Published in final edited form as:

Brain Res. 2015 December 2; 1628(0 0): 265–272. doi:10.1016/j.brainres.2015.07.034.

Epigenetics and Therapeutic Targets Mediating Neuroprotection

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Abstract

The rapidly evolving science of epigenetics is transforming our understanding of the nervous system in health and disease and holds great promise for the development of novel diagnostic and therapeutic approaches targeting neurological diseases. Increasing evidence suggests that epigenetic factors and mechanisms serve as important mediators of the pathogenic processes that lead to irrevocable neural injury and of countervailing homeostatic and regenerative responses. Epigenetics is, therefore, of considerable translational significance to the field of neuroprotection. In this brief review, we provide an overview of epigenetic mechanisms and highlight the emerging roles played by epigenetic processes in neural cell dysfunction and death and in resultant neuroprotective responses.

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Competing Interests

The authors declare no competing financial interests.

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Keywords

neurodegeneration; preconditioning; stress responses; chromatin remodeling; post-transcriptional; DNA methylation; sirtuins; heat shock factor-1; RE-1 silencing transcription factor

Introduction

The emerging science of epigenetics is providing novel insights into factors and mechanisms that are at the nexus of brain development and aging, neural cell and network homeostasis and plasticity, and neurological disease pathogenesis (Mehler, 2008). Here, we discuss the implications of these recent advances for the field of neuroprotection, focusing on the roles of epigenetic processes in mediating neural cell dysfunction and death associated with a broad range of pathologies and, also, in the deployment of corresponding homeostatic and regenerative responses. We also discuss how epigenetic approaches have the potential to identify novel therapeutic targets for adult onset neurodegenerative disorders exhibiting evidence of developmental pathogenesis, such as Huntington's disease.

Epigenetics

Recent scientific and technological progress is revolutionizing our understanding of how complex genomic programs (e.g., transcriptional activation, repression, various 'poised' states, long-term gene silencing; X chromosome inactivation [XCI]; genomic imprinting) are mediated in diverse contexts (e.g., development, aging, trans-generational inheritance, and disease pathogenesis). The study of so-called epigenetic mechanisms—including DNA methylation, histone and chromatin modifications and non-coding RNA (ncRNA) regulation (see below)—has been a focal point in these advances. Yet, the term 'epigenetic' lacks a universally accepted definition (Maggert and Keith, 2015). Some have used it broadly to describe processes that are related to gene regulation, gene-environmental interactions, and phenotypic plasticity. Our definition of epigenetic is consistent with this view. By contrast, others use epigenetic to refer to phenomena that are involved in cellular memory states, specifically those that are heritable but not associated with changes in DNA sequences.

Our view of the field of epigenetics is that it focuses on defining the dynamic and intricate regulatory and functional interactions which occur between DNA, RNA, and protein molecules and ultimately give rise to cellular, and other higher-order, phenotypes. This definition embraces the paradigm-shifting and inextricably linked scientific advances of the post-genomic era (i.e., discovery and characterization of novel classes of functional genomic elements, pervasive transcription from the genome in both sense and antisense directions, and the seminal roles played by non-coding RNAs [ncRNAs] (Amaral et al., 2008; Bernstein et al., 2012)) and provides conceptual and experimental frameworks for an inclusive view of genomic architecture and associated molecular, cellular and systems level processes.

We believe that our definition of epigenetic is more pertinent in the nervous system and for post-mitotic neurons, in which the processes of DNA methylation, histone and chromatin modifications and non-coding ncRNA regulation clearly play important roles. These phenomena are highly integrated into the mechanisms responsible for orchestrating nervous

system structure and activity across the lifespan (Mehler, 2008). Indeed, increasing evidence suggests that epigenetic factors play critical roles in brain development and patterning, neural stem cell maintenance and differentiation, neural cell fate specification, adult neurogenesis, synaptic and neural network connectivity and plasticity underlying learning and memory, circadian rhythms, as well as the trans-generational inheritance of cognitive and behavioral traits.

Epigenetic factors and mechanisms

The major epigenetic mechanisms that have now been recognized are DNA methylation and hydroxymethylation, histone modifications and higher-order chromatin remodeling, and ncRNA regulation (Table 1).

Methylation and hydroxymethylation of the 5 positions on cytosine residues, forming 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC), are referred to, respectively, as DNA methylation and hydroxymethylation. These epigenetic modifications are distributed throughout the genome in specific gene regulatory regions (e.g., promoters and enhancers), inter- and intra-genic sequences, repetitive elements, and other genomic contexts in complex patterns that are dynamically regulated and subject to active maintenance and demethylation processes. The enzymes responsible for catalyzing 5mC and 5hmC formation, respectively, are the DNA methyltransferases (DNMTs) and the Ten-Eleven Translocation (TET) enzymes. Those mediating DNA demethylation include DNA excision repair, cytidine deaminase, and Gadd45 proteins. The roles of 5mC and 5hmC marks seem to be genomic site- and cellular context-specific and include modulating transcriptional activation, long-term gene silencing, transposable element activity, genomic imprinting, XCI, and genomic stability. However, 5mC within promoter elements—the best-characterized epigenetic mark—is generally linked to transcriptional repression. Specific families of proteins recognize and bind to methylated loci (e.g., methyl-CpG-binding domain [MBD] proteins including methyl-CpG-binding protein 2 [MeCP2]) and are referred to as “readers” of epigenetic modifications. In turn, these factors can recruit myriad effector proteins, having a diverse set of roles in transcriptional regulation and chromatin modification, to methylated loci. Importantly, levels of 5mC and 5hmC and the expression and function of associated enzymes, and related factors are cell type and tissue specific and sexually dimorphic, and they vary during the lifespan and in response to diet, environmental exposures, and other stimuli. Particularly, in brain, these marks are selectively enriched in neurons (Guo et al., 2013; Kozlenkov et al., 2013), neuronal and glial subtype specific (Kozlenkov et al., 2013), dynamically regulated throughout development and aging (Lister et al., 2013), coupled with activity dependent plasticity underlying learning and memory (Day et al., 2013; Kaas et al., 2013; Rudenko et al., 2013), and associated with trans-generational inheritance of cognitive and behavioral phenotypes (Dias and Ressler, 2013).

The genome is packaged within the cell nucleus into a compact structure referred to as chromatin that is comprised of DNA as well as histone proteins and associated factors (Mehler, 2008; Portela and Esteller, 2010). The smallest unit of chromatin is a nucleosome, ~146 base pairs of DNA wrapped around a histone octamer containing two of each core histone protein (i.e., H2A, H2B, H3, and H4). Linker DNA folded around linker histones

(i.e., H1) connects nucleosomes together, forming the characteristic beads-on-a-string appearance of chromatin fibers. These repeating elements are organized into progressively higher-order structures, including those that are very condensed (i.e., heterochromatin) and those that are relatively open (i.e., euchromatin) with the DNA template accessible to nuclear factors. Thus, chromatin states have significant modulatory roles in the execution of genomic programs, such as transcriptional activation, long-term gene silencing, transposable element activity, genomic imprinting, XCI, DNA replication and repair, and genomic stability. Notably, local and higher-order chromatin structures are not simply static but very dynamic. They are subject to alterations at the level of individual histone proteins and nucleosomes as well as over larger regions mediated by a broad range of histone modifying enzymes and chromatin remodeling proteins that serve as “writers” and “erasers” of epigenetic marks. Families of enzymes, including histone deacetylases (HDACs), histone acetyltransferases (HATs), histone demethylases (HDMs), histone methyltransferases (HMTs), and numerous others, catalyze site-specific histone protein post-translational modifications (PTMs). These PTMs, individually and in hierarchical combinations, influence the molecular properties of the nucleosome, which can impact, as one example, its interactions with chromatin reader proteins harboring binding domains selective for specific PTMs. In addition, nucleosomes can be repositioned exposing underlying DNA sequences, and they can be remodeled (e.g., replacement of canonical histones by variant histones) along with higher-order chromatin states. Macromolecular regulatory complexes frequently containing numerous epigenetic protein subunits can simultaneously read, erase, and write epigenetic marks across the entire spectrum of chromatin states. Their actions are integrated with cellular pathways responsive to environmental and interoceptive signals. The expression of these factors and the elaboration of associated profiles of epigenetic marks are, as in the case of DNA methylation, very dynamic and highly regulated in brain during development and aging in a genomic locus-selective, cell type-specific, and environmentally responsive manner. Indeed, chromatin and chromatin modulatory factors are implicated in mediating brain patterning (Mazzoni et al., 2013), neural stem cell function, neurogenesis and gliogenesis (Schauer et al., 2013; Yu et al., 2013), neuronal migration (Di Meglio et al., 2013; Nott et al., 2013), neural network connectivity (Di Meglio et al., 2013), sexual dimorphism in neural circuitry (Ito et al., 2012), homeostasis (Chatoo et al., 2009), synaptic plasticity (e.g., learning and memory) (Kerimoglu et al., 2013; Sando et al., 2012; Vogel-Ciernia et al., 2013), and brain aging (Cheung et al., 2010).

Transfer RNAs and ribosomal RNA are classic examples of ncRNAs that have very important and well-known biological actions. Even so, one of the most significant advances of the post-genomic era has been the identification of a multitude of novel classes and subclasses of ncRNAs that are transcribed from both strands of the genome in complex non-linear patterns. While the majority of these recently discovered ncRNAs is yet to be studied in detail, those that have seem to play critical roles in a broad, and rapidly increasing, range of cellular processes. These newly recognized classes of ncRNAs are divided based on size into those that are short or long (i.e., greater than 200 nucleotides). The best-studied classes of short ncRNAs include microRNAs (miRNAs), endogenous short-interfering RNAs, PIWI-interacting RNAs, and small nucleolar RNAs. Each possesses particular biogenesis pathways and mechanisms of action. They subserve diverse and complementary functions.

miRNAs are, perhaps, the most relevant of these short ncRNAs. They are involved in post-transcriptional regulation of genes and gene networks. These single stranded 20–23 nucleotide transcripts bind preferentially to the 3' untranslated regions of mRNAs through sequence-specific interactions, leading to sequestration or degradation of these target mRNAs (rather than translation). Several different miRNAs can bind to an individual mRNA. Conversely, a particular miRNA can regulate many distinct mRNAs. By contrast, long ncRNAs (lncRNAs) are more heterogeneous and their properties are less well defined. One of the key strategies for understanding lncRNAs is to examine their genomic contexts, especially their orientations relative to protein coding genes. Some lncRNAs are transcribed from intergenic regions (long intergenic/intervening ncRNAs), whereas other lncRNAs have antisense or overlapping relationships with protein-coding genes. These transcripts are often linked functionally, with the lncRNA regulating the local chromatin environment and the transcription and post-transcriptional processing of the associated protein-coding gene. In addition, lncRNAs are also involved in a spectrum of other activities, recruiting transcriptional and epigenetic regulators to specific loci, forming nuclear subdomains, modulating nuclear-cytoplasmic transport, and controlling local protein synthesis at synapses. The expression of ncRNAs is selectively enriched in brain, highly spatially and temporally orchestrated, and implicated in mediating neural development and aging, cellular diversity, homeostasis and stress responses, synaptic and neural network connectivity and plasticity (Qureshi and Mehler, 2012; Qureshi and Mehler, 2013a).

Epigenetics and neural cell injury

It is becoming increasingly clear that epigenetic mechanisms are involved both in mediating neural cell injury and also in orchestrating countervailing neuroprotective responses. Epigenetic factors and processes are highly integrated into the cellular mechanisms underlying neural cell dysfunction and death in a broad range of disease states, in which, they serve not simply as bystanders but as key mediators of pathology. Indeed, manipulating epigenetic factors and processes in disease models with genetic or pharmacological approaches can significantly modulate the extent of neural damage.

For example, one recent study reported that tau-mediated neurodegeneration involves an epigenetic component (Frost et al., 2014). The authors found that brains from transgenic tau models and hippocampal neurons from Alzheimer's disease (AD) patients exhibit a global relaxation of chromatin, signified by decreased levels of histone H3 lysine 9 dimethylation (H3K9me2), heterochromatin protein 1-alpha, and heterochromatin formation. Importantly, the magnitude of chromatin relaxation correlated with tau-related neurotoxicity. Modulating heterochromatin formation via genetic manipulations modified the neurodegenerative phenotype, implying a causal relationship. The interconnections between epigenetic mechanisms and tau and tauopathies are much more complex, however. Another study performed utilizing a *Drosophila* model that produces human tau identified a miRNA, miR-219, which targets the tau transcript (Santa-Maria et al., 2015). Reducing and overexpressing miR-219 increased and decreased tau-related toxic effects, respectively. These two examples illustrate how epigenetic mechanisms might be involved in tauopathies as downstream effectors of tau and also as upstream regulators of tau, itself. There is also evidence that epigenetic processes may be involved in mediating the effects of the H1

haplotype, the major genetic risk factor for a subset of tauopathies (i.e., progressive supranuclear palsy). A genome-wide study of DNA methylation profiles found that the H1 haplotype has a dose dependent effect on methylation within the associated 17q21.31 chromosomal region in brain, and also remarkably in blood (Li et al., 2014).

Epigenetic factors and mechanisms are similarly embedded within a very broad spectrum of other pathogenic processes. Here, we list but a few interesting examples. In ataxia telangiectasia, the nuclear accumulation of HDAC4 and increased H3K27me3, mediated by Polycomb repressive complex 2, contributes directly to neuronal cell death (Li et al., 2012; Li et al., 2013). In spinocerebellar ataxia type 7, mutant ataxin 7 disrupts ncRNA regulatory circuitry that includes the miRNA, miR-124, and the lncRNA, lnc-SCA7, leading to increased *ATXN7* expression in neuronal cells, particularly within the retina and cerebellum, and likely contributing to cell type-specific vulnerability to neurodegeneration (Tan et al., 2014). In oxidative stress-induced mouse cerebellar granule neuron apoptosis, HDAC2 is deregulated and its interaction with forkhead box O3 is disrupted, impairing FOXO3-dependent gene transcription by promoting increased histone H4K16 acetylation in the p21 promoter region and upregulating p21 (Peng et al., 2015). In brain ischemia, increased levels of the histone H3 serine 28 phosphorylation mark alter the genomic localization and function of chromatin remodeling complexes (i.e., polycomb repressive complex 1 and Trithorax proteins), leading to neuronal necrosis (Liu et al., 2014). Inhibiting this epigenetic cascade reduces the extent of necrosis.

Epigenetics and neuroprotective responses

Conversely, epigenetic factors and mechanisms are also involved in neuroprotective responses. One study demonstrated, for example, that increased levels of Polycomb group proteins provoke global transcriptional repression and are thus responsible for the beneficial effects of ischemic preconditioning on the brain (Stapels et al., 2010). The authors showed that knocking down these epigenetic factors inhibits the development of ischemic tolerance and also that overexpressing two of these proteins, *Scmh1* or *Bmi1*, induces tolerance even without any preconditioning stimulus. A similar relationship seems to exist between the activation of epigenetic factors and the emergence of epileptic tolerance, which is similarly associated with a pervasive downregulation of gene expression. An analysis of the protective effects of brief seizures in a mouse model of status epilepticus revealed differentially temporally and spatially regulated profiles of chromatin modulatory proteins, including increased expression of *Ezh2*, *Suz12*, and *Yy2* and decreased *Ring 1B* and *Bmi1* (Reynolds et al., 2015). These data could imply the existence of a common neuroprotective epigenetic program active in these states, and perhaps other disease entities. Additional functional studies targeting these factors have shown the potential to mitigate neural cell injury. Genetic ablation of *Bmi1* promotes robust photoreceptor survival in *Rd1* mice, which typically display severe early onset retinal degeneration, by attenuating cell cycle-related death process (Zencak et al., 2013). Together, these data suggest that *Bmi1* and related factors are potential therapeutic targets for neuroprotection and that novel and robust neuroprotective strategies will need to be pathological state-specific, hierarchical and multidimensional in scope with *in vivo* readouts of epigenetic as well as biological efficacy.

Emerging evidence is elucidating how these and other epigenetic factors are responsible for mediating a very diverse set of homeostatic and stress responses. As one example, a recent study demonstrated that Dnmt3a activity in neurons of the paraventricular nucleus of the hypothalamus (PVH) is linked to central control of energy metabolism (Kohno et al., 2014). Specifically, the authors found that mice lacking Dnmt3a in neurons within the forebrain, including the PVH, become obese and exhibit increased abdominal and subcutaneous fat accumulation, hyperphagia, decreased energy expenditure, and glucose intolerance. These effects on energy balance were mediated by decreased levels of tyrosine hydroxylase promoter methylation and a corresponding increase in the expression of tyrosine hydroxylase within the PVH. Sirtuin 1 (SIRT1) is another epigenetic factor that catalyzes the deacetylation of both histone and non-histone proteins. It has emerging roles in modulating metabolic pathways and circadian rhythms as well as neuroprotection (Orozco-Solis and Sassone-Corsi, 2014). One study recently reported an age-related decrease in SIRT1 associated with aging of microglia, and that deficiency of SIRT1 in mice microglia leads to hypomethylation of the interleukin-1-beta (IL-1-beta) proximal promoter and IL-1-beta upregulation, which seems to play a causal role in age-related cognitive decline and neurodegeneration (Cho et al., 2015). These studies demonstrate how epigenetic factors and processes are integrated into diverse functions, which are linked to neural homeostasis, such as energy balance and metabolism and innate immunity. These data imply that targeting specific and seminal epigenetic factors and mechanisms could potentially reprogram these processes, thereby facilitating neuroprotection.

Epigenetic mechanisms are also highly integrated into the heat-shock response. Heat shock factor-1 (HSF1) is the major factor regulating cytoprotective transcriptional programs in response to heat-shock. It acts partly by inducing genome-wide deacetylation via interactions with HDAC1 and HDAC2 (Fritah et al., 2009). Heat shock RNA 1 is a lncRNA that facilitates HSF1 activation, including its trimerization and association with eukaryotic elongation factor 1A (Shamovsky and Nudler, 2009). In fact, ncRNAs seem to have numerous roles in the heat shock response (Place and Noonan, 2014). Also interestingly, HSF1 is implicated in the neuroprotection via an epigenetic mechanism independent of its canonical functions. Specifically, HSF1 protects neurons from cell death through a non-canonical heat shock protein- and trimerization-independent pathway, which is mediated by SIRT1 (Verma et al., 2014). This mechanism may be relevant for explaining the influence of HSF1 on the expression of neurodegenerative phenotypes. In particular, a recent study showed that HSF1 modulates the accumulation of pathogenic androgen receptor (AR) levels in spinal and bulbar muscular atrophy (Kondo et al., 2013). Depleting HSF1 expands the distribution of the pathology, and introducing HSF1 into the brain reduces pathogenic AR accumulation and neural injury. These findings illustrate the complexity of the layers of interconnections that can exist between epigenetic influences and a specific stress response. These examples also imply that targeting epigenetic mechanisms, including proteins and regulatory ncRNAs, can potentially promote neuroprotection and impact canonical and non-canonical pathways differentially.

Another important and relevant example is provided by the RE1-silencing transcription factor (REST). REST is a key transcriptional and epigenetic regulator of neural genes including both protein coding and ncRNA genes during development and adult life (Qureshi

et al., 2010). REST is involved in repressing genes that promote cell death and activating genes that protect against oxidative stress and amyloid beta-protein toxicity (Lu et al., 2014). REST expression is induced during normal brain aging, particularly in cortical and hippocampal neurons. REST levels correlate with cognitive health and longevity. Further, a genetic variant of REST (*rs3796529*) is protective against hippocampal atrophy in patients with amnesic mild cognitive impairment (Nho et al., 2015). Conversely, nuclear REST expression is reduced in disease states such as AD, frontotemporal dementia, and dementia with Lewy bodies. These findings suggest that modulating REST could be valuable therapeutically and several approaches are now being investigated to target REST, including small molecules, RNA interference, decoy oligonucleotides, and synthetic peptide nucleic acid oligomers (Conforti et al., 2013; Leone et al., 2008; Rigamonti et al., 2007; Rigamonti et al., 2009).

Huntington's disease

These observations provide hope that the field of epigenetics has the potential to identify novel and transformative therapeutic targets for adult onset neurodegenerative disorders, especially those with preclinical stages of disease lasting years or even decades and having evidence of developmental pathogenesis, implying the existence of an extended window for treatment. Huntington's disease (HD) represents one such developmental-degenerative disorder (Molero et al., 2009; Molina-Calavita et al., 2014; Nguyen et al., 2013a; Nguyen et al., 2013b; Nguyen et al., 2014; Paulsen et al., 2008; Woda et al., 2005). Several provocative studies have provided insights into the roles of epigenetic factors and mechanisms in HD, including development (Dietz et al., 2015) and adult life (Bai et al., 2015), and suggested that targeting these, perhaps early in life or even in previous generations, could have therapeutic value. Targeting HDAC4 in a HD mouse model has demonstrated the potential to reduce cytoplasmic aggregate formation and rescue the neurodegenerative phenotype (Mielcarek et al., 2013). Also, REST has been linked closely with the molecular pathophysiology of HD. It is believed that the huntingtin protein (Htt) participates in sequestering REST in the cytoplasm. By contrast, mutant Htt (mHtt) promotes REST translocation into the nucleus and is implicated in transcriptional dysregulation, one of the hallmarks of HD, affecting both protein coding and short and long ncRNA transcripts (Soldati et al., 2013; Zuccato et al., 2003). Studying transcriptional networks in HD has identified a number of interesting relationships including deregulation of miRNAs derived from HOX gene clusters that may be involved in neuroprotective responses (i.e., miR-10b-5p, miR-196a-5p, miR-196b-5p, and miR-615-3p) (Hoss et al., 2014), reciprocal regulatory relationships between deregulated miRNAs (miR-9/9*) and REST (and CoREST) (Packer et al., 2008), the expression of a lncRNA with roles in pluripotency and neural lineage commitment in striatal tissue that correlates with the degree of HD pathological disease severity (Lin et al., 2014), and preferential downregulation of genes controlled by super-enhancers (Achour et al., 2015). SIRT1 is another promising target for neuroprotection in HD. Though, there is controversy as to whether activation (Jeong et al., 2012; Jiang et al., 2012) or inhibition (Smith et al., 2014) of SIRT1 is likely to be beneficial. Notably, HSF1 also has neuroprotective effects in HD, which are likely mediated in part by SIRT1 (Verma et al., 2014). Further, HSF1 targets the Htt interacting protein, Huntingtin

Yeast Partner K (HYPK), which is also induced by cellular stress, consistent with the potentially specific role of HSF1 in HD neuroprotection (Das and Bhattacharyya, 2014; Sakurai et al., 2014). Another very intriguing study recently reported that pharmacological modulation of epigenetic factors can have beneficial effects in HD that are trans-generational (Jia et al., 2015). The authors showed that a HDAC1/3 inhibitor alters epigenetic profiles not only in treated mice but also in sperm from male mice and their offspring and, remarkably, also improves HD disease phenotypes in the first filial generation. In particular, they identified increased lysine-specific demethylase 5D expression and decreased levels of histone H3K4 methylation. Although similar strides are beginning to be seen with other neurodegenerative diseases, HD is the most advanced in terms of our understanding of the nuanced and multilayered epigenetic processes affecting disease pathogenesis as well as potential links to an earlier developmental diathesis. This latter point is important both in relation to possible greater therapeutic efficacy afforded by access to an earlier prodromal phase of illness as well as to our greater understanding of epigenetic mechanisms mediating classical neurodevelopmental disorders.

Epigenetic medicine is still in its infancy (Qureshi and Mehler, 2013b; Szyf, 2015). Nevertheless, these findings suggest that a broad range of epigenetic features could serve as diagnostic and therapeutic targets in HD and beyond. Epigenetic factors operate in tandem with pathological genetic mechanisms and epigenetic alterations seem to frequently precede overt disease pathology, implying that they could have diagnostic or prognostic value, even in an autosomal dominant disorder such as HD. It is important to emphasize that epigenetic states are inherently malleable, making them outstanding choices for therapeutic intervention. In our view, modulating epigenetic mechanisms complements and could promote other emerging treatment paradigms, including those focused on lowering Htt, improving Htt clearance, increasing neurotrophic support, preserving and enhancing synaptic function, immunomodulation, and metabolic reprogramming (Wild et al., 2015). Indeed, we believe that targeting epigenetic factors could facilitate the execution of each these strategies. Epigenetic approaches could also preferentially be aimed at mitigating specific pathological hallmarks of HD, such as transcriptional dysregulation. It is possible to envision different epigenetic/non-epigenetic strategies being employed at distinct stages of disease evolution. For example, trans-generational epigenetic reprogramming might be used prior to conception. Other stage-selective treatments (and combinations thereof) could be designed for pre-symptomatic and manifest HD, respectively.

Conclusion

Our evolving understanding of the complexity of epigenetic processes and mechanisms is revolutionizing the field of neuroprotection by helping to define the molecular basis of neural cell injury and disease. It is also providing a spectrum of novel approaches to reestablish cellular and systems level homeostasis as well as prevent and reverse disease processes. In this review, we have tried to stress the nested and interdependent epigenetic processes underlying such pathological as well as corresponding reparative processes, including pre-conditioning paradigms. These observations suggest that neural cell injury and death involve pathological modulation of individual causal genes and appropriate functional gene networks orchestrated by a compendium of local as well as genome-wide profiles of

epigenetic dysregulation. Therefore, relevant therapeutic strategies to prevent or forestall neural cell injury, death and associated neural network impairments will require multifaceted approaches that employ a spectrum of complementary epigenetic processes and mechanisms occurring over a continuum of dynamic and context-specific temporal and spatial intervals. The ability to manipulate different classes of epigenetic effector molecules to promote direct cellular reprogramming and neural network remodeling in the intact brain and the periphery in tandem and with conditional and inducible molecular constructs as well as other emerging epigenome engineering technologies offers great promise for making meaningful inroads into the treatment of complex neurological diseases. These strategies may be important during prodromal phases of disease as well as potentially in response to multi-generational susceptibilities to these disease states.

Acknowledgments

We regret that space constraints have prevented the citation of many relevant and important references. M.F.M. is supported by grants from the National Institutes of Health (NS071571, HD071593, MH66290), as well as by the F.M. Kirby, Alpern Family, Mildred and Bernard H. Kayden and Roslyn and Leslie Goldstein Foundations.

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Highlights

- Epigenetic phenomena orchestrate nervous system structure and activity across the lifespan.
- Epigenetic mechanisms also mediate neural cell injury and countervailing neuroprotective responses.
- Epigenetics has the potential to identify transformative therapeutic targets for adult onset neurodegenerative disorders.

Table 1

Major epigenetic mechanisms that have now been recognized and associated factors.

Epigenetic mechanisms	Associated epigenetic factors
DNA methylation and hydroxymethylation	DNA methyltransferase enzymes Ten-Eleven Translocation enzymes Thymine DNA glycosylase Gadd45 proteins Apolipoprotein B editing catalytic subunit/activation-induced deaminase (APOBEC/AID) cytidine deaminase enzymes Methyl-CpG-binding domain proteins
Histone modifications and higher-order chromatin remodeling	Core, linker and variant histone proteins Histone deacetylase enzymes Histone acetyltransferase enzymes Histone demethylase enzymes Histone methyltransferase enzymes ATP-dependent chromatin remodeling complexes Polycomb proteins Trithorax proteins RE1-silencing transcription factor (REST)
Non-coding RNA regulation	MicroRNAs Endogenous short-interfering RNAs PIWI-interacting RNAs Small nucleolar RNAs Long ncRNAs