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## Epigenetic mechanisms governing the process of neurodegeneration

Irfan A. Qureshi<sup>1,2,3,6</sup> and Mark F. Mehler<sup>1,2,3,4,5,6</sup>

<sup>1</sup>Roslyn and Leslie Goldstein Laboratory for Stem Cell Biology and Regenerative Medicine, Albert Einstein College of Medicine, Bronx, New York, NY 10461, USA

<sup>2</sup>Institute for Brain Disorders and Neural Regeneration, Albert Einstein College of Medicine, Bronx, New York, NY 10461, USA

<sup>3</sup>Department of Neurology, Albert Einstein College of Medicine, Bronx, New York, NY 10461, USA

<sup>4</sup>Department of Neuroscience, Albert Einstein College of Medicine, Bronx, New York, NY 10461, USA

<sup>5</sup>Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, New York, NY 10461, USA

<sup>6</sup>Rose F. Kennedy Center for Research on Intellectual and Developmental Disabilities, Albert Einstein College of Medicine, Bronx, New York, NY 10461, USA

### Abstract

Studies elucidating how and why neurodegeneration unfolds suggest that a complex interplay between genetic and environmental factors is responsible for disease pathogenesis. Recent breakthroughs in the field of epigenetics promise to advance our understanding of these mechanisms and to promote the development of useful and effective pre-clinical risk stratification strategies, molecular diagnostic and prognostic methods, and disease-modifying treatments.

### Keywords

chromatin; epigenetic; histone deacetylase; histone modification; neurodegenerative disease; non-coding RNA

### 1.0 Introduction

Neurodegenerative diseases are becoming increasingly prevalent in our aging population and represent major sources of morbidity and mortality and a growing societal burden. Studies

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Irfan A. Qureshi, Albert Einstein College of Medicine, Rose F. Kennedy Center, 1410 Pelham Parkway South, Room 401, Bronx, NY 10461, Tel: 718-430-4288, Fax: 718-430-8551, irfan@jhu.edu. Mark F. Mehler, Albert Einstein College of Medicine, Rose F. Kennedy Center, 1410 Pelham Parkway South, Room 220, Bronx, NY 10461, Tel: 718-430-3543, Fax: 718-430-8785, mark.mehler@einstein.yu.edu.

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#### Competing interests statement

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focused on elucidating the bases for these disorders have revealed that only a small percentage are caused by readily identifiable genetic abnormalities with Mendelian patterns of inheritance (Lill and Bertram, 2011). For example, expansion-repeat mutations in the *huntingtin* (*HTT*) gene give rise to Huntington's disease (HD) in a highly penetrant autosomal dominant fashion. Mutations in the  *$\alpha$ -synuclein* (*SNCA*), *parkin* (*PARK2*), *PTEN induced putative kinase 1* (*PINK1*), *parkinson protein 7* (*PARK7/DJ-1*), *leucine-rich repeat kinase 2* (*LRRK2*) and *glucosidase,  $\beta$ , acid* (*GBA*) genes and the *amyloid precursor protein* (*APP*) and *presenilin1/2* (*PS1/2*) genes are linked, respectively, to familial forms of Parkinson's disease (PD) and Alzheimer's disease (AD). However, unlike HD, the vast majority of cases of PD, AD, and other neurodegenerative diseases (e.g., amyotrophic lateral sclerosis [ALS] and frontotemporal dementia [FTD]) arise from the complex and poorly characterized interplay that occurs between myriad genetic risk factors with varying frequencies and effect sizes as well as the cumulative effects of a lifetime of nutritional and environmental exposures (Lill and Bertram, 2011; Saxena and Caroni, 2011). Countless studies have focused on elucidating the distinct and overlapping genetic and environmental factors and molecular mechanisms that underlie the pathogenesis of these disorders and how they might converge to promote the development of an individual disease state, often having heterogeneous manifestations, or the development of multiple disorders exhibiting a spectrum of common pathological features (e.g., protein aggregation). It is generally believed that for each distinct neurodegenerative disease, selectively vulnerable neuronal populations undergo cell death as a consequence of potentially interrelated processes, including but not limited to cellular stress (e.g., oxidative damage) and impairments in the effectiveness of stress responses (e.g., the ubiquitin-proteasome system) and RNA metabolism, mitochondrial dysfunction, and protein aggregation and propagation. Despite the discovery and ongoing refinement of these basic insights, however, our understanding of neurodegenerative disease pathogenesis remains fragmentary and poorly defined. There is a corresponding dearth of reliable clinical tools for risk stratification, early diagnosis and prognostication, and monitoring disease progression; and there are few, if any, therapies currently available to modify the natural history of these diseases, even if such tests were to exist.

The science of epigenetics offers new scientific paradigms and tools and techniques for uncovering the pathophysiology of neurodegenerative disease states (Mehler, 2008b). Conrad Waddington originally coined the term epigenetics referring to "the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being". In other words, epigenetics describes how gene expression and function are controlled in individual cells and tissues and how gene-gene and gene-environmental interactions are mediated during development and adult life. Since the completion of the Human Genome Project, the field of epigenetics has been advancing at an extraordinarily rapid pace, driven by technological innovations such as next-generation sequencing. Here, we briefly discuss the major epigenetic mechanisms that have been described, including DNA methylation and hydroxymethylation, histone modifications and higher order chromatin remodeling, and non-coding RNA (ncRNA) regulation. We highlight how abnormalities in these highly interconnected epigenetic pathways are linked to specific neurodegenerative diseases and also how they are involved in mechanisms underlying neurodegeneration. Importantly, these observations may provide insights into why specific neuronal subtypes might be vulnerable to injury in particular neurodegenerative disease states, what specific genetic and environmental factors might interact to modify the risk of disease onset and progression, how familial and sporadic forms of a disease might be interrelated, and how the effects of aging might contribute to these risks and also to identify novel strategies for diagnosing and treating these devastating disorders.

## 2.0 DNA methylation and hydroxymethylation in neurodegeneration

### 2.1 DNA methylation and hydroxymethylation

DNA methylation describes the covalent modification of cytosine residues in DNA, which leads to the formation 5-methylcytosine (5mC). It occurs in gene regulatory regions, such as promoter element CpG dinucleotides, and also at other genomic sites (e.g., gene bodies and intergenic regions) (Auclair and Weber, 2012; Mehler, 2008b). DNA methyltransferase (DNMT) enzymes catalyze *de novo* methylation and maintain methylation “marks”, using *S*-adenosylmethionine as the methyl group donor. Functionally, DNA methylation is thought to inhibit the transcriptional machinery from accessing DNA, leading to decreased transcription of genes with high levels of promoter methylation. Proteins that recognize methylated DNA (e.g., the methyl-CpG-binding domain [MBD] family of proteins) can recruit a range of additional epigenetic modulatory factors to these loci. DNA methylation is generally associated with transcriptional repression and long-term gene silencing, and it also plays a role in the establishment and maintenance of higher order epigenetic states (e.g., X chromosome inactivation [XCI] and genomic imprinting). In addition, DNA methylation has been linked to gene activation, but the mechanism by which this occurs is poorly understood (Auclair and Weber, 2012).

While cellular DNA methylation states are subject to reprogramming during developmental stages, DNA methylation signatures at specific loci are thought to be relatively stable once cell identity is established. However, emerging evidence is now suggesting that DNA methylation is much more dynamic than previously understood. An increasing number of factors are being implicated in promoting active DNA demethylation, including those involved in DNA excision repair and cytidine deamination pathways (Auclair and Weber, 2012; Wu and Zhang, 2010). Intriguingly, the Ten-Eleven Translocation (TET) family of enzymes oxidizes 5mC generating another modified cytosine residue, 5-hydroxymethylcytosine (5hmC), which seems to counterbalance the functions of 5mC by inhibiting the binding of MBD proteins (Jin et al., 2010; Valinluck et al., 2004). The expression of these DNA (de)methylation enzymes and associated profiles of 5mC and 5hmC continue to evolve in brain regions throughout the lifespan in humans and in others species (Hernandez et al., 2011; Numata et al., 2012; Siegmund et al., 2007; Szulwach et al., 2011). Even at a subcellular level, 5hmC is present in age-dependent patterns within the mitochondrial genome of cells in the frontal cortex (Shock et al., 2011). Further, DNA methylation profiles are modulated by neuronal activity-dependent plasticity (Guo et al., 2011), and DNMT enzymes and DNA methylation are implicated in mediating hallmark neurobiological processes, such as learning and memory (Day and Sweatt, 2010).

These observations imply that DNA methylation and hydroxymethylation are important mechanisms mediating nervous system homeostasis and plasticity and that deregulation of associated factors and profiles might be involved in neurodegenerative disease pathogenesis, particularly for diseases associated with aging.

### 2.2 Deregulation of DNA methylation and hydroxymethylation pathways and profiles in neurodegenerative diseases

Mutations in DNA methylation factors are implicated in causing neurodegenerative diseases. For example, recent linkage and sequencing analyses have shown that mutations in exons 20 and 21 of the *DNMT1* gene cause hereditary forms of neurodegeneration with central and peripheral manifestations including, respectively, a sensory neuropathy, dementia and hearing loss syndrome (Klein et al., 2011) and a cerebellar ataxia, deafness and narcolepsy syndrome (Winkelmann et al., 2012). These mutations are associated with abnormal DNMT1 protein folding and impaired function and, in turn, with aberrations in DNA

methylation profiles, such as global hypomethylation and genomic site-selective hypermethylation.

These findings are consistent with others showing that abnormalities in the expression and function of DNA methylation factors can modulate neurodegeneration in cell culture and animal models. For example, one study reported that knocking down *DNMT1* increases expansion repeat instability in a human cell culture assay system and that *Dnmt1* deficiency in mice is associated with aberrant DNA methylation and expansion of CAG repeats in the germline at the spinocerebellar ataxia type 1 (*SCA1*) locus (Dion et al., 2008). Another study performed utilizing a mouse motor neuron cell line demonstrated that forced expression of *Dnmt3a* causes neurodegeneration, that *Dnmt1* and *Dnmt3a* expression and 5mC levels increase during camptothecin-induced apoptosis, and that *Dnmt3a* loss of function or depletion and DNMT inhibitors reduce apoptosis *in vitro* (Chestnut et al., 2011). It also showed that provoking apoptosis in adult mouse spinal cord motor neurons via sciatic nerve avulsion leads to increased levels of *Dnmt3a* and 5mC and that DNMT inhibitors prevent apoptosis *in vivo*. Furthermore, the study found corresponding alterations in *Dnmt1*, *Dnmt3a* and 5mC levels in motor neurons from pathological tissues derived from patients with ALS.

Differential profiles of DNA methylation are present in neurodegenerative disease associated gene loci, implicating them in the pathogenesis of sporadic forms of these disorders. For example, mutations in the *SNCA* gene and alterations in the dosage of the wild type gene are, respectively, associated with familial and sporadic forms of PD (Corti et al., 2011). One interesting analysis of substantia nigra (SN), putamen, and cortex specimens derived from patients with sporadic PD revealed significantly decreased levels of DNA methylation in a *SNCA* gene promoter region, suggesting that hypomethylation is responsible for an increase in levels of *SNCA* (Jowaed et al., 2010). A complementary study identified a CpG region in the *SNCA* gene with significantly lower levels of DNA methylation specifically in the SN but not the anterior cingulate and putamen of sporadic PD patients, potentially providing insight into the differential vulnerability of this brain region to neurodegeneration in PD (Matsumoto et al., 2010). In addition, other PD risk associated genes also exhibit differential levels of DNA methylation. A genome-wide association meta-analysis performed by the International Parkinson's Disease Genomics Consortium reported that PD susceptibility modifying variants at the *PARK16*, *GPNMB*, and *STX1B* loci are associated with methylation (and expression) changes in frontal cortex and cerebellar tissues (2011).

Moreover, for the *frataxin (FXN)* gene locus, which harbors an expansion GAA repeat mutation in Friedreich's ataxia, characteristic DNA methylation profiles have recently been correlated with mutant *FXN* expression levels, age of onset of symptoms, and clinical disease severity rating scores (Evans-Galea et al., 2012).

### 3.0 Histone modifications and higher order chromatin remodeling in neurodegeneration

#### 3.1 Histone modifications and higher order chromatin remodeling

DNA exists as a highly compact structure within the cell nucleus that is referred to as chromatin (Mehler, 2008a). The nucleosome represents the most basic element of chromatin. It is comprised of DNA, which is wrapped around an octamer of histone proteins (i.e., H2A, H2B, H3, H4). Nucleosomes assemble into higher order chromatin states that represent varying degrees of condensation having different functional implications. For example, in loosely packaged chromatin, DNA sequences are relatively accessible to the diverse range of factors present in nucleus, including the machinery responsible for

transcription and DNA replication and repair. Furthermore, chromatin organization determines the location of each gene locus within the nucleus itself, including proximity to particular chromosomal territories and nuclear domains with specialized functions. Thus, chromatin plays important regulatory roles and its architecture is dynamic, evolving with the lifecycle of the cell and in response to environmental cues.

Epigenetic regulatory factors include those with the capacity to “write”, “erase”, and “read” chromatin states. Histone proteins are subject to post-translational modifications (e.g., acetylation and methylation) mediated by histone modifying enzymes, such as histone acetylases and histone methyltransferases (i.e., writers) and histone deacetylases and histone demethylases (i.e., erasers). These histone modifications form hierarchical “histone codes”, which are recognized by proteins with specific domains, such as bromodomains and chromodomains (i.e., readers). These diverse epigenetic regulatory factors often assemble into macromolecular complexes that, together, remodel chromatin states.

One interesting example, the REST/NRSF complex, can incorporate the co-factors, Sin3A and CoREST; the methyl-CpG binding protein, MECP2; the histone deacetylase enzymes, HDAC1 and HDAC2; and other chromatin remodeling enzymes, BAF57, BRG1 and BAF170 (Mehler et al., 2010). This REST/NRSF complex targets genomic loci encoding ncRNAs (see below) as well as genes including growth factors, axon guidance cues, ion channels, neurotransmitter receptors, and synaptic vesicle proteins with key roles in the establishment of neural cell identity and neural network connectivity and plasticity, illustrating the complex and combinatorial nature of epigenetic regulation and also its importance within the nervous system.

### 3.2 Histone modification and higher order chromatin remodeling pathways and profiles in neurodegenerative diseases

Unlike mutations in DNA methylation-related factors, mutations in histone modifying enzymes and higher order chromatin remodeling factors have not been linked, unequivocally, to neurodegenerative disease states. However, there is abundant evidence illustrating how abnormalities in the expression and function of histone modifying enzymes and higher order chromatin remodeling factors are intimately involved in the cellular pathways that lead to neurodegeneration. For example, abnormal subcellular localization of epigenetic factors is linked to neurodegeneration. Deficiency of the ataxia telangiectasia mutated (ATM) protein leads to the accumulation of HDAC4 in the neuronal cell nucleus, which promotes neurodegeneration (Li et al., 2012). Similarly, HTT is involved in the nuclear-cytoplasmic shuttling of REST/NRSF (Shimojo, 2008). Aberrant REST/NRSF activity in HD cells, animal models and post-mortem brains is, in turn, implicated in the transcriptional deregulation that is one of the hallmarks of the disease (Zuccato et al., 2007).

The abnormal expression of epigenetic factors is also associated with neurodegeneration. Specifically, characterization of the expression profiles of HDAC enzymes in brain and spinal cord specimens has demonstrated that ALS patients have reduced levels of *HDAC11* mRNA and increased *HDAC2* mRNA compared with controls (Janssen et al., 2010). Also, forced expression of HDAC3 causes selective degeneration of neuronal cells, including cerebellar granule neurons and cortical neuron via a glycogen synthase kinase 3 $\beta$ -dependent mechanism (Bardai and D'Mello, 2011). Epigenetic factors can also interact directly with disease-causing proteins. The ataxin-1 protein (ATXN1), which causes SCA1 when mutated, forms a complex with a HAT enzyme, KAT5/Tip60, in the murine cerebellum; and, partial loss of KAT5/Tip60 (i.e., *KAT5/Tip60* haploinsufficiency) delays Purkinje cell degeneration in a mouse model of SCA1 during the mid-stage of disease (Gehrking et al., 2011). Similarly, the ataxin-7 protein (ATXN7), which causes SCA7 when mutated, serves as a core component of epigenetic regulatory complexes—the SPT3/TAF9/GCN5 and



USP22 complexes, which have histone acetyltransferase and deubiquitination activity, respectively (Lang et al., 2011; Sopher et al., 2011).

In addition, particular profiles of histone modifications and higher order chromatin states are present in neurodegenerative diseases. For example, in the rd1 mouse model for retinal degeneration, HDAC activity and histone acetylation levels rise prior to degeneration of photoreceptors, and HDAC inhibition reduces cell death (Sancho-Pelluz et al., 2010). Exposure to the pesticides, paraquat and dieldrin, which may be linked with PD, induces increases in H3 acetylation in mesencephalic dopaminergic neurons, which may play a role in their degeneration (Song et al., 2010). Also, in a mouse model of Purkinje cell degeneration, Purkinje cells exhibit large scale reorganization of chromatin, telomere clustering, and heterochromatin formation that are hallmarks of degeneration (Baltanas et al., 2011).

## 4.0 Non-coding RNA regulation in neurodegeneration

### 4.1 Non-coding RNA regulation

The vast majority of human genomic DNA is non-protein-coding and, it seems to be transcribed almost entirely, from both positive and negative strands, leading to the formation of large numbers of ncRNAs (Mehler, 2008b). Furthermore, each nucleotide (nt) can be transcribed as a part of multiple distinct transcripts because of the way in which ncRNAs and protein-coding genes are oriented within the genome. ncRNAs can overlap protein-coding genes as well as other ncRNAs. Notably, ncRNAs can be transcribed not only from the nuclear genome but also from the mitochondrial genome. It has been suggested that these ncRNAs are, in terms of absolute numbers and total mass, more abundant than protein-coding RNAs in human cells, including neural cells (Kapranov et al., 2010). Evolutionary innovations in human brain form and function have even been linked to the emergence ncRNAs under positive selective pressure (Hu et al., 2011).

ncRNAs can be divided into various functional classes, including those, which are well known, such as transfer RNAs (tRNAs) and ribosomal RNAs. Of the myriads that have more recently been discovered, microRNAs (miRNAs) and long ncRNAs (lncRNAs) are two of the most important classes (Mehler, 2008b). They have emerging roles in controlling the expression and function of individual genes and large gene networks through transcriptional, post-transcriptional, and epigenetic mechanisms. miRNAs are 19–22 nt single stranded RNAs that regulate target messenger RNAs (mRNAs) via sequence-specific interactions. They generally bind to the 3' untranslated regions (UTRs) of these mRNAs inhibiting their translation by sequestering them for storage and transport or for degradation via the RNA-induced silencing complex (RISC). Remarkably, a single miRNA has the potential to regulate many different mRNAs, and an individual mRNA can be targeted by multiple miRNAs, highlighting the complexity of these miRNA networks. miRNAs are implicated in regulating genes involved in essential neurobiological processes, ranging from development and plasticity to aging, stress responses and disease pathogenesis.

lncRNAs, defined empirically as ncRNAs > 200 nt in length (but possibly orders of magnitude greater) because the methods used to characterize them are based on size, have a diverse and emerging spectrum of functions (Mehler, 2008b; Wang and Chang, 2011). These factors can interact with other nucleic acid molecules in a highly sequence-specific manner and also with proteins and other molecules through three-dimensional structural motifs and other biophysical relationships. Given this dual nature, lncRNAs have been described as “guideposts” that can recruit relatively non-selective transcriptional and epigenetic (e.g., histone modifying enzymes and chromatin remodeling complexes) regulatory factors to specific genomic sites, including potentially an individual locus or

multiple loci distributed throughout the genome. They can act as scaffolds for the assembly of nuclear domains (e.g., paraspeckles) containing factors responsible for post-transcriptional RNA processing (e.g., alternative splicing) and other specialized functions (e.g., rapid activation of stress response genes). They can act as “sinks” for capturing specific RNAs and protein molecules, reducing their availability and changing the stoichiometry of cellular processes. They can mediate nuclear-cytoplasmic transport. They can participate in translational control (e.g., local protein synthesis in synaptic compartments) (Mercer et al., 2009; Qureshi et al., 2010). Only a small number of lncRNAs have been interrogated in detail within the nervous system, but many more are expressed in highly specific regional, cellular, subcellular and environmentally responsive profiles, highlighting their potential importance in diverse neurobiological functions and disease states.

#### 4.2 Non-coding RNA pathways and profiles in neurodegenerative diseases

Abnormalities in ncRNA pathways and profiles are associated with neurodegeneration (Salta and De Strooper, 2012). In fact, genetic ablation of the miRNA biogenesis factor, *Dicer*, can lead to various forms of neurodegeneration in animal models (Hebert et al., 2010; Schaefer et al., 2007; Shin et al., 2009; Tao et al., 2011). In addition, genes that cause neurodegenerative diseases when mutated are implicated in modulating miRNA functions. For example, the PD-associated factor, LRRK2, regulates miRNA pathways through interactions with components of the RISC complex (Gehrke et al., 2010). Mutant LRRK2-mediated dopaminergic neuronal degeneration is mediated, in part, by deregulating the activity of *let-7* and *miR-184\** and the expression of their targets, E2F1 and DP. Furthermore, abnormal expression of ncRNAs is also associated with neurodegeneration. *mir-34* is a highly conserved miRNA that is upregulated in the *Drosophila* brain during adulthood and even more so with aging (Liu et al., 2012). Deleting the *mir-34* gene leads to a phenotype associated with accelerated brain aging, neurodegeneration, and reduced lifespan that can be rescued by restoring the age-associated expression of *mir-34*. Interestingly, expression levels of the *miR-34* family member, *miR-34b*, are elevated in plasma in preclinical stages of HD (Gaughwin et al., 2011) and those of *miR-34c* are elevated in the hippocampus of patients with AD (Zovoilis et al., 2011). Similarly, the expression profiles for many other miRNAs are deregulated in neurodegenerative disease-derived tissues, with important implications. For example, *let-7b* levels are elevated in cerebrospinal fluid (CSF) from patients with AD, activate Toll-like receptor 7 signaling, and thereby promote neurodegeneration (Lehmann et al., 2012). Decreased expression levels of miRNAs from the *miR-29a/b-1* cluster have been found in brain tissues from a subset of patients with sporadic AD (Hebert et al., 2008). These levels are inversely correlated with expression of one of the target mRNAs for these miRNAs,  $\beta$ -secretase 1 (BACE1), which is implicated in the pathophysiology of AD. In another example, midbrain tissue from patients with PD is deficient in *miR-133b*, a miRNA that is specifically expressed in dopaminergic neurons (Kim et al., 2007). Also, a study performed utilizing blood samples found that differentially expressed miRNAs can distinguish patients with PD from control subjects (i.e., *miR-1*, *miR-22\** and *miR-29*) and medicated patients with PD from non-medicated ones (i.e., *miR-16-2\**, *miR-26a2\** and *miR30a*), highlighting the potential clinical utility of these factors (Margis and Rieder, 2011).

In addition to miRNAs, other ncRNAs are being linked to neurodegeneration. For example, processing of tRNAs by angiogenin (ANG), a stress-activated ribonuclease, can lead to the formation of stress-induced tRNA fragments that promote stress granule assembly; interact with factors with roles in RNA metabolism, including those linked to neurodegenerative diseases (TAR DNA binding protein and fragile X mental retardation protein); and inhibit protein translation (Cole et al., 2009; Emara et al., 2010; Haussecker et al., 2010; Ivanov et

al., 2011; Lee et al., 2009). Loss of function mutations in the gene encoding ANG have been linked to ALS (Greenway et al., 2006), and ANG protects motor neurons against excitotoxicity, endoplasmic reticulum stress, and hypoxia (Kieran et al., 2008; Sebastia et al., 2009). Moreover, lncRNAs, such as the *BACE1-AS*, are implicated in regulating the expression and function of various genes that are linked to neurodegenerative diseases (Qureshi et al., 2010).

## Perspectives

While it is clear that epigenetic mechanisms are responsible for orchestrating neural development, plasticity, aging, homeostasis, and stress responses, we are just beginning to understand the roles played by DNA methylation and hydroxymethylation, histone modifications and higher order chromatin remodeling, and ncRNA regulation in the pathophysiology of neurodegenerative diseases. Nevertheless, important insights and questions have emerged. Firstly, genetic variation associated with modifying neurodegenerative disease risk has previously been interpreted almost exclusively in the context of protein-coding genes. In the epigenetic era, our analyses of these variations must also consider whether these gene loci can also give rise to ncRNAs and how these variations might alter ncRNA-protein, ncRNA-DNA, ncRNA-mRNA, and ncRNA-ncRNA interactions. Secondly, we must also account for how genetic variation can impact the epigenetic landscape. For example, at a single nt level, gain or loss of cytosine residues might lead to a change in possible methylation sites, and over larger genomic regions, different DNA sequences seem to be differentially susceptible to epigenetic modifications (Yang et al., 2012). Thirdly, we must reexamine our existing knowledge of neurodegenerative disease mechanisms, such as impairments in mitochondrial function, stress responses, and RNA metabolism, from an epigenetic perspective. For example, what are the roles of normal and pathological mitochondrial DNA methylation and ncRNAs in mediating the bioenergetic failure associated with aging and neurodegeneration? Given that diverse cellular stress responses systems implicated in the neurodegeneration (e.g., DNA damage, endoplasmic reticulum stress, autophagy, ubiquitin-proteasome, heat shock, and inflammation) are under epigenetic control, can we identify preclinical stages of disease by evaluating abnormal epigenetic marks associated with genes within these pathways? Also, because mutations in RNA binding proteins and disruptions in RNA metabolism are increasingly thought to be factors in neurodegenerative disease pathogenesis, can we compensate for these RNA-associated pathogenic alterations by modulating the epigenetic pathways that regulate transcription, RNA editing, splicing and transport, mRNA translation and RNA quality control?

Before these questions can be answered, however, many future studies are necessary to analyze epigenetic pathways and the elaboration of epigenetic profiles and to correlate these molecular signatures with clinical features and outcomes. Notably, major international efforts such as the Human Epigenome Project have already been launched in order to begin cataloging and interpreting epigenetic profiles in health and disease (2008). These epigenomic data must ultimately be integrated with genomic and other phenomic (e.g., transcriptomic, proteomic, and metabolomic) profiles in order to build a comprehensive understanding of neurodegenerative diseases and the process of neurodegeneration. This complexity notwithstanding, a plethora of studies have already highlighted the potential for epigenetic medicine in neurodegenerative disease and diagnostics evaluating epigenetic factors and pathways and complementary therapeutic agents targeting epigenetic factors are very actively being developed. For example, ncRNA expression levels in easily accessible tissues, such as CSF and blood, may provide signatures of central disease activity, as correlations are present between ncRNA expression profiles in brain and those in other tissues (Jeyaseelan et al., 2008; Tan et al., 2009). Moreover, microvesicles circulating in



blood that contain various ncRNAs can be secreted from all different types of neural cells (Chen et al., 2010; Skog et al., 2008). Strategies targeting HDACs, including the use of first-generation small molecule HDAC inhibitors approved by the FDA for other indications, have shown significant ability to mitigate neurodegeneration in preclinical studies (Biermann et al., 2011; Chen et al., 2009; Colussi et al., 2010; Hahnen et al., 2008; Mai et al., 2009; Ryu et al., 2003; Smith et al., 2010; Steffan et al., 2001; Suzuki, 2009; Zhao et al., 2006). Recent studies demonstrating that abnormalities in HDAC2-mediated histone acetylation of genes involved in learning and memory underlie cognitive symptoms in neurodegenerative diseases, such as AD, and that they can be reversed by inhibiting HDAC2 are also particularly intriguing (Graff et al., 2012). In fact, much more selective small molecule, oligonucleotide and related treatment approaches are being developed to modulate the epigenome and are poised to revolutionize neurodegenerative disease treatment (Arrowsmith et al., 2012; Bader et al., 2010; Li et al., 2010).

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