng et al., 2015
Neuroblastoma Cells	NEAT1 knockdown reduces AB-induced apoptosis and p-Tau levels	LncRNA	Ke et al., 2019

Table 2.

Therapeutic Potential of Epigenetic Modulators in Parkinson's Disease

Model	Therapeutic Potential	Modification	Citation
Tg-α-syn mice	Lentiviral administration of DNMT1 restores nuclear localization dysregulated by α-syn	DNA methylation	Desplats et al., 2011
Tg-α-syn Drosophila	SB and SAHA decrease apoptosis in dorsomedial neurons	Histone acetylation	Kontopoulos et al., 2006
N27 cells	Anarchic acid reverses Dieldrin-induced H3/H4 acetylation and apoptosis	Histone acetylation	Song et al., 2010
N27 cells	Anarchic acid reverses Paraquat-induced H3/H4 acetylation and apoptosis	Histone acetylation	Song et al., 2011
Tg-α-syn Drosophila	AKG2 reduces α-syn-induced neurotoxicity in dorsomedial neurons	Histone acetylation	Outeiro et al., 2007
Dopaminergic neurons	SB and TSA increase GDNF and BDNF expression	Histone acetylation	Wu et al., 2008
Dopaminergic neurons	SAHA is protective against neurotoxin-induced apoptosis	Histone acetylation	Chen et al., 2012
MN9D cells, MPP+	miR-124 mimic calpain 1, p25, and cdk5 to prevent cytotoxicity	MiRNA	Kanagaraj et al., 2014
Tg-LRRK2 Cortical neurons	Overexpression of miR-205 reduces LRRK2 protein concentration and rescues neurite outgrowths	MiRNA	Cho et a., 2013
Cortical neurons	Overexpression of miR-7 and miR-153 downregulates SNCA mRNA expression	MiRNA	Doxakis, 2010
Tg-α-syn Neuroblastoma cells	Overexpression of miR-7 prevents α-syn-induced sensitivity to H_2O_2 cytotoxicity	MiRNA	Junn et al., 2009
Neuroblastoma cells, MPP+	Overexpression of miR-7 or VDAC1 reduces MPP+-induced oxidative stress and cell death	MiRNA	Chaudhuri et al., 2016
MiR-155$^{-/-}$ mice	miR-155 knockout reduces inflammatory response to α-syn	MiRNA	Thome et al., 2016
Human plasma	A miRNA biomarker strategy predicts PD wit 91% sensitivity and 100% specificity	MiRNA	Khoo et al., 2012
Cortical neurons, MPP+	MiR-7 and miR-153 is protective via mTOR and SAPK/JNK pathways	MiRNA	Fragkouli & Doxakis, 2014
Neuroblastoma cells, MPP+	MiR-7 targets RelA to provide neuroprotection	MiRNA	Choi et al., 2014
Tg-α-Syn mice, MPTP	MiR-7 targets NLRP3 to provide neuroprotection	MiRNA	Zhou et al., 2016
C57 mice, MPTP and neuroblastoma cells, MPP+	Overexpression of miR-124 downregulates apoptotic and autophagic pathways	MiRNA	Wang et al., 2016
PC12 cells, 6-OHDA	MiR-221 prevents cytotoxicity by targeting PTEN	MiRNA	Li et al., 2018
C57 mice, MPTP	H2S treatment downregulates miR-135a-5p to increase ROCK2 expression	MiRNA	Liu et al., 2016
Neuroblastoma cells, MPTP	MiR-185 overexpression prevents apoptosis	MiRNA	Wen et al., 2018
PC12 cells, MPP+	MiR-181c overexpression prevents apoptosis	MiRNA	Wei et al., 2017
Neuroblastoma cells, rotenone	Inhibition of miR-384–5p reverses ER stress	MiRNA	Jiang et al., 2016
Neuroblastoma cells, MPP+	Knockout of HOTAIR attenuates neurotoxicity	LncRNA	Wang et al., 2017
Tg-LRRK2 Drosophila	Overexpression of miR-7 or miR-184* in dopaminergic neurons targets DP and E2F1 as well as rescues flies from mLRRK2	MiRNA	Gehrke et al., 2010
C57 mice, MPTP and neuroblastoma cells, MPP+	Inhibition of HAGLROS is protective by regulation of miR-100 and the mTOR pathway	LncRNA	Peng et al., 2019
Neuroblastoma cells, MPP+	P21 knockdown reduces ROS, neuroinflammation, and apoptosis	LncRNA	Ding et al., 2019

Model	Therapeutic Potential	Modification	Citation
Neuroblastoma cells, MPP+	Knockdown of SNGH1 or overexpression of miR-15b-5p is neuroprotective	LncRNA, miRNA	Xie et al., 2019
Neuroblastoma cells, MPP+	Knockdown of SNGH1 decreases α-Syn aggregation through miR-15b-5p upregulation	LncRNA, miRNA	Chen et al., 2018
MN9D cells, MPP+ and C57 mice, MPTP	Silencing of SNGH1 acts through miRNA and the mTOR pathway to provide neuroprotection	LncRNA	Qian et al., 2019
C57 mice, MPTP	Downregulation of SNGH1 acts through upregulation of miR-7 suppress inflammation	LncRNA, miRNA	Cao et al., 2018
MN9D cells, MPP+	Knockdown of MALAT1 deceases α-Syn-mediated cytotoxicity	LncRNA	Chen et al., 2018
Neuroblastoma cells, MPP+ and C57 mice, MPTP	β-Asarone downregulates MALAT1 to prevent α-Syn accumulation	LncRNA	Zhang et al., 2016
Neuroblastoma cells and HEK293T cells, paraquat	NEAT1 is upregulated and mediates fenofibrate and simvastatin-induced neuroprotection	LncRNA	Simchovitz et al., 2019
Neuroblastoma cells, MPP+	Silencing NEAT1 derepresses miR-124, reduces inflammatory markers, and decreases apoptosis	LncRNA, miRNA	Xie et al., 2019
Neuroblastoma cells, MPP+	NORAD overexpression decreases apoptosis, ROS, and LDH	LncRNA	Song et al., 2019
Neuroblastoma cells, MPP+	UAC1 knockdown reduces caspase activity and apoptosis	LncRNA	Lu et al., 2018
Wistar rats, 6-OHDA	UAC1 downregulation is neuroprotective by way of oxidative stress and inflammation reduction	LncRNA	Cai et al., 2019

Table 3.

Therapeutic Potential of Epigenetic Modulators in Huntington's Disease

Model	Therapeutic Potential	Modification	Citation
mHTT Drosophila	Selisistat improves survival and decreases cytotoxic inclusions	Histone acetylation	Smith et al., 2014
mHTT Drosophila	AK1 and AGK2 are neuroprotective by way of sterol biosynthesis downregulation	Histone acetylation	Luthi-Carter et al., 2010
Htn-Q150 C. elegans	Knockdown of HDA3 reduces polyglutamine toxicity	Histone acetylation	Bates et al., 2006
Tg-R6/2 mice	HDACi 4b reverses H3 hypoacetylation and improves functional recovery	Histone acetylation	Thomas et al., 2008
HTT-Q73 PC12 cells	miR-10b-5p mimic increases cell survival	MiRNA	Hoss et al., 2014
HTT-Q84 Neuroblastoma cells	Overexpression of miR-196a increases neurite outgrowth	MiRNA	Fu et al., 2015
R6/2 mice	MiR-132 overexpression provided neuroprotection and delayed disease progression	MiRNA	Fukuoka et al., 2018
Tg-R6/2 mice	Overexpression of miR-196a enhances neurite outgrowths and improves learning and memory	MiRNA	Her et al., 2017
HD neural progenitor cells	Overexpression of miR-196a normalized mitochondrial activity and decreased apoptosis	MiRNA	Kunkanjanawan, et al., 2016
STHdh(Q111)/Hdh(Q111) cells	Exogenous expression of miR-146a, miR-432, and miR-19a reversed cell cycle defects and apoptosis	MiRNA	Das et al., 2015
STHdh^{Q7}/*Hdh*^{Q7} cells	Overexpression of HYPK and Hsp70 reverses miR-125b, miR-146a, and miR-150 expressions while reducing mHTT aggregates	MiRNA	Ghose et al., 2011
Neuronal stem cells derived from R6/2 mice	MiR-27a overexpression decreased mHTT aggregates	MiRNA	Ban et al., 2017
mHTT sheep	HTT targeting by way of artificial miRNA safely reduces mHTT mRNA and protein	MiRNA	Pfister et al., 2018
Primary Striatal cell and cortical neurons, mHTT and 3-NP	MiR-22 overexpression is neuroprotective	MiRNA	Jovicic et al., 2013
R6/2 neurons	MiR-27a overexpression decreases mHTT aggregates by way of MDR-1	MiRNA	Ban et al., 2017
Neuroblastoma cells, H_2O_2	Neat1 transfection increases tolerance to oxidative stress	LncRNA	Sunwoo et al., 2017
HEK293 cells and neuroblastoma cells	Overexpression of HTTAS_v1 decreases HTT levels in a gene-specific manner	LncRNA	Chung et al., 2011

Table 4.

Therapeutic Potential of Epigenetic Modulators in Ischemic Stroke

Model	Therapeutic Potential	Modification	Citation
129/SV mice, MCAO	5'-aza-dC as well as TSA reduced infarct size	DNA methylation	Endres et al., 2000
SD rats, HI	5'-aza-dC protects against nicotine-induced susceptibility	DNA methylation	Li et al., 2013
Wistar rats, photothrombotic stroke	TST or TST+5'-aza-dC upregulates BDNF and improves neurological score	DNA methylation	Choi et al., 2018
HT22 cells	5'aza-dC downregulates DNMT1, induces S phase arrest, and inhibits early apoptosis while promoting late apoptosis	DNA methylation	Yang et al., 2017
ICR mice, MCAO	SC1 reverses mitochondrial 5hmC upregulation by inhibiting TET2 leading to increased levels of ATP	DNA hydroxymethylation	Ji et al., 2018
C57 mice, MCAO	Overexpression of Polycomb proteins SCMH1 and BMI1 is neuroprotective	Polycomb protein	Stapels et al., 2010
Cortical neurons, CA and 3-NP	Overexpression of BMI1 acts by way of antioxidant genes to provide protection	Polycomb protein	Abdouh et al., 2012
Wistar rats, 4-VO	VPA confers inflammatory protection and improves functional recovery	Histone acetylation	Xuan et al., 2012
SD rats, MCAO	VPA, SB, or TSA prevent hypoacetylation of H3, prevent inflammation, and reduce infarct volume	Histone acetylation	Kim et al., 2007
C57 mice, MCAO	SAHA reverses H3 hypoacetylation, promotes Hsp70 and BCL-2, and reduces infarct volume	Histone acetylation	Faraco et al., 2006
C57 mice, HI	4-PBA improves functional recovery via protection from apoptotic mechanisms	Histone acetylation	Qi et al., 2004
Optic nerves, OGD	SAHA and MS-275 rescue white matter	Histone acetylation	Baltan et al., 2011
Cortical neurons	Despite reducing ischemic infarct, HDAC inhibitors are cytotoxic to cells they do not protect	Histone acetylation	Langley et al., 2008
SD rats, forebrain ischemia	MiR-181a antagomir decreases CA1 neuron death	MiRNA	Moon et al., 2013
Primary astrocytes, GD	MiR-181a inhibition decreases apoptosis via upregulation of BCL-2 and MCL-1	MiRNA	Ouyang et al., 2012
C57 mice, MCAO	Overexpression of miR-124 is neuroprotective by downregulation of REST and Usp-14	MiRNA	Doeppner et al., 2013
C57 mice, MCAO	MiR-124 agomir reduces infarct volume	MiRNA	Sun et al., 2013
C57 mice, MCAO	Liposomated miR-124 reduces inflammatory markers and infarct volume	MiRNA	Hamzei et al., 2016
PC12 cells, OGD	MiR-124 mimic activates the PI3K/AKT pathway and reduces apoptosis	MiRNA	Wang et al., 2017
SD rats, MCAO	MiR-124 knockdown or miR-124 antagomir is neuroprotective	MiRNA	Zhu et al., 2014
SD rats, MCAO	MiR-155 inhibition reduces infarct volume	MiRNA	Xing et al., 2016
C57 mice, MCAO	MiR-155 inhibition reduces infarct volume	MiRNA	Caballero-Garrido et al., 2015
Oligodendrocyte precursors	MiR-146a overexpression increases myelination	MiRNA	Liu et al., 2017
Neuroblastoma cells, OGD	MiR-146a inhibition prevents apoptosis via Fblx10 upregulation	MiRNA	Li et al., 2017
C57 mice, MCAO	Lentiviral overexpression of miR-424 is neuroprotective via cell cycle arrest and inflammatory suppression	MiRNA	Zhao et al., 2013
C57 mice, MCAO	MiR-424 antagomir is neuroprotective by way of oxidative stress prevention	MiRNA	Liu et al., 2015

Model	Therapeutic Potential	Modification	Citation
C57 mice, MCAO	The inhibitor TAT-p53-DBD270–281 uncouples MEG3 from p53 to provide neuroprotection	LncRNA	Yan et al., 2016
SHR rats, MCAO	Knockdown of FosDT derepresses REST genes and improves functional recovery	LncRNA	Mehta et al., 2015
C57 mice, MCAO	MiR-181a antagomir reduces inflammation and infarct size while improving behavioral recovery	MiRNA	Xu et al., 2015
PC12 cells, OGD	MiR-210 overexpression protects against apoptotic events	MiRNA	Qiu et al., 2013
C57 mice, MCAO	MiR-210 overexpression increases BDNF and improves neurological scores	MiRNA	Zeng et al., 2016
SD rats, MCAO	MiR-210 promotes vagus nerve stimulation-mediated recovery	MiRNA	Jiang et al., 2015
C57 mice, MCAO	Inhibition of miR-210 attenuates inflammatory response	MiRNA	Huang et al., 2018
C57 mice, MCAO	Inhibition of MALAT1 is neuroprotective by way of decreasing autophagy	LncRNA	Guo et al., 2017
SD rats, MCAO	Sh-MEG3 administration improves functional recovery and promotes angiogenesis	LncRNA	Liu et al., 2017
Human serum	Peng et al. used let-7e to predict acute stroke with 73.4% sensitivity and 82.8% specificity	MiRNA	Peng et al., 2015
C57 mice, MCAO	MEG3 knockdown prevents apoptosis	LncRNA	Yan et al., 2017
BV2 cells, OGD	H19 knockdown reduces inflammation to provide neuroprotection	LncRNA	Wang et al., 2017
Neuroblastoma cells, OGD	Overexpression of N1LR prevents apoptosis	LncRNA	Wu et al., 2017
C57 mice, MCAO and cortical neurons, OGD	Knockdown of GAS5 is neuroprotective via decreased competition with miR-137	LncRNA, miRNA	Chen et al., 2018

Table 5.

Therapeutic Potential of Epigenetic Modulators in Hemorrhagic Stroke

Model	Therapeutic Potential	Modification	Citation
Intracranial aneurysm humans	RIC, a method used to protect against post-SAH events, dysregulates cell cycle and inflammatory genes	DNA methylation	Nikkola et al., 2015
CD-1 mice, ICH	SAHA reverses H3 and H4 hypoacetylation to provide neuroprotection	Histone acetylation	Sukumari-Ramesh et al., 2016
SD rats, ICH	VPA prevents inflammation via activation of H3 genes	Histone acetylation	Sinn et al., 2007
Microglia, erythrocyte lysate ICH	miR-124 mimics reduce M1 markers and increase M2 markers	MiRNA	Yu et al., 2017
C57 mice, endovascular perforation	Melatonin is neuroprotective by way of H19-let-7a-NGF interaction	MiRNA, lncRNA	Yang et al., 2018
SD rats, ICH	Let-7c antagomir reduces reactive microglia and neutrophils as well as improves functional outcome	MiRNA	Kim et al., 2014
SD rats, ICH	miR-126 mimics reduces reactive microglia and neutrophils as well as apoptosis	MiRNA	Xi et al., 2017
C57 mice, ICH	Augmentation of miR-132 reduces permeability of the BBB	MiRNA	Zhang et al., 2017
BALB/c mice, ICH	Inhibition of miR-144 downregulates autophagy, reduces inflammation, and leads to improved functional recovery	MiRNA	Yu et al., 2017
SD rats, ICH	Restoration of miR-27a-3p is neuroprotective by way of aquaporin-11	MiRNA	Xi et al., 2018

Table 6.

Therapeutic Potential of Epigenetic Modulators in Traumatic Brain Injury

Model	Therapeutic Advantage	Modification	Citation
Sabra mice, CHI	ITF2357 reverses downregulation of Hsp70 and H3 hypoacetylation to provide neuroprotection	Histone acetylation	Shein et al., 2009
C57 mice, CCI	SB in combination with water maze training improves memory	Histone acetylation	Dash et al., 2009
SD rats, CCI	VPA reduces inflammation and apoptosis	Histone acetylation	Tai et al., 2014
C57 mice, CCI	VPA in combination with lithium prevents H3 hypoacetylation and reduces lesion volume	Histone acetylation	Yu et al., 2013
SD rats, CCI	VPA prevents the hypoacetylation of H3 and H4 while decreasing the permeability of the BBB	Histone acetylation	Dash et al., 2010
C57 mice, CCI	Fluoxetine prevents H3 and H4 hypoacetylation while inducing hippocampal neurogenesis	Histone acetylation	Wang et al., 2011
Wistar rats, HCb	RvD1 administration is neuroprotective via ALX/FPR2	MiRNA	Bisicchia et al., 2018
SD rats, FPI	MiR-21 agomir upregulates (Ang-1)/Tie-2 to decrease BBB leakage	MiRNA	Ge et al., 2015
SD rats, CCI	H_2 gas increases miR-21 and improves BBB permeability	MiRNA	Wang et al., 2018
Wistar rats, weight drop	Formononetin reverses miR-155 downregulation and improves functional recovery	MiRNA	Li et al., 2017
C57 mice, CCI	MiR-155 antagomir prevents against inflammation and reduces lesion volume	MiRNA	Henry et al., 2019
C57 mice, CCI	MiR-23a and miR-27a mimics provide neuroprotection via decreased apoptotic markers	MiRNA	Sabirzhanov et al., 2014
Cortical neurons, scratch	MiR-21 overexpression is neuroprotective	MiRNA	Han et al., 2014
HT-22 neurons, scratch	MiR-21–5p overexpressing cells or exosomes aid in neuroprotection of other neurons	MiRNA	Li et al., 2019
SD rats, fluid percussion	MiR-21 agomir prevents apoptosis and promotes angiogenesis	MiRNA	Ge et al., 2014
SD rats, weight drop	MiR-23a overexpression downregulates ATG12 to suppress autophagy	MiRNA	Sun et al., 2018
SD rats, weight drop	MiR-27a overexpression downregulates FoxO3a to suppress autophagy	MiRNA	Sun et al., 2017
BV2 microglia, rTBI and C57 mice, rTBI	Exosomes derived from miR-124–3p overexpressing microglia are neuroprotective	MiRNA	Huang et al., 2018
C57 mice, CCI	Let-7c-5p mimic decreases microglial activation to provide functional recovery	MiRNA	Lv et al., 2018
C57 mice, CCI	Neat1 knockdown is neuroprotective	LncRNA	Zhong et al., 2017
SD rats, weight drop	MiR-144 antagomir improves functional recovery and long-term potentiation	MiRNA	Sun et al., 2017
C57 mice, CCI	Voluntary running wheel improves functional recovery and dysregulates miR-34a and miR-21	MiRNA	Bao et al., 2014
C57 mice, CCI	Voluntary running wheel improves functional recovery and dysregulates several miRNA	MiRNA	Miao et al., 2015
SD rats, fluid percussion	Therapeutic hypothermia improves functional recovery and dysregulates miR-874 and miR-451	MiRNA	Truettner et al., 2011

Table 7.

Therapeutic Potential of Epigenetic Modulators in Epilepsy

Model	Therapeutic Potential	Modification	Citation
Wistar rats, pilocarpine	Ketogenic diet reduces global methylation and seizure severity	DNA methylation	Kobow et al., 2013
C57 mice, kainic acid	RG108 prevents RASgrf1 methylation and reduces seizures	DNA methylation	Chen et al., 2017
SD rats, kainic acid	Methionine restores BDNF methylation to improve memory	DNA methylation	Parrish et al., 2015
SD rats, pilocarpine	TSA reverses deacetylation of H4 at the GRIA2 promoter	Histone acetylation	Huang et al., 2002
WAG/Rij rats	Pretreatment of SB, VPA, or both reduces seizure severity	Histone acetylation	Citraro et al., 2019
C57 mice, hippocampus kindling	SB improves functional recovery and reduces epileptic morphology	Histone acetylation	Reddy et al., 2018
Human serum	Epilepsy can be predicted with 81% specificity by miRNA biomarkers	MiRNA	Wang et al., 2015
C57 mice, pilocarpine	miR-134 antagomir reduced number of mice that developed seizures and reduced severity in those that did	MiRNA	24874920
C57 mice, pentylenetetrazol	miR-134 antagomir reduces seizure severity and epileptic behavior	MiRNA	28325299
C57 mice, kainic acid	miR-132 antagomir reduces neurotoxicity after seizures	MiRNA	21945804
SD rats, kainic acid	Upregulating miR-124 has both anti-epileptic and pro-epileptic effects	MiRNA	26947066
SD rats, kainic acid	Inhibition of H19 prevents neurotoxicity after seizures	LncRNA	29795132