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Epigenetic Principles and Mechanisms Underlying Nervous System Functions in Health and Disease

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Abstract

Epigenetics and epigenomic medicine encompass a new science of brain and behavior that are already providing unique insights into the mechanisms underlying brain development, evolution, neuronal and network plasticity and homeostasis, senescence, the etiology of diverse neurological diseases and neural regenerative processes. Epigenetic mechanisms include DNA methylation, histone modifications, nucleosome repositioning, higher-order chromatin remodeling, non-coding RNAs, and RNA and DNA editing. RNA is centrally involved in directing these processes, implying that the transcriptional state of the cell is the primary determinant of epigenetic memory. This transcriptional state can be modified by internal and external cues affecting gene expression and post-transcriptional processing, but also by RNA and DNA editing through activity-dependent intracellular transport and modulation of RNAs and RNA regulatory supercomplexes, and through trans-neuronal and systemic trafficking of functional RNA subclasses. These integrated processes promote dynamic reorganization of nuclear architecture and the genomic landscape to modulate functional gene and neural networks with complex temporal and spatial trajectories. Epigenetics represents the long sought after molecular interface mediating gene-environmental interactions during critical periods throughout the lifecycle. The discipline of environmental epigenomics has begun to identify combinatorial profiles of environmental stressors modulating the latency, initiation and progression of specific neurological disorders, and more selective disease biomarkers and graded molecular responses to emerging therapeutic interventions. Pharmacoepigenomic therapies will promote accelerated recovery of impaired and seemingly irrevocably lost cognitive, behavioral, sensorimotor functions through epigenetic reprogramming of endogenous regional neural stem cell fate decisions, targeted tissue remodeling and restoration of neural network integrity, plasticity and connectivity.

Keywords

Epigenetics; chromatin remodeling; non-coding RNAs; RNA and DNA editing; RNA regulatory networks; nuclear architecture; stem cell biology; learning and memory; neuropsychiatric diseases; neurodevelopmental disorders; neurodegenerative diseases; neurooncology; neuroimmunology; cerebrovascular disorders; environmental epigenomics; pharmacoepigenomics

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1. DNA methylation and methyl CpG binding proteins

The four cardinal and interdependent epigenetics mechanisms, including DNA methylation; histone code, nucleosome and higher-order chromatin remodeling; non-coding RNAs (ncRNAs); RNA editing and DNA recoding, have all been implicated in orchestrating a seemingly infinite variety of molecular and cellular processes essential for higher nervous system functions and evolutionary innovations (Feng et al., 2007; Klose and Bird, 2006; Kondo, 2006; Mehler and Mattick, 2007; Taniura et al., 2007; Tsankova et al., 2007). DNA methylation represses local and genome-wide gene transcription through the transfer of methyl groups from S-adenosyl methionine to DNA sequences containing cytosine dinucleotides (CpG) and is catalyzed by DNA methyltransferases (DNMTs) endowed with “maintenance” of methylation (DNMT1) or “de novo” methylation (DNMT3A/B/L) important for distinct developmental and mature neural functions (Klose and Bird, 2006). A related RNA methyltransferase (DNMT2) is involved in gene silencing during development (Rai et al., 2007). Within the genome, non-coding regions within individual genes (intronic) and between separate genes (intergenic) are heavily methylated to preserve genomic integrity, to repress expression of germline genes in somatic cells and to establish and maintain cell identity by stabilizing DNA associated with chromosome segregation during mitosis (centromeres), cellular aging (telomeres), mobile parasitic repeat sequences introduced primarily through evolutionary waves of viral invasion (DNA transposons, retrotransposons) as well as by facilitating gene dosage effects and diversification of gene expression from maternal and paternal alleles (genomic imprinting and X-chromosome inactivation) (Wilson et al., 2007). Gene promoter elements display more complex and changing patterns of DNA methylation, where transcriptional repression generally correlates with the degree of methylation within promoter CpG clusters or islands and the extent of interference with transcription factor binding (Freitag and Selker, 2005; Weber et al., 2007).

DNA methylation also exhibits intricate interactions with multiple components of the epigenetic machinery (enzymes mediating nucleosome and higher order chromatin remodeling, ncRNAs and RNA editing) and participates in the orderly elaboration of epigenetic marks essential for mediating rapidly reversible as well as short- and long-term gene silencing and multigenerational inheritance (Metivier et al., 2008; Nightingale et al., 2006). Profiles of DNA methylation are intimately linked to patterns of histone protein post-translational modifications by methyl CpG binding proteins (MBDs) that are recruited to methylated DNA in association with large and dynamic protein complexes containing specific types of histone-modifying enzymes that reinforce and stabilize gene repression patterns and orchestrate DNA replication and repair (Klose and Bird, 2006). MBDs, such as MeCP2, may mediate genomic imprinting by promoting selective gene pair (allele)-specific chromatin looping of methylated sequences in imprinted regions resulting in allele-selective profiles of gene expression (Yasui et al., 2007).

Recent studies suggest that individual DNA methylation signatures may account for differences in neuronal identity and in regional functional specialization (Ladd-Acosta et al., 2007). De novo DNA methylation has been shown to prevent the premature expression of neural stem cell-associated as well as alternate differentiation programs (Weber et al., 2007). Levels of DNMT1 are high in the embryonic nervous system and function to maintain profiles of DNA methylation in dividing neural precursors (Feng et al., 2007). DNMT1 is also expressed in post-mitotic neurons and glia in the perinatal and adult brain where it facilitates cellular turnover and specific forms of DNA repair (Feng et al., 2007). DNMT3B is expressed in early embryonic neural progenitors during neurogenesis, whereas DNMT3A is expressed at later developmental stages and in the adult brain in all undifferentiated and differentiated neural cell types, with peak expression occurring during the critical postnatal window of neuronal

maturation with residual expression during adult life, particularly within stem cell generative zones mediating constitutive neurogenesis (Feng et al., 2007). The expression and enzymatic activity profiles of DNMTs are actively modulated by an array of physiological and pathological states and interactions with DNMT3L, and the continued expression and precise regulation of DNMTs is essential for mediating neuronal survival, plasticity and stress responses (Klose and Bird, 2006; Ooi et al., 2007). DNA methylation also directly regulates the timing of astrocyte differentiation by modulating the methylation status of specific transcription factor binding motifs present within multiple glial maturational genes (Feng et al., 2007; Kondo, 2006). Multiple MBDs are also actively involved in brain development and adult function, including the diverse roles of MeCP2 as both a transcriptional activator as well as a repressor in post-mitotic neurons, and MBD1 in adult neurogenesis (Chahrour et al., 2008; Feng et al., 2007; Kondo, 2006).

A wide variety of Mecp2 mutant mice have been generated and molecular, histopathological and behavioral examination has provided significant insights into the pathogenesis of Rett syndrome (Chahrour and Zoghbi, 2007). These studies indicate that MeCP2 is essential for progressive stages of postnatal brain development and mature neuronal function, modulates synaptic function and plasticity, autonomic responses and complex neurobehavioral and motoric repertoires, regulates axonal targeting and neural network deployment, has preferential roles in nervous system functioning, and MeCP2 expression levels are under stringent regulation to prevent a spectrum of neurodevelopmental and neuropsychiatric conditions. Moreover, these animal models indicate that the neurological dysfunction in Rett syndrome may be functionally reversible due to epigenetic plasticity inherent in the activity profiles of MeCP2 and potentially other MBDs (Giacometti et al., 2007; Guy et al., 2007).

2. Histone code modifications, nucleosome repositioning and chromatin remodeling

The ability to continually modulate the precise profiles of expression of single genes and functional gene networks within individual nerve cells and neural networks throughout the brain in response to complex metabolic signals, diverse cellular processes and intricate profiles of environmental cues requires the dynamic remodeling of a multilayered network of chromatin architecture transacted by an ever expanding array of enzymes and associated signal transduction pathways (Bhaumik et al., 2007; Feng et al., 2007; Ito, 2007; Kouzarides, 2007; Ruthenburg et al., 2007; Schwartz and Pirrotta, 2007). Chromatin is composed of units of DNA along with histone and non-histone proteins that promote the proper three-dimensional folding of DNA and the dynamic regulation of whole genome functions within the nucleus (Kouzarides, 2007). The smallest functional unit of chromatin, the nucleosome consists of a small stretch (147 base pairs) of DNA wrapped around a core of pairs of integral (H2A, H2B, H3, H4) histone proteins, as well as linker (H1) and specialized variant histones (Godde and Ura, 2008; Ito, 2007; Kamakaka and Biggins, 2005). The organization of nucleosomes promotes fine-tuning and local control of DNA folding, precise access of transcription factors and co-factors to DNA regulatory regions and the orderly progression of gene transcription and DNA repair processes (Berger, 2007; Ruthenburg et al., 2007). Moreover, the nucleosome contains regional molecular recruitment and signaling platforms for coordinating genome-wide, higher-order chromatin remodeling (Berger, 2007; Ruthenburg et al., 2007).

Chromatin exists in a spectrum of functional states interspersed between condensed and inactive (heterochromatin) and open and active (euchromatin) forms, with some genomic regions present in a highly repressed long-term inactive state to promote genomic stability, some in an inactive but permissive state to facilitate seminal cellular processes such as cell division, and some in a poised state associated with transcriptional memory and the expression of variant histone marks to properly modulate cellular mechanisms underlying neural

developmental maturation (Berger, 2007; Downs et al., 2007; Grewal and Jia, 2007; Kouzarides, 2007; Raisner and Madhani, 2006; Su and Tarakhovsky, 2006). “Constitutive” heterochromatin utilizes numerous epigenetic mechanisms to spread across large chromosomal regions and regulates diverse cell processes such as genomic stability, long-range gene modulation, recruitment of non-coding regulatory RNAs and establishment of gene dosage effects, including selective expression of genes from maternal and/or paternal-derived alleles (Chen et al., 2008a; Downs et al., 2007; Grewal and Jia, 2007; Kouzarides, 2007; Schwartz and Pirrotta, 2007). By contrast, “facultative “heterochromatin exhibits cell-selective profiles of deployment associated with developmental morphogenesis and cellular differentiation (Chen et al., 2008a; Downs et al., 2007; Grewal and Jia, 2007; Kouzarides, 2007; Schwartz and Pirrotta, 2007). Maintenance of chromatin architecture requires complex interactions between adjacent regions of heterochromatin and euchromatin mediated by diverse boundary elements (transcription factors [CCCTC-binding factor: CTCF], variant histones [H2A.Z] and heterochromatin protein [HP1] subtypes) that preserve the integrity of gene expression while also creating higher-order DNA loops to facilitate the interactions of distant gene regulatory elements and to recruit additional chromatin-modifying enzyme complexes (Akhtar and Gasser, 2007; Berger, 2007; Downs et al., 2007; Grewal and Jia, 2007; Raisner and Madhani, 2006; Schuettengruber et al., 2007).

Primary histone modifications encompass an elaborate epigenetic lexicon that demarcates functional genomic microdomains, acting as molecular beacons to attract chromatin-modifying factors containing specific interaction domains required to selectively modulate the progression and fidelity of essential cellular processes including transcription, translation, DNA replication and repair (Ito, 2007; Kouzarides, 2007; Ruthenburg et al., 2007; Schwartz and Pirrotta, 2007). Intricate and changing profiles of post-translational covalent modifications (methylation, acetylation, phosphorylation, ubiquitylation, SUMOylation, ADP-ribosylation, deimination, proline isomerization) of different histone proteins at specific amino acid residues (lysine [K], arginine [R], serine [S], threonine [T], glutamate [E]) predominantly on their amino-terminal tails and at defined genomic loci are orchestrated by an expanding array of enzymes with complex activity profiles (Kouzarides, 2007). These histone-modifying enzymes add or remove histone modifications in response to local profiles of complementary histone modifications, coordinate actions of higher-order chromatin modifiers and additional cellular signaling pathways and associated metabolic and environmental cues that collectively modulate gene expression and function with exquisite degrees of spatial and temporal resolution (Hogan and Varga-Weisz, 2007; Kouzarides, 2007; Nightingale et al., 2006; Ruthenburg et al., 2007; Taniura et al., 2007). Histone-modifying enzymes can also concurrently modulate cellular processes linked to gene expression through separate actions on non-histone proteins (Taniura et al., 2007). In addition, histone-modifying enzymes are often components of larger multiprotein and even transcriptional supercomplexes involved in coordinated intra- and inter-chromosomal interactions, dramatic reorganization of nuclear territories and transient creation of “transcription factories” to execute integrated genome-wide gene expression profiles, functional outcomes and flexible and evolving gene and neural network programs (Akhtar and Gasser, 2007; Ooi and Wood, 2007; Rosenfeld et al., 2006; Ruthenburg et al., 2007; Schneider and Grosschedl, 2007).

Chromatin profiles or “codes” are important for ensuring the versatility and the heritability of diverse epigenetic processes including genomic imprinting, X-chromosome inactivation, heterochromatin formation, gene silencing and also incomplete epigenetic reprogramming whose molecular signals may be transmitted across multiple generations independent of the original inciting environmental stimuli (Anway et al., 2008; Dolinoy et al., 2007; Grewal and Jia, 2007; Groth et al., 2007; Hajkova et al., 2008; Reik, 2007; Sasaki and Matsui, 2008). Higher-order chromatin codes are transacted by distinct polycomb (PcG) and trithorax (TrxG) group complexes that bind to regulatory regions of multiple gene targets through PcG-

("*PRE*") and TrxG- ("*TRE*") response elements and thereby establish reversible signaling platforms to recruit and orchestrate the functions of enzymes involved in DNA methylation, histone modification, ATP-dependent nucleosome remodeling and regulatory RNA processing (Schuettengruber et al., 2007). PcG- and TrxG-mediated chromosome condensation and relaxation, respectively, are essential for promoting essential cellular processes including mitosis and apoptosis as well as DNA replication, repair, recombination and transcription (Berger, 2007; Downs et al., 2007; Groth et al., 2007; Hogan and Varga-Weisz, 2007; Ruthenburg et al., 2007; Schuettengruber et al., 2007). By contrast, nucleosome-remodeling enzymes promote more local nucleosome repositioning to orchestrate the directionality and sequential elaboration of transcriptional events and to prevent transcription initiation from cryptic sites and "read-through" to adjacent genes (Hogan and Varga-Weisz, 2007; Whitehouse et al., 2007). Components of the histone and higher-order chromatin codes are essential for preserving the organization of distinct functional nuclear microdomains and for enhancing the fidelity of linked genomic processes such as the coupling of gene transcription to RNA post-transcriptional processing including gene splicing, stability, error detection, nuclear export, cellular localization, as well as maintenance of epigenetic transcriptional memory by the actions of the variant histone, H2A.Z, all initiated and localized at the nuclear pore complex (Akhtar and Gasser, 2007; Raisner and Madhani, 2006). Histone modifications and chromatin reorganization have been implicated in neural stem cell maintenance and progressive cell fate restriction, neuronal and glial subtype specification and maturation, neuronal homeostasis, neural network plasticity, learning and memory, sophisticated cognitive and behavioral capacities, brain aging and the pathogenesis of diverse neurological and psychiatric disorders (Bhaumik et al., 2007; Blasco, 2007; Feng et al., 2007; Hsieh and Gage, 2004; Kondo, 2006; Kouzarides, 2007; Mikkelsen et al., 2007; Ooi and Wood, 2007; Shi et al., 2007b; Taniura et al., 2007; Tsankova et al., 2007).

3. Non-coding RNAs: functional subclasses and genomic context

The proportion of non-protein coding regions within eukaryotic genomes has expanded significantly as a function of developmental complexity during evolution (Frith et al., 2005; Mattick, 2004; Pang et al., 2006; Taft et al., 2007). By contrast, the number of protein-coding genes has remained relatively static (Frith et al., 2005; Mattick, 2004; Pang et al., 2006; Taft et al., 2007). Moreover, recent studies have demonstrated that the vast majority of these non-protein coding regions are actively transcribed, often in intricate modular and interleaved patterns from both DNA strands (Gingeras, 2007; Kapranov et al., 2007b). A large proportion of these transcripts are further processed to give rise to small and longer regulatory ncRNAs that function through sequence-specific or "digital" recognition of DNA, RNA and higher-order DNA: RNA complexes as well as via conformational or "analogue" interactions with RNA binding proteins (RBPs) and other protein-based signaling networks (Keene, 2007; Mattick and Makunin, 2005; 2006; St Laurent and Wahlestedt, 2007). These ncRNAs promote developmental and adult homeostatic and plasticity programs and the integration of environmental inputs through changes in DNA methylation, chromatin architecture, epigenetic memory, RNA structure, processing and stability, transcription, translation and associated RNA post-transcriptional events (Amaral et al., 2008; Mattick, 2007; Mehler and Mattick, 2007). Chromatin remodeling enzymes and chromatin-modifying complexes possess little known affinity for DNA sequences, whereas many proteins involved in chromatin dynamics have the capability to bind to RNA and to multifunctional complexes containing RNA (Barski et al., 2007; Bernstein et al., 2006; Kouzarides, 2007; Mikkelsen et al., 2007; Rodriguez-Campos and Azorin, 2007). These specialized protein-nucleic acid interactions are significantly enhanced by the presence of numerous selective binding domains present within chromatin remodeling enzymes and related gene effector proteins (Ruthenburg et al., 2007). Moreover, many regulatory sequences involved in chromatin architecture and the expression of associated protein-coding genes are under complex and exquisite spatiotemporal modulation

(Chapman and Carrington, 2007; Mattick, 2007). Further, a subset of these non-coding transcripts influence gene activation by targeting ubiquitous protein regulators (Ash1, HP1 and chromatin insulator proteins) to cognate sequences in adjacent ("cis-acting") regulatory response elements, including PREs and TREs that are themselves transcribed as ncRNAs (Grimaud et al., 2006; Lei and Corces, 2006; Maison et al., 2002; Sanchez-Elsner et al., 2006; Schmitt and Paro, 2006). Non-coding transcription, particularly longer ncRNAs, can also alter more global chromatin structure, particularly during neural development, by recruiting chromatin remodeling factors and complexes to regulate developmental "morphogenic" gene clusters as well as by modulating histone and CpG island methylation at considerable distances from the active sites of ncRNA transcription (Carninci et al., 2005; Schmitt et al., 2005; Tufarelli et al., 2003). Numerous classes of ncRNAs are preferentially expressed within the mammalian nervous system, in concert with evolutionary adaptations in genomic architecture necessary to promote the biogenesis and functions of these RNA regulatory pathways (Mattick, 2007; Mattick and Makunin, 2006; Mehler and Mattick, 2006; 2007). These observations suggest that the explosive evolutionary innovations in human brain form and function, environmental responsiveness as well as susceptibility to a spectrum of complex neurological and psychiatric diseases may be intimately linked to the multifunctional properties of ncRNAs and their associated digital and analogue signaling networks (Mehler and Mattick, 2007; St Laurent and Wahlestedt, 2007).

MicroRNAs (miRNAs) are 21-23 nucleotide regulatory ncRNAs that either repress translation or inhibit the stability and deployment of their target RNAs, and a large number of mammalian brain-specific miRNAs have been described with specialized roles in neural development, maintenance of mature neural traits, and synaptic and neural network plasticity (Cao et al., 2006; Kosik, 2006; Mehler and Mattick, 2007). Numerous miRNAs are expressed in specific neuronal subtypes, particularly in the neocortex and the cerebellum (Kosik, 2006; Mehler and Mattick, 2007). Transcripts encoding synaptic proteins comprise the largest subclass of predicted miRNA targets, suggesting seminal roles for miRNAs in activity-dependent synaptic plasticity and memory formation, and alterations in miRNAs have been implicated in a diverse range of neurological and psychiatric conditions, particularly those associated with prominent developmental components to pathogenesis (Ashraf and Kunes, 2006; Mehler and Mattick, 2007). miRNAs function through argonaute protein-associated complexes that represent versatile mediators of several additional RNA gene-silencing pathways (Diederichs and Haber, 2007; Hutvagner and Simard, 2008; Peters and Meister, 2007; Wu and Belasco, 2008). A single miRNA may differentially repress or even activate the expression and thereby modulate the functions of as many as 1000 target genes in association with combinations of RBPs present at the appropriate 3' untranslated region (UTR) or at additional regulatory sites of the target gene (Vasudevan et al., 2007). MiRNAs also rapidly and reversibly fine-tune gene expression levels and promote the engagement of specific functional gene networks in an environmentally responsive manner (Kosik, 2006; Shimoni et al., 2007; Tsang et al., 2007). The complexity of miRNA regulatory networks has been underscored by the finding that RNA editing (see below) affects every step in the biogenesis, processing and stability of mature miRNAs and dramatically alters the profiles of miRNA targets (Gao, 2008; Kosik, 2006; Yang et al., 2006). To add another layer of contextual intricacy, the miRNA biogenesis pathways differ depending on their genomic (intronic versus intergenic) origins (Okamura et al., 2007; Ruby et al., 2007). Furthermore, recent bioinformatics studies suggest that the vast majority of miRNAs have yet to be identified and validated, and many appear to be primate- and even human-lineage specific and undergoing rapid evolutionary selection (Mattick, 2007). Selective loss of Dicer, the enzyme involved in the final step of generation of mature miRNAs from nuclear pre-miRNA precursors, in mouse forebrain excitatory neurons results in impaired cortical and hippocampal morphogenesis, alterations in dendrite branching and spine length, abnormal axonal pathfinding and enhanced apoptosis of developing neuroblasts (Davis et al., 2008b). Moreover, key intracellular signaling transducers of diverse neurodevelopmental

events directly regulate miRNA biogenesis (Davis et al., 2008a). These observations reinforce the seminal roles of miRNAs in CNS development and how loss of miRNA biogenesis mirrors the neuropathological findings associated with a spectrum of neurological disorders associated with cognitive and behavioral impairments.

In addition to miRNAs, a variety of other ncRNA subclasses have been identified with diverse genomic and cellular functions especially in the nervous system. Small nucleolar RNAs (snoRNAs) and related ncRNAs provide regulatory controls for enhancing developmental and adult functional complexity through their effects on chromosome segregation and maintenance, genomic imprinting, RNA splicing, transcription, translation and cell cycle regulation (Huttenhofer et al., 2002; Rogelj and Giese, 2004; Rogelj et al., 2003). SnoRNAs guide at least two types of site-selective modifications of nucleotides directed by two distinct subfamilies, and the most common snoRNAs participate in ribosomal RNA (rRNA) modifications during ribosomal biogenesis (Lestrade and Weber, 2006; Meier, 2005). A spectrum of brain-specific snoRNAs has been identified, and many display differential profiles of expression within areas associated with learning and memory (Rogelj et al., 2003). Furthermore, a snoRNA, HBII-52, modifies the RNA editing and alternate splicing of a specific serotonin receptor subunit (5-HT [2C]), and this has important implications for the pathogenesis of specific neurodevelopmental and neuropsychiatric diseases, particularly those associated with deregulation of genomic imprinting (Kishore and Stamm, 2006; Rogelj and Giese, 2004). SnoRNAs, miRNAs as well as longer ncRNAs are associated with and participate in the process of genomic imprinting, and these allele-specific genomic regulatory events affect brain development and mature neural functions in innumerable ways that are just beginning to be fully appreciated (Mehler and Mattick, 2007). Allele-specific gene regulation is associated with complex and cell- and developmental-specific profiles of gene expression in brain, and disruption of imprinted loci has been implicated in the pathogenesis of numerous neurological disorders associated with intricate cognitive and behavioral phenotypes (Davies et al., 2006; Kishino, 2006; Pauler et al., 2007; Yang and Kuroda, 2007; Zaratiegui et al., 2007). ScaRNAs, a related subclass of ncRNAs, direct modifications of “spliceosomal” RNAs involved in alternate splicing of gene transcripts to create diverse functional protein isoforms (Bessonov et al., 2008; Meier, 2005). It is highly likely that additional subclasses of small ncRNAs located at selected genomic loci within transcriptional units, 5’ regulatory regions and at intergenic sites will be identified that are essential for fine-tuning transcriptional activities and also for facilitating RNA silencing pathways through the mediation of argonaute proteins (Aftab et al., 2008; Han et al., 2007; Hock et al., 2007; Hutvagner and Simard, 2008; Li et al., 2008a). These diverse RNA species may fine-tune local and long distance gene expression by formation of higher order RNA: DNA complexes and by acting as molecular beacons for specific transcriptional and epigenetic regulators and co-regulators and may therefore have enormous therapeutic potential for selective targeting of disease-associated epigenetic lesions. Several additional classes of ncRNAs, including telomeric RNA, signal recognition particle RNA and piwi protein-interacting RNAs (piRNAs), are involved in the regulation of genomic architecture, the maintenance of germline genomic integrity, the aging process and have been linked to many other seminal cellular events (Amaral et al., 2008; Blasco, 2007; Chapman and Carrington, 2007; Mehler and Mattick, 2007; Yang and Kuroda, 2007; Zaratiegui et al., 2007). NcRNAs also direct and collaborate with selective RBPs to modulate transcriptional programs in response to complex environmental signals through conformational and activity-dependent (“allosteric”) modifications to RBPs, and by counteracting histone code signatures at specific transcriptional units (Wang et al., 2008c). Although transfer RNAs (tRNAs) and rRNAs have long been recognized and assumed to have general cellular housekeeping roles, these specialized subclasses of ncRNAs have more recently been implicated in an expanding range of developmental and adult nervous system functions as indicated by the effects of targeted mutations of tRNAs and rRNAs in the pathogenesis of a spectrum of neurodevelopmental, neurodegenerative and neuropsychiatric diseases, including the complex and often evolving

phenotypes associated with the mitochondrial encephalomyopathies (Dimauro, 2004; Mehler and Mattick, 2007).

Recent studies suggest that hundreds of thousands of longer polyadenylated and non-polyadenylated ncRNAs are also transcribed from the mammalian genome (Kapranov et al., 2007a; Kapranov et al., 2007b). Many of these more complex RNAs are developmentally regulated, exquisitely environmentally responsive, alternately spliced, show unusual abundance within the nervous system and are rapidly evolving even within the primate and the human lineages (Inagaki et al., 2005; Kapranov et al., 2007b; Pang et al., 2006; Ravasi et al., 2006). Within these longer ncRNAs, a subset has been designated as macroRNAs or long expressed non-coding regions (*ENORs*), with some *ENOR* loci producing multiple macroRNAs all enriched in brain (Furuno et al., 2006; Mehler and Mattick, 2007). Frequently, these genomic loci exhibit evidence of antisense transcription, genomic imprinting, X-chromosome inactivation and represent host sites for miRNAs and snoRNAs (Mehler and Mattick, 2007). Several classes of longer ncRNAs are implicated in the development of axonal and dendritic connections, in neuronal nucleocytoplasmic bidirectional RNA transport and local targeting and in promoting immediate as well as delayed local protein synthesis and additional synaptic modulatory functions associated with neural network plasticity and long-term adjustments to synaptic strength (Mehler and Mattick, 2007). In association with diverse RBPs, including the fragile X mental retardation protein (FMRP), longer ncRNAs participate in the generation of late phases of long-term plasticity (LTP) underlying memory consolidation, including the linked processes of “synaptic tagging and cross-tagging” and additional properties essential for precise information transmission and modifications (Dahm et al., 2007; Mehler and Mattick, 2007; Reymann and Frey, 2007). Synaptic tagging marks synapses destined to undergo plastic changes associated with transcriptional modulation, whereas synaptic cross-tagging helps to facilitate enhanced synaptic plasticity of linked synaptic inputs (Reymann and Frey, 2007). RNA-mediated processes may also be involved in regulating prion-like switching associated with specific forms of synaptic plasticity, and deregulation of these processes may predispose to certain types of neurodegenerative diseases including the spongiform encephalopathies (Darnell, 2003; Mehler and Mattick, 2007; Si et al., 2003a; Si et al., 2003b). In addition, SWI/SNF-like ATP chromatin remodeling subunits have the potential to acquire prion-like properties and may exhibit novel “protein-only” inheritance patterns associated with modifications in chromatin remodeling and global gene regulation (Du et al., 2008). Moreover, mutations resulting in expansion of oligopeptide repeats contained within prion proteins are also linked to inherited prion disease states through enhanced conformational versatility, the generation of a series of aggregation intermediates and enhanced prion conversion (Tank et al., 2007).

A large proportion of mammalian protein-coding genes have associated (“cis-acting”) antisense transcripts that differentially regulate their expression and function, and these additional classes of longer RNAs are also particularly abundant in the nervous system where they mediate all aspects of brain patterning, stem cell maintenance and maturation, neurogenesis and gliogenesis, neural stress responses as well as mature neuronal homeostasis and plasticity (Katayama et al., 2005; Korneev and O’Shea, 2005; Mehler and Mattick, 2007). Disruption of these cis-acting antisense transcripts has been implicated in a broad array of neurodevelopmental, neurodegenerative as well as neuropsychiatric diseases (Mehler and Mattick, 2007). There is also an increasing appreciation of the roles of long distance (“trans-acting”) antisense RNAs, produced during evolution by gene duplication coupled to DNA inversion, in normal neurological processes as well as in the specific disease states (Korneev and O’Shea, 2002; Mehler and Mattick, 2007). Other gene silencing pathways, in addition to miRNAs, piRNAs and natural antisense RNAs (Chapman and Carrington, 2007), include newly discovered variants of the latter antisense transcripts termed endogenous small interfering RNAs (endo-siRNAs) that can be generated both directly and through double-

stranded RNA intermediates from a subset of pseudogenes (derivatives of parent genes with altered structure and function), and a second class of endo-siRNAs that can further enforce repression of mobile parasitic repetitive elements in concert with piRNAs (Tam et al., 2008; Watanabe et al., 2008).

Human accelerated regions (HARs) within the genome, which exhibit high degrees of mammalian conservation but accelerated evolution since divergence from our common ancestor with chimpanzees, have recently been identified outside of protein-coding sequences, with a significant subset located adjacent to key neurodevelopmental genes (Pollard et al., 2006).

Interestingly, the most rapidly evolving of these loci, HAR1 is a component of the initial exon of a large spliced ncRNA (*HARF1*) that is expressed in Cajal-Retzius neurons of the developing neocortex (Pollard et al., 2006). *HARF1* appears to be co-expressed with reelin, a factor important for cortical neuroblast migration and maturation and the elaboration of the proper laminar organization of the human neocortex (Pollard et al., 2006). Moreover, an alternately spliced brain transcript, *HAR1Ra* contains the HAR1 region in its first exon and exhibits dynamic spatiotemporal expression patterns, suggesting later developmental roles associated with the down regulation of *HARF1* by antisense-directed gene repression (Pollard et al., 2006). Further, reelin exhibits enhanced expression during primate evolution and also undergoes RNA editing (Levanon et al., 2004; Molnar et al., 2006). Deregulation of the reelin locus by multiple epigenetic mechanisms has been implicated in the etiology of complex neuropsychiatric diseases including schizophrenia (Tamura et al., 2007).

4. RNA and DNA editing of the transcriptome, the proteome and the genome

Through the mediation of dynamic and reversible base recoding, two subclasses of RNA editing enzymes can differentially modulate the levels of expression as well as the functional properties of a broad array of protein-coding genes as well as ncRNAs (Amariglio and Rechavi, 2007; Bass, 2002; Kawahara and Nishikura, 2006). A dramatic increase in RNA editing has occurred during mammalian evolution, with the hominid lineage and particularly the human brain exhibiting the highest levels and the most complex forms of adenosine to inosine (A-I) RNA editing mediated by adenosine deaminases acting on RNAs (ADARs) (Bass, 2002; Valente and Nishikura, 2005). Three ADAR enzymes exist in mammals with ADAR3 restricted to the nervous system and ADAR1 and ADAR2 preferentially expressed in brain (Bass, 2002; Chen et al., 2000). RNA editing enzymes display intricate and changing profiles of regional and temporal expression and subcellular localization during neural development, and complex modulation by behavioral state, environmental cues, genetic background and by feedback regulation and cellular signaling pathways (Mattick and Mehler, 2008; Mehler and Mattick, 2007). ADARs can undergo complex forms of alternate splicing, homo- and hetero-dimer formation, differential binding to diverse RNA species and can participate in dynamic profiles of multi-site editing of individual RNAs with diverse functional consequences (Mattick and Mehler, 2008; Mehler and Mattick, 2007). A different form of regulatory control is exerted by adenosine deaminases acting on tRNAs (ADAT1-3). ADATs function to modify codon recognition in the process of mRNA decoding, and thereby enhance the fidelity and efficiency by which tRNAs participate in the generation of protein diversity within the developing and adult nervous systems (Valente and Nishikura, 2005). RNA editing was initially thought to orchestrate higher order nervous system functions by selectively editing and changing the biophysical properties of selective protein-coding genes that modulate fast neurotransmission and multiple stages of presynaptic vesicle release through fine-tuning of the signaling properties of neurons within activated neural networks (Amariglio and Rechavi, 2007; Bass, 2002; Valente and Nishikura, 2005). More recently, however, a greatly expanded repertoire of RNA editing events has been identified (Mattick and Mehler, 2008). For example, RNA editing

can alter the biogenesis, mature molecular properties and the target specificities of miRNAs (Gao, 2008; Kosik, 2006; Mattick and Mehler, 2008). Moreover, RNA editing can modify an immense array of additional gene products, including those derived from mRNAs as well as non-coding sequences expressed in the nervous system (Mattick and Mehler, 2008; Mehler and Mattick, 2007; St Laurent and Wahlestedt, 2007). These edited gene products play a wide variety of neurodevelopmental and adult regulatory roles in promoting neural homeostasis and plasticity, including complex epigenetic modulation of learning and memory (Mattick and Mehler, 2008). In the context of RNA regulatory pathways, RNA editing can also alter the choice and location of splicing sites, modulate snoRNA precursors, antisense RNAs, RBPs, genomic imprinting and X-chromosome inactivation, and impart additional dynamic changes to overall chromatin architecture (Mattick and Mehler, 2008; Mehler and Mattick, 2007). A series of animal models have demonstrated that RNA editing is essential for orchestrating the complex cognitive and behavioral output of the developing and mature nervous system, and deregulation of ADAR activities through hypo- or hyper-editing of RNAs is associated with a spectrum of neurodevelopmental, neurodegenerative and neuropsychiatric diseases as well as brain cancers (Jepson and Reenan, 2007; Mehler and Mattick, 2007; Tonkin et al., 2002; Valente and Nishikura, 2005; Wang et al., 2004).

A separate class of editing enzymes is represented by the cytidine deaminases, termed the “apolipoprotein B editing catalytic subunit” (APOBEC) family, which can recode both RNA and DNA by changing cytidine and deoxycytidine to uridine and deoxyuridine, respectively (Navaratnam and Sarwar, 2006). There are four mouse enzymes (APOBEC-1, -2, CEM15 and activation-induced cytidine deaminase [AID]), whereas in humans the CEM15/APOBEC-3 family has been expanded to encompass seven members including APOBEC-3G, which is expressed in post-mitotic neurons and exhibits positive evolutionary selection (Mattick and Mehler, 2008; Navaratnam and Sarwar, 2006; Sabeti et al., 2006; Sawyer et al., 2004). APOBEC enzymes have diverse DNA, RNA and transcription-associated targets, complex profiles of subcellular localization, nucleocytoplasmic shuttling, regulation by alternate splicing, post-translational modifications, interactions with RNA regulatory factors, co-factors, chaperones, RBPs and higher-order molecular complexes and dynamic profiles of modulation by numerous metabolites and environmental states. APOBEC enzymes interact with many RBPs and regulate synaptic function by modulating the decay of miRNA-targeted mRNAs in synapse-associated processing bodies and stress granules and by preventing the inhibition of local protein synthesis by miRNAs (Mattick and Mehler, 2008; Navaratnam and Sarwar, 2006). APOBEC-mediated editing is essential for restricting the migration of diverse transposable repetitive elements in the genome, thereby preserving genomic integrity, for enhancing anti-retroviral activity, and for promoting targeted recombination, somatic hypermutation and gene conversion events, particularly in the immune system, in conjunction with AID to enhance molecular diversity, plasticity and host defense functions (Huang et al., 2007b; Mattick and Mehler, 2008; Mehler and Mattick, 2007; Muckenfuss et al., 2006; Navaratnam and Sarwar, 2006). Deregulation of APOBEC enzyme function is associated with a spectrum of neurological diseases including conditions in which cognitive function is significantly compromised (Mattick and Mehler, 2008).

There is accumulating evidence that ADAR- and APOBEC-mediated editing and recoding functions are functionally linked, in part, though the actions of specific classes of DNA repair enzymes, particularly the Y-family of DNA polymerases that possess reverse transcriptase activity (Franklin et al., 2004; Steele et al., 2006; Yavuz et al., 2002). In the nervous system, this mechanism may allow transient but salient environmentally-mediated “short-term” memory or cognitive traces encoded via synapse-associated RNA editing of specific transcripts to be trafficked in a retrograde fashion back to the nucleus and more permanently stored and further processed and manipulated as “long-term” memory traces by direct DNA recoding of the neuronal genome (Mattick and Mehler, 2008; Mehler and Mattick, 2007). These RNA-

directed DNA modification events may be mediated by several molecular mechanisms that are active in the nervous system, including DNA repair enzyme-linked reverse transcriptases, adaptation of long interspersed nuclear element-1 (*LINE-1*) repetitive element-encoded reverse transcriptases in association with different short interspersed nuclear elements (*SINE*) repetitive elements (*Alu* sequences) and programmed genomic rearrangements including RNA-directed DNA recombination events (Dewannieux et al., 2003; Garcia-Perez et al., 2007; Mattick and Mehler, 2008; Storici et al., 2007; Nowacki et al., 2008). Interestingly, a subset of the enzymes involved in promoting RNA-directed DNA modifications are themselves edited suggesting an additional layer of contextual control (Mattick and Mehler, 2008). Moreover, more than 90% of A-I RNA editing targets specific profiles of *Alu* elements, which have undergone massive expansion in the hominid lineage to now comprise greater than 10 % of the human genome (Jepson and Reenan, 2007; Mehler and Mattick, 2007), suggesting their evolutionary co-adaptation as modular substrates for RNA editing driven by selection for complex higher-order cognitive processes and adaptations (Mattick and Mehler, 2008). Alu elements exert profound effects on all levels of modulation of gene form and function through actions on gene-environmental interactions, homeostasis, plasticity, stress responses, ontogeny as well as disease susceptibility (Hasler and Strub, 2006; Jurka, 2004; Muotri et al., 2007). These intriguing observations suggest that dynamic editing of the genome, the transcriptome and the proteome occurs at diverse neuroanatomical loci representing different types of memory and cognitive processes, during progressive phases of memory trace formation and modification as well as within different levels of nervous system organization from synaptic and axodendritic microdomains to adaptable neural network connections (Mattick and Mehler, 2008; Mehler and Mattick, 2007). The mapping of environmental stimuli onto synapses by editing of RNA transcripts, their retrograde intraneuronal trafficking and their informational transformation into corresponding nuclear DNA recoding events distributed in neuronal genomes within relevant neural networks followed by corresponding synapse-associated and locally translated mRNAs and linked ncRNA effector molecules allows the progressive evolution of informational signals from a stimulus-based feature and contextual code to a more abstract, flexible and reversible storage and retrieval code capable of organizing and elaborating appropriate behavioral responses (Mattick and Mehler, 2008). This represents a paradigm for defining epigenetically mediated learning and memory and higher-order cognitive processing in the human brain in health and disease, with major implications for the development of novel classes of pharmacoepigenomic agents for remediation of neurodevelopmental, neurodegenerative and neuropsychiatric diseases.

5. The functional architecture of the emerging genomic and epigenomic landscape

The new genomic landscape is characterized by the presence of numerous regulatory regions and epigenetic effectors that are located well beyond canonical 5’ promoter/enhancer regions of genes and employ a seemingly endless spectrum of molecular mechanisms to orchestrate graded gene expression and function in unique ways (Bejerano et al., 2006; Kapranov et al., 2007a; Kapranov et al., 2007b; Misteli, 2007; Schneider and Grosschedl, 2007). In fact, much of the genome is comprised of complex regulatory elements that give rise to multifunctional ncRNA transcripts (Kapranov et al., 2007a). These widely-distributed ncRNA transcripts frequently exhibit alternate splicing with extensive overlap of transcriptional units including a large proportion antisense to both protein-coding as well as ncRNA transcripts, those bidirectional in association with protein-coding transcripts and possessing common regulatory elements allowing concordant or discordant gene expression and additional transcripts contained within the body (introns or exons) of other genes and exhibiting coordinate expression and complex functional modulation (Kapranov et al., 2007a; Kapranov et al., 2007b; Munroe and Zhu, 2006). This nested, overlapping and interleaved profile of human

gene organization allows precise maintenance of gene identity through the use of intricate modulation of transcription, alternate splicing and maintenance of 3' gene end-formation, while allowing exceptional plasticity as well as molecular diversity in the elaboration of interlacing transcripts (Frith et al., 2007; Kapranov et al., 2007b). There is also evidence of extensive long-range interconnected transcriptional regulation with the presence of alternate regulatory elements extending as far as 1 megabase upstream or downstream of the transcriptional start site or within intronic regions or exons of specific genes including sophisticated enhancers, locus control regions (LCRs), repressors/silencers, imprinting control centers (ICCs) and insulators (Kleinjan and van Heyningen, 2005; Ling and Hoffman, 2007; Misteli, 2007; Savarese and Grosschedl, 2006; Schneider and Grosschedl, 2007). Additional genes are frequently arrayed between these regulatory regions and their target genes, and this genomic architecture allows for novel modulation of gene function, including splicing between different RNA species ("trans-splicing") and for the joining of multiple exons from separate protein-coding and non-coding genes ("gene fusion") (Kleinjan and van Heyningen, 2005; Mattick, 2007; Misteli, 2007; Savarese and Grosschedl, 2006; Schneider and Grosschedl, 2007). Long-range transcriptional activity can itself function as a localized or more genome-wide regulatory process by resetting and remodeling of the chromatin code (Ahmed and Brickner, 2007; Berger, 2007; Kleinjan and van Heyningen, 2005). Bidirectional promoters can simultaneously regulate gene expression profiles from both DNA strands, enhancers and LCRs can augment promoter activities by expediting the looping of intervening DNA, an enhancer associated with one allele can activate the promoter of a second allele ("transvection") and single enhancer elements can differentially interact with complementary promoter elements on different chromosomes to orchestrate the precise temporospatial patterns of expression of members of a related gene family in response to specific environmental cues (Fraser and Bickmore, 2007; Kapranov et al., 2007b; Misteli, 2007; Savarese and Grosschedl, 2006; Schneider and Grosschedl, 2007). This complex genomic architecture offers a rich substrate for the generation of multiple classes of longer ncRNAs that have diverse regulatory roles, serve as precursors for short ncRNAs, including miRNAs and snoRNAs, and function in concert with other intronic RNAs co-regulated with their parent genes (Gingeras, 2007; Kapranov et al., 2007a). All of these interrelated molecular species represent unique modes of global, trans-acting RNA signals to orchestrate genome-wide gene expression profiles and functional outputs in concert with localized, cis-acting RNAs (cis-antisense RNAs) and with additional regulatory output represented by dynamic higher order DNA-RNA, RNA-RNA and both DNA- and RNA-based protein interactions (Herbert, 2004; Misteli, 2007; Placido et al., 2007; Schneider and Grosschedl, 2007; St Laurent and Wahlestedt, 2007). Many of our emerging insights concerning modern genomic architecture have come directly from the observations of the ENCODE project consortium, including the presence of robust transcription and dispersed regulation throughout the genome and on both DNA strands, large numbers of unannotated transcription start sites, high degrees of alternative splicing, complex regulatory regions and elements often actively transcribed, graded and interlaced genic and intergenic boundaries, multiple classes of ncRNAs, intricate and fine-grained gene evolutionary constraints and changing concepts of "neutral evolution" as well as large components of the genome representing rapidly evolving DNA and RNA species (Birney et al., 2007; Gerstein et al., 2007; Pheasant and Mattick, 2007; Weinstock, 2007).

It is increasingly apparent that intricate and nuanced DNA/RNA/protein interactions depend upon complex three-dimensional interactions of the genome with components of the nuclear architecture and with novel forms of self-organization mediated by probabilistic ("stochastic") events associated with proximity of evolving molecular complexes to regulatory factors (Fraser and Bickmore, 2007; Misteli, 2007; Schneider and Grosschedl, 2007). These genomic and nuclear processes often involve the creation and evolution of functional nuclear microenvironments through long-range regulatory interactions between disparate DNA elements and associated epigenetic processes that orchestrate DNA accessibility and higher-

order structural modifications that facilitate intimate intra- and inter-chromosomal interactions (Fraser and Bickmore, 2007; Misteli, 2007; Schneider and Grosschedl, 2007). In areas of the nuclear periphery associated with nuclear pore complexes (NPCs), genes from widely disseminated genomic loci are actively recruited to form transcription "factories" that are maintained for different classes of genes by LCR elements and by specific histone modifications that promote active transcription as well as heritable transcriptional epigenetic memory through the actions of variant histones such as H2A.Z and the requisite preservation of boundary elements separating euchromatic from heterochromatic regions (Brickner et al., 2007; Dryhurst et al., 2004; Fraser and Bickmore, 2007; Misteli, 2007; Sarcinella et al., 2007). The presence of active transcriptional synergies and epigenetic memory mechanisms in association with NPCs ensures the functional integration of transcriptional and post-transcriptional processing and associated RNA quality control, nuclear export, nucleocytoplasmic shuttling and associated epigenetic reprogramming events (Ahmed and Brickner, 2007; Akhtar and Gasser, 2007; Fraser and Bickmore, 2007; Isken and Maquat, 2007; Schneider and Grosschedl, 2007). By contrast, components of the nuclear lamina tether genes and functional gene networks to areas of the nuclear periphery in association with lamin and silent information regulators ("Sir" or sirtuin) proteins that interact with more global transcriptional repressor networks including those associated with heterochromatin and telomeric foci, respectively (Ahmed and Brickner, 2007; Akhtar and Gasser, 2007). These integrated epigenetic regulatory mechanisms have profound implications for the development of novel neurological therapeutic agents, particularly in the area of neurodegenerative diseases.

Changes in chromatin structure play an essential role in chromosome repositioning that is frequently cell cycle dependent and promote extensive intermingling of chromosome territories through decondensation and "looping out" of DNA regions to facilitate inter-chromosomal interactions including clustering of common gene regulatory elements (Kleinjan and van Heyningen, 2005; Ling and Hoffman, 2007; Misteli, 2007; Schneider and Grosschedl, 2007). "Homologous" inter-chromosomal interactions are facilitated through extensive cross-talk and include allelic pairing to support the functions of one of the two chromosome gene copies via transvection and X-chromosome inactivation through the mediation of X-chromosome inactivation centers (Xic), the designation of active and inactive chromatin states and the targeting of the inactive X (Xi) to perinucleolar regions (Schneider and Grosschedl, 2007). By contrast, "non-homologous" inter-chromosomal interactions utilize special protein factors to allow genes from multiple chromosomes but with common functions, such as ribosomal genes, to come together within specialized nuclear microdomains (the nucleolus) by promoting extensive DNA folding into inter-chromosomal loops (Grummt, 2007; Schneider and Grosschedl, 2007). The establishment, maintenance, heritability and dynamic crosstalk associated with these diverse forms of inter-chromosomal interactions are orchestrated by multiple layers of epigenetic regulatory controls involving DNA methylation, chromatin remodeling, multiple classes of ncRNAs as well as RNA editing (Grummt, 2007; Schneider and Grosschedl, 2007). Moreover, these innovations in genomic as well as nuclear architecture are further modulated by transposable repetitive elements that account for almost half of the DNA sequences of the entire human genome (Kim et al., 2006a; Mills et al., 2007; Slotkin and Martienssen, 2007). Although only a small subset (*Alu*, *LINE-1*, *SVA* including human endogenous retrovirus K [*HERV-K*]) of these repetitive elements remain active and mobile in the human genome, these and other more ancient repetitive elements can produce genetic diversity and functional innovations as well as cause numerous neurological diseases when deregulated by duplication, migration and integration into specific genetic loci or by facilitating chromosome rearrangements (Hasler and Strub, 2006; Jurka, 2004; Kim et al., 2006a; Mills et al., 2007; Muotri et al., 2007; Slotkin and Martienssen, 2007). Complex interactions occur between active transposable elements including "autonomous" (*LINE-1*) and "non-autonomous" (*Alu*, *SVA*) mobilization mediated through LINE-1-encoded proteins that can activate numerous and varied active and sometimes more ancient silenced repetitive elements

(Muotri et al., 2007). Through the complex modulation of an intricate and multifunctional spectrum of epigenetic regulators, transposable elements contribute to the structural and functional properties associated with centromeres, telomeres, insulators, promoters, enhancers, intron-exon boundaries, genomic imprinting and X-chromosome inactivation, transcription, alternate splicing, polyadenylation, RNA editing, translation, epialleles (heritable but reversible epigenetic changes in allelic gene expression), allelic interactions resulting in heritable changes to one allele ("paramutation") as well as extensive exaption (evolutionary or acquired gain of regulatory functions) including exonization (Cam et al., 2008; Hasler and Strub, 2006; Jurka, 2004; Kim et al., 2006a; Mills et al., 2007; Muotri et al., 2007; Piriyapongsa et al., 2007; Slotkin and Martienssen, 2007). Interestingly, neural fate decisions may be orchestrated, in part, by *LINE-1*-mediated retrotransposition due to a potential insertional preference for neural developmental genes (Muotri et al., 2007).

6. The advent of RNA regulatory networks for higher-order nervous system functions

The adaptation of increasingly sophisticated RNA regulatory circuits for promoting evolutionary innovations in human brain form and function may have arisen because of several unique properties of regulatory RNAs (Amaral et al., 2008; Ciesla, 2006; Felden, 2007; Keene, 2007; Ladurner, 2006; Nowacki et al., 2008; Serganov and Patel, 2007). RNA couples sequence-specific (digital) and conformational (analogue) information within the same molecule, lowers the bioenergetic costs of information processing, participates in accelerated and largely unconstrained evolutionary innovations, serves as sensitive and rapidly reversible biosensors of both environmental as well as interoceptive cues, and can readily adapt to intricate, multilayered and challenging environmental conditions (St Laurent and Wahlestedt, 2007). These unique molecular features of RNAs allow them to promote complex DNA/RNA/protein interactions and dynamic crosstalk between traditional protein-based signal transduction cascades and the more malleable properties of the genomic architecture, particularly with the advent of RBPs to enhance the temporal and spatial modulation of gene expression and function (Keene, 2007; St Laurent and Wahlestedt, 2007). Brain has always been a conspicuous consumer of energy resources, and the ability of RNAs to function as molecular adaptors by their ability to assume an almost infinite variety of analogue shapes at a fraction of the bioenergetic costs of the more limited conformational repertoire of proteins has resulted in a partial solution to the bioenergetic crisis occurring during higher eukaryotic nervous system evolution, while at the same time establishing a sophisticated molecular interface mediating gene-environmental interactions during neural development and adult neuronal homeostasis and neural network plasticity (St Laurent and Wahlestedt, 2007). By the nature of its conformational versatility, specific RNAs can rapidly evolve into novel functional roles because these molecular species are not constrained by the elaborate protein signaling apparatus they have co-opted to integrate massive amounts of relevant digital information as well as a spectrum of subtle and complex environmental cues and endogenous homeostatic signals in their complementary role as unique biosensors and as "riboswitches" (Ciesla, 2006; Ladurner, 2006; Serganov and Patel, 2007; St Laurent and Wahlestedt, 2007).

Within the nervous system, RNAs also participate in elaborate activity-dependent temporal and spatial modulation of gene and integrated gene network expression and function through the dynamic repression, activation and sequestration of diverse RNAs during bidirectional axodendritic transport in association with RBPs contained within neuronal granules and at synaptic terminals through the presence of unique analogue-mediated digital reservoirs represented by processing bodies and stress granules (Ashraf and Kunes, 2006; Bramham and Wells, 2007; Dahm et al., 2007; Eulalio et al., 2007; Keene, 2007; St Laurent and Wahlestedt, 2007). These "RNA operons" are composed of trans-acting factors such as numerous RBPs, additional RNA interactors (argonaute proteins), ncRNAs and associated RNA biogenesis and

feedback pathway components and regulatory metabolites that interact with multiple digital regulatory elements particularly 3' UTRs in mRNAs. Therefore, these RNA operons can adopt complex combinatorial and coordinate signaling outcomes by differentially modulating the expression and functional status of individual molecular components (Keene, 2007; Vasudevan et al., 2007). The use of several interrelated RNA operons to dynamically modulate the informational content at multiple levels of the gene regulatory hierarchy through the mediation of localized and distributed gene expression and copy number results in the elaboration of dynamic and interchangeable higher-order "RNA regulons" to help orchestrate sophisticated epigenetic memory states established at different levels of the neuraxis (Keene, 2007; Mattick and Mehler, 2008). These finely tuned neural processes can be further modulated by the processes of RNA editing and DNA recoding (Mattick and Mehler, 2008). Moreover, accumulating evidence suggests that additional embedded information, contained in sophisticated analogue and/or digital form, including DNA and RNA stereoisomers, introns and linked intergenic regions and through codon degeneracy, can furnish a wealth of additional regulatory information to promote dynamic higher-order cognitive processing states (Felden, 2007; Herbert, 2004; Jepson and Reenan, 2007; Kapranov et al., 2007b; Keene, 2007; Lev-Maor et al., 2007; Mattick and Mehler, 2008; Mehler and Mattick, 2007; St Laurent and Wahlestedt, 2007). Further, ncRNAs have been implicated in orchestrating intricate regulatory processes at every level of gene expression and function including chromatin architecture and epigenetic memory, transcription, post-transcriptional processing, translation and also trans-neuronal as well as intercellular RNA transport and signaling (Amaral et al., 2008; Dinger et al., 2008). Interestingly, nervous system-specific genes exhibit structurally unique introns and UTRs with the rapid evolution of non-coding RNA regions between evolutionary neutrality and positive selection (Mattick, 2007; Pang et al., 2006; Pheasant and Mattick, 2007; Taft et al., 2007). Recent studies have begun to uncover a previously hidden world of RNA trafficking between adjacent cells, to more distal cells within the same tissue and organ system, within the systemic circulation and even through specific pathways for transmission of somatic RNAs back to the germline to participate in alternate forms of accelerated evolution and multigenerational inheritance of complex cognitive and behavioral traits (Dinger et al., 2008; Mattick and Mehler, 2008; Valadi et al., 2007). These RNA intercellular pathways have great potential relevance for nervous system function and appear to participate in complex regulated transport of diverse RNA species through multiple signaling mechanisms that preserve the integrity of the cargo and the associated informational traces and their ability to undergo directed propagation and signal transformation and evolution (Dinger et al., 2008; Mattick and Mehler, 2008; Valadi et al., 2007). The prospects for elucidating the intricate molecular and cellular mechanisms orchestrating different forms of activity-dependent trans-neuronal RNA signaling have major implications for our understanding of synaptic plasticity, neural network functioning through oscillatory synchrony, cognitive adaptations during human brain evolution, environmental epigenetics, the pathogenesis of complex neuropsychiatric diseases as well as for dynamic epigenetic reprogramming and the development of novel pharmacoepigenomic agents.

7. Epigenetic principles governing neural stem cell fate decisions and cellular differentiation

Recent studies suggest that the epigenetic regulation of stem cell maintenance and cell fate decisions are complex and multifaceted, involving the transition from global transcriptional hyperactivity of coding and non-coding regions to progressive large scale gene silencing mediated by elevated levels of chromatin remodeling factors, altered binding of chromatin proteins and unique histone modification profiles without overall changes in histone-modifying activities (Efroni et al., 2008). Moreover, epigenetic priming of stem cell lineage restriction and fate specification is orchestrated by clonal heterogeneity of gene expression profiles

reflecting the presence of a series of metastable states characterized by distinct slowly fluctuating global transcriptional profiles required to produce unique cell identities through probabilistic (stochastic) mechanisms (Chang et al., 2008). The epigenetic remodeling factor, Bmi1 promotes neural stem cell maintenance by enhancing self-renewal and by preventing mitogen-activated protein kinase (MAPK)-mediated G1 cell cycle progression from creating a susceptible window during the late G1 phase for several alternate cell fate processes including cellular differentiation, apoptosis, cell transformation, telomere attrition and induction of senescence (Orford and Scadden, 2008; Shi et al., 2007b). When signals from the stem cell niche activate Bmi1, this PcG factor then collaborates with pluripotency genes to keep neural differentiation genes in a repressed but "poised" state, in part, through the elaboration of a "bivalent" chromatin signature at targeted promoter sites comprised of selective dual activator and repressor histone post-translational modifications (Orford and Scadden, 2008; Shi et al., 2007b; Spivakov and Fisher, 2007). Bmi1 also actively prevents certain late G1 cell fates, including inhibition of cellular senescence, by repressing the cyclin dependent kinase inhibitors, $p16^{INK4A}$ and $p19^{ARF}$ (Orford and Scadden, 2008; Shi et al., 2007b)). Neural stem cell self-renewal is also mediated by a spectrum of additional epigenetic modifiers including histone deacetylaces (HDACs), miRNAs, RBPs (pumilio) and other histone-modifying enzymes (Cheng et al., 2005; Hsieh and Gage, 2004; Kondo, 2006; Orford and Scadden, 2008; Shi et al., 2007b). The complexity of the stem cell ground state has been demonstrated by the sophistication of the circuitry employed to orchestrate stem cell maintenance and progressive neural fate decisions including the utilization of multiple neurotransmitter signaling pathways in concert with epigenetic regulators (Diamandis et al., 2007). For example, through the mediation of gamma-amino butyric acid $(GABA)_A$ receptor ($GABA_AR$) signaling, the variant histone, H2AX regulates neural stem cell proliferation independent of late G1 fate decisions, imparting a degree of plasticity to essential stem cell processes during development, adult homeostasis, aging and in response to injury or disease-associated processes (Andang et al., 2008; Orford and Scadden, 2008). Moreover, progressive stem cell lineage restriction and maturation involve the dynamic interplay between PcG factors, MAPK signaling pathways and parallel linked regulatory cascades encompassing tumor suppressor genes, metabolite-sensitive transcription factors and reactive oxygen species, all under exquisite epigenetic regulation (Orford and Scadden, 2008).

Neural stem cell lineage restriction, neuronal differentiation and synaptogenesis are orchestrated, in large part, by the neuron-restrictive silencing factor/ RE-1 silencing transcription factor, NRSF/REST, which is a dynamic modular scaffold for the epigenetic supercomplexes that are required for the environmentally-responsive transition from the undifferentiated stem cell state through the stages of neuronal and glial subtype specification, maturation and maintenance (Ballas and Mandel, 2005; Ooi and Wood, 2007; Otto et al., 2007; Singh et al., 2008). REST promotes context-dependent gene repression, gene activation and long-term gene silencing by binding to diverse RE-1 consequence sequences at multiple upstream, downstream and intragenic (intronic) genomic regulatory sites associated with numerous protein-coding genes as well as ncRNAs (Ballas and Mandel, 2005; Ooi and Wood, 2007). Upon DNA binding, REST recruits specific epigenetic and associated transcriptional regulatory factors to both N- and C-terminal REST modular domains, participates in alternate splicing to create several REST isoforms with activator or repressor functions, interacts directly with the machinery of gene activation and accompanying dynamic chromatin remodeling, undergoes chaperone-mediated REST nuclear importation and also interacts with and forms complex regulatory loops with diverse classes of ncRNAs (Ballas and Mandel, 2005; Ooi and Wood, 2007). A unique double-stranded neuron-restrictive silencing element (dsNRSE) RNA converts REST from a transcriptional repressor in non-neuronal cells to a transcriptional activator during progressive neuronal subtype specification and differentiation (Kuwabara et al., 2004). In addition, through complex feedforward and feedback regulation, diverse miRNA species collaborate with REST to fine-tune the processes of neuronal subtype specification,

maturation and neural network integration (Hobert, 2006; Visvanathan et al., 2007; Wu and Xie, 2006). REST recruits DNMTs, MBDs, multiple classes of histone-modifying and chromatin remodeling enzymes, heterochromatin proteins, transcription factors, cell cycle regulators, co-regulators (CoREST) and ubiquitin proteasome degradation co-factors that allow dynamic shifts in RE1 gene site occupancy, REST expression profiles and the orderly, interdependent and stepwise modification of DNA, histones, nucleosomes, higher-order chromatin codes and associated cellular processes (Ballas and Mandel, 2005; Guardavaccaro et al., 2008; Ooi and Wood, 2007). These intricate, multilayered epigenetic regulatory processes allow REST to orchestrate the precise temporal, spatial and quantitative regulation of gene expression across integrated gene networks involved in promoting stem cell self-renewal and pluripotency and in sculpting neural cell identity, maturation, connectivity as well as activity-dependent plasticity (Ballas and Mandel, 2005; Ooi and Wood, 2007; Singh et al., 2008).

Neural lineage commitment involves a number of epigenetic mechanisms including but not limited to DNA methylation, histone modification, chromatin remodeling, ncRNA expression and RNA editing (Cheng et al., 2005; Feng et al., 2007; Hsieh and Gage, 2004; Kondo, 2006; Lessard et al., 2007; Miller and Gauthier, 2007; Muotri and Gage, 2006; Shi et al., 2007b; Williams et al., 2006). Neurogenic and gliogenic growth factors and cytokines promote neural lineage specification and maturation by large-scale reorganization of appropriate gene promoters through dynamic and complex modulation of DNMTs, MBDs, and histone-modifying and chromatin remodeling enzymes (Feng et al., 2007; Kondo, 2006; Lessard et al., 2007; Miller and Gauthier, 2007; Williams et al., 2006). In contrast, nuclear co-repressor complexes maintain the neural stem cell state by repression of the expression of direct targets of neuronal differentiation factors, thereby preventing the recruitment of histone-modifying enzymes that activate neurogenic gene expression (Jepsen et al., 2007; Miller and Gauthier, 2007; Rosenfeld et al., 2006). Neurogenic differentiation programs promote the derepression of neurogenic genes by removing repressive histone marks initially added by PcG proteins and their associated histone-modifying enzymes through the actions of alternate histone-modifying enzymes and also by passive loss of these repressive marks (Jepsen et al., 2007; Rampalli et al., 2007). Differential MAPK pathway engagement can recruit different DNMTs and distinct classes of “activating” histone-modifying enzymes, including cAMP response element binding protein [CREB] binding protein (CBP)/p300, and can target TrxG-mediated epigenetic changes at neural promoters to reinforce and sustain profiles of gene activation favoring neurogenesis or gliogenesis (Miller and Gauthier, 2007; Rampalli et al., 2007; Taniura et al., 2007). Latent transcription factors can selectively sequester CBP/p300 into macromolecular complexes that act as dynamic hubs to sequentially promote neurogenesis and later gliogenesis by successively binding to and activating neurogenic and later gliogenic gene promoters (Miller and Gauthier, 2007). Changes in the subunit composition of specific ATP-dependent chromatin remodeling complexes are required to promote dynamic chromatin reorganization and thus to allow distinct neurogenic and gliogenic signals to target neural transcription factors involved in neural lineage subtype specification and maturation (Lessard et al., 2007). These neural factors directly recruit diverse classes of histone-modifying enzymes and ATP-dependent chromatin remodeling factors, modulate the actions of latent transcription factors and activate different components of the MAPK signaling pathway in a context-specific manner (Briscoe and Novitch, 2007; Lessard et al., 2007; Miller and Gauthier, 2007; Rampalli et al., 2007; Taniura et al., 2007). The timely orchestration of specific neuronal and glial fate decisions, subtype specification and subsequent maturational processes including myelination also involves the differential and successive actions of specific histone-modifying enzymes, particularly those involved in histone acetylation and deacetylation (Shen and Casaccia-Bonnefil, 2007). Moreover, neuronal differentiation involves dynamic changes in HP1 isoforms required to promote the long-term silencing of repressed cell cycle-associated (E2F) genes, in the composite profile of variant histones, in the expression and alternate splicing of telomerase, in the composition of PcG and

TrxG complexes, in the post-transcriptional switch regulating the expression of a specific neuronal isoform of an essential alternate splicing protein (polypyrimidine tract binding protein [PTB]), and in the expression of polyADP ribose polymerases (PARPs) (Bosch and Suau, 1995; Boutz et al., 2007; Cohen-Armon et al., 2007; Kaneko et al., 2006; Kim et al., 2007c; Panteleeva et al., 2007; Sjakste and Sjakste, 2007). For example, the regulation of telomerase causes dynamic modulation of DNA methylation, histone-modifying enzymes and HP1 binding to modulate DNA repair, cell cycle checkpoint arrest and to prevent DNA recombination during a critical neurogenic developmental window of vulnerability, the miRNA-mediated change in PTB isoform expression promotes global reprogramming of neuronal alternate splicing, and the expression of PARP sets the epigenetic "tone" for neuronal differentiation by enhancing downstream signaling components of the MAPK pathway involved in creation of a stable post-mitotic epigenetic landscape (Bosch and Suau, 1995; Boutz et al., 2007; Kaneko et al., 2006; Kim et al., 2007c; Makeyev et al., 2007; Panteleeva et al., 2007). During the aging process, further consolidation of the differentiation process is accomplished by epigenetically-mediated creation of senescence-activated heterochromatic foci (SAHF), a process by which $p16^{INK4A}$ collaborates to prevent the inappropriate activation of proliferation or apoptosis in response to mitogenic cues, and thereby provides protection against the development of cancer and neurodegenerative diseases (Narita et al., 2006; Orford and Scadden, 2008). NcRNAs (miRNAs, other short and longer ncRNAs) and RNA editing are also integral components of the epigenetic regulation of progressive phases of neural lineage maturation from regional patterning of neural stem cell niches to progressive stem cell lineage restriction and maturation and adult neural plasticity and homeostatic responses (Mehler and Mattick, 2007; Muotri and Gage, 2006).

8. Epigenetic mechanisms underlying neuronal and neural network plasticity

The molecular transition from memory encoding and initial consolidation to progressive long-term memory storage, retrieval and reconsolidation involves complex layers of local and system-wide epigenetic modifications associated with transcriptional, post-transcriptional, translational and post-translational changes that influence molecular pathways and interactive networks at the intracellular, synaptic and systems levels of information processing, integration, transformation, stabilization, and reconfiguration (Ashraf and Kunes, 2006; Ashraf et al., 2006; Bell et al., 2008; Bramham and Wells, 2007; Chwang et al., 2007; Dahm et al., 2007; Hanson and Madison, 2007; Hong et al., 2005; Levenson and Sweatt, 2005; Matsumoto et al., 2007; Miller et al., 2007; Miller and Sweatt, 2007; Narayanan et al., 2007; Nelson et al., 2008a; Wood et al., 2006; Zhang et al., 2008). A dynamic interplay exists between primary DNA and histone modifications that create transient and more enduring patterns of synaptic and neural network modifications (Levenson and Sweatt, 2005; Miller et al., 2007). Memory consolidation is promoted by DNA methylation through the concerted actions of DNA methyltransferases and functional demethylases acting at genomic regulatory regions to differentially orchestrate the expression of specific profiles of synaptic plasticity and memory suppressor genes (Miller and Sweatt, 2007). Histone-associated post-translational modifications, particularly phosphorylation, acetylation and methylation, orchestrate long-term memory dynamics through regulation of specific promoters of plasticity-associated transcription factors (i.e., CCAAT/ enhancer binding protein: C/EBP), excitatory and neuromodulatory receptors, cytoskeletal proteins, cell adhesion molecules and metabolic enzymes (Levenson and Sweatt, 2005; Wood et al., 2006). Differential regulation of distinct types of post-translational histone modifications adds an additional layer of organizational complexity and context-specificity through the elaboration of unique patterns of neuronal and associated neural network epigenetic "state transition" signatures associated with selective forms of long-term memory (Chwang et al., 2007; Fischer et al., 2007; Hong et al., 2005; Levenson and Sweatt, 2005; Wood et al., 2006). Memory consolidation is further enhanced by changing profiles of gene modulation associated with targeted histone code modifications

mediated by synaptic receptor-associated changes in intracellular signal transduction pathways that help to coordinate and integrate multiple environmental and intracellular cues (Taniura et al., 2007). These targeted changes within specific gene networks may also play a role in activating adult neurogenesis from regional neural stem cell niches to participate in selective forms of learning and memory (Aimone et al., 2006; Hsieh and Gage, 2005; Zhang et al., 2008; Zhao et al., 2008).

Recent studies have begun to define the integrated mechanisms responsible for converting a temporary memory trace into an enduring long-term memory engram at the molecular, cellular and systems levels of brain organization (Froemke et al., 2007; Govindarajan et al., 2006; Li et al., 2007a; Sajikumar et al., 2005; Shema et al., 2007; Wang et al., 2006). At the synaptic level, LTP maintenance is selectively mediated, in part, by de novo protein synthesis and by the persistent activity of a brain-specific protein kinase (PKMzeta) through regulated protein synthesis from pre-existing gene transcripts and by the maintenance of maximal levels of its activation within a sparsely distributed subset of synapses (Kelly et al., 2007; Pastalkova et al., 2006; Sajikumar et al., 2005; Shema et al., 2007). These molecular processes enhance later memory recall from partial stimulus cues and maximize more compact and reliable information storage with high temporal precision (Lin et al., 2006; Pastalkova et al., 2006; Sajikumar et al., 2005; Shema et al., 2007). Induction of the late phase of LTP displays associative properties that allows the integration of spatial, temporal, contextual, relational and systems-wide information at specific functional dendrite subcompartments by synaptic tagging and cross tagging of informational inputs (see above) with distinct stimulus strengths, content and synaptic sites and by late associative reinforcement through the dynamic modulation of plasticity-related proteins, including PKMzeta, gene transcription, gene and protein processing, NMDA and non-glutamatergic (i.e., dopamine) modulatory neurotransmitters and activity-dependent setting and resetting of these complex and varied synaptic “tag” complexes (Morris, 2006; Reymann and Frey, 2007; Sajikumar et al., 2005). The consolidation phase of LTP is mediated by neurotrophin-, NMDA receptor-, MAPK pathway- and activity-dependent local synthesis of the Arc plasticity protein, whereas LTP maintenance requires Arc-dependent stabilization of PKMzeta synthesis, long-term expression and function (Messaoudi et al., 2007). Epigenetic tagging during these progressive stages of memory consolidation and maintenance involves complementary signaling pathways including MAPK/ extracellular signal-regulated kinase (ERK)- and CBP/p300-mediated histone H3 acetylation, MAPK/ mitogen- and stress-activated protein kinase (MSK) subpathway-mediated histone H3 phosphorylation, PARP/ERK-mediated histone H4 acetylation, associated modifications to histone H1 linker proteins and additional genome-wide chromatin remodeling resulting in downstream activation of immediate early gene responses (Chwang et al., 2007; Guan et al., 2005; Levenson and Sweatt, 2005; Matsumoto et al., 2007; Taniura et al., 2007; Wood et al., 2006).

Regulation of splicing factors and associated epigenetic regulatory pathways may promote localized or more widespread exon reprogramming as well as intron retention that can also dynamically modulate memory consolidation, reconsolidation, storage and retrieval (Bell et al., 2008; Bramham and Wells, 2007; Dahm et al., 2007; Eulalio et al., 2007; Filipowicz et al., 2008). These processes can occur through altered coupling of alternate splicing to RNA turnover and through epigenetic modifications to specific protein products to modulate their functions, subcellular localization and expression levels in ways that can create context-specific changes in neuronal biophysical properties and associated activity profiles of multilevel signal transduction cascades (Ashraf and Kunes, 2006; Bell et al., 2008; Bramham and Wells, 2007; Dahm et al., 2007; Eulalio et al., 2007; Filipowicz et al., 2008; Jepson and Reenan, 2007). Neuronal activity-dependent post-transcriptional changes in receptor-, exosome- or gap junction-mediated local and more long-distance trans-neuronal RNA transfer and recipient cell processing of mRNAs and regulatory ncRNAs may coordinately regulate

distributed neural network connectivity, activation and plasticity through establishment of neuronal oscillatory synchrony required to promote multimodal stimulus feature binding and dynamic interactions between networks mediating diverse cognitive processing components (Dinger et al., 2008; Guan et al., 2005; Jensen et al., 2007; LeBeau et al., 2003; Matsumoto et al., 2007; Mattick and Mehler, 2008; Mehler, 2002b; Rozental et al., 2000; Traub et al., 2002). It is increasingly apparent that the establishment of distinct memory states involves differential protein translation from diverse, complex and mobile dendritic and axonal mRNA pools present within functional neuronal distal microdomains (Bramham and Wells, 2007; Cox et al., 2008; Dahm et al., 2007). These translational processes are transacted by multiple RBPs and neuronal transport granules and the context-specific deployment of several distinct modes of protein translation mediated through neuronal activity-dependent modulation of excitatory receptors and differential access to mRNA and ncRNA regulatory regions and associated gene modulatory factors (Ashraf and Kunes, 2006; Ashraf et al., 2006; Bramham and Wells, 2007; Dahm et al., 2007; Eulalio et al., 2007; Filipowicz et al., 2008; Keene, 2007). NcRNAs are also intimately involved in local translational modulation (Amaral et al., 2008; Mehler and Mattick, 2007). Further, dynamic regulation of ncRNA transcription may also significantly modulate memory dynamics by influencing the molecular composition of higher-order chromatin complexes through direct regulation of polycomb and trithorax group DNA regulatory elements (Schmitt and Paro, 2006). Excitatory receptors also promote different forms of synaptic plasticity through dynamic modulation of the kinetics of translocation of neuronal granules and local mRNA translation, and these processes may, in turn, be further regulated by feedback modulation from RBPs and by associated intracellular trafficking of excitatory receptors (Bramham and Wells, 2007; Dahm et al., 2007; Eulalio et al., 2007; Lau and Zukin, 2007; Mehler and Mattick, 2007). An additional layer of long-term memory regulation is represented by the site-specific post-translational modification of different excitatory synaptic receptors by phosphorylation in concert with complementary post-translational histone modifications transacted by common neuromodulatory receptor-mediated intracellular signal transduction pathways (Bramham and Wells, 2007; Taniura et al., 2007). Similar phosphorylation-dependent control of individual translation initiation factors also represents critical molecular hubs mediating long-term synaptic plasticity and associated memory consolidation (Bramham and Wells, 2007). Cumulative changes in the biophysical properties of protein: RNA: DNA complexes and their functional interactions further define dynamic profiles of neural network connectivity and activity-dependent signaling parameters (Mattick and Mehler, 2008; St Laurent and Wahlestedt, 2007).

The general principles of multi-layered and genome-wide epigenetic regulation allow the precise mapping of evolving environmental inputs and their transformation into long-term memory traces that exhibit more abstract, categorical and hierarchical genomic as well as neural network organization, and therefore lead to uniquely adaptable modes of memory retrieval, utilization and reconsolidation (Govindarajan et al., 2006; Levenson and Sweatt, 2005; Lin et al., 2006; Mattick and Mehler, 2008; Mehler and Mattick, 2007; Morris, 2006; St Laurent and Wahlestedt, 2007; Tronson and Taylor, 2007; Wang et al., 2006; Wood et al., 2006). Synaptic plasticity appears to involve an intermediate phase associated with de novo protein synthesis from pre-existing localized gene transcripts and a late phase associated with direct transcriptional modulation (Bramham and Wells, 2007). During the intermediate plasticity phase, epigenetic processes that affect mRNA stability, molecular and functional complexity and translation are activated, particularly those involving the actions of miRNAs, siRNAs and RNA editing (Amaral et al., 2008; Ashraf and Kunes, 2006; Bramham and Wells, 2007; Dahm et al., 2007; Eulalio et al., 2007; Mattick and Mehler, 2008; Mehler and Mattick, 2007). By contrast, during the late plasticity phase, epigenetic mechanisms that regulate gene transcription and employ multiple post-transcriptional processes are recruited (Amaral et al., 2008; Mehler and Mattick, 2007). Plasticity associated genes are known to regulate the transcription of multiple classes of ncRNAs including miRNAs (Ashraf and Kunes, 2006;

Bramham and Wells, 2007; Dahm et al., 2007; Mehler and Mattick, 2007). NcRNAs are embedded within complex gene loci containing protein-coding genes, imprinted genes and other components of the epigenetic code that are themselves modulated by changes in activity-dependent cues, thereby allowing both small and longer ncRNAs to orchestrate dynamic changes in chromatin organization and associated regulation of neural plasticity and connectivity (Amaral et al., 2008; Kishino, 2006; Mehler and Mattick, 2007; Mercer et al., 2008). Furthermore, analysis of RNA editing targets has revealed that factors involved in epigenetic modulation of long-term memory functions and synaptic plasticity and in linking components of RNA editing and DNA recoding are also edited, thus suggesting an additional layer of dynamic contextual regulation (Mattick and Mehler, 2008). Within the genome, the preeminence of *Alu* repetitive elements and the preferential role of RNA editing in brain suggest the possibility of their evolutionary co-adaptation, with Alu elements representing unique modular substrates for RNA editing and their selection as vehicles to promote higher order synaptic plasticity and memory formation (Mattick and Mehler, 2008). Through the mechanism of RNA-directed DNA modifications, mediated by DNA repair enzymes or LINE-1 element-associated reverse transcriptases, or recombination-activating gene-1/2 (Rag1/2)-directed recombination events, productive short-term plasticity events can be rewritten back to the genome and are potentially infinitely modifiable through targeted DNA recoding and bidirectional modification of synaptic RNAs to establish distributed long-term memory traces through the actions of DNA editing enzymes (Dewannieux et al., 2003; Garcia-Perez et al., 2007; Jessen et al., 2001; Mattick and Mehler, 2008; Nowacki et al., 2008; Storici et al., 2007). Within these activated neural networks, information transformation from a feature-based to a more abstract code or “memory trace” may be mediated, in part, by diverse catalytic roles, orientational dynamics as well as intermediate substrate specificities of reverse transcriptases linking RNA editing to DNA recoding (Abbondanzieri et al., 2008; Lin et al., 2006; Mattick and Mehler, 2008). Moreover, such dynamic long-term plasticity mechanisms may be subject to trans-generational inheritance of complex cognitive traits through RNA transfer to the germline mediated by specific protein-coding gene pathways and associated ncRNA subclasses, including miRNAs and trans-acting RNAs, as well as DNA methyltransferases (Dinger et al., 2008; Mattick and Mehler, 2008; Nelson et al., 2008a). Interestingly, transcriptional networks that regulate reconsolidation memory appear to overlap with those that modulate the expression and activity of different DNA/RNA editing enzymes (Mattick and Mehler, 2008; Mehler and Mattick, 2007; Tronson and Taylor, 2007).

9. Epigenetics and neurodevelopmental disorders

There is increasing recognition that autism spectrum disorders (ASDs) may represent fundamental disorders of epigenetic regulation (Herbert et al., 2006; Persico and Bourgeron, 2006; Schanen, 2006). Epigenetic mutations (Fragile X syndrome, FXS) and mutations in seminal epigenetic regulatory factors (Rett syndrome, MeCP2) result in ASDs (Schanen, 2006). Some key epigenetic mechanisms linked to ASDs include parent-of-origin effects and cytogenetic impairment in imprinted domains like those present on chromosome 15q11-13, the site of deletions in Prader-Willi and Angelman syndromes. Neuropathological specimens from ASD patients, including those with Rett and Angelman syndromes, have confirmed the presence of epigenetic abnormalities including aberrant DNA methylation at candidate imprinted gene loci (Herbert et al., 2006; Persico and Bourgeron, 2006; Schaefer et al., 2007). These and other imprinted loci implicated in ASDs encompass complex genomic regulatory regions containing intricate amalgams of imprinted and non-imprinted genes involved in neural development, neuronal excitability and neural transmission, synaptic plasticity, neural network connectivity, brain homeostasis, environmental responsiveness and associated dynamic spatiotemporally defined CNS processes (Kishino, 2006; Mehler and Mattick, 2007; Rogelj and Giese, 2004; Wilkinson et al., 2007). These observations may account for a range of additional features associated with ASDs, including incomplete

monozygotic concordance, enhanced susceptibility to environmental triggers, etiologic and phenotypic heterogeneity, unusual rates of developmental regression and progression, systemic abnormalities and increasing disease incidence and prevalence (Herbert et al., 2006; Persico and Bourgeron, 2006; Schanen, 2006). Various epigenetic processes regulate imprinted loci including multiple classes of regulatory ncRNAs, DNA methylation, MBDs, chromatin remodeling, gene-environmental interactions, and intricate cis- and trans-acting and inter-allelic genomic modulatory processes (Royo and Cavaille, 2008; Schanen, 2006; Wilkinson et al., 2007 424). Complex features of ASDs may be partially explained by the unique biological characteristics of imprinted genes and associated epigenetic processes, including selective expression at distinct developmental stages and within specific brain regions and tissues, inheritance with high mutation rates resulting in epigenetic dysregulation, regulatory effects of imprinted or non-imprinted genes, downstream effects on non-imprinted genes, complex gene dosage effects of maternal and paternal alleles and associated highly pleiotropic effects and hierarchical gene ("epistatic") relationships (Badcock and Crespi, 2006; Persico and Bourgeron, 2006; Royo and Cavaille, 2008; Schanen, 2006; Wilkinson et al., 2007). Recently, selective alterations in a subset of miRNAs have been described in post-mortem cerebellar cortex specimens from ASD patients (Abu-Elneel et al., 2008). Interestingly, the profiles of miRNA alterations coincided with predictive target genes previously implicated in ASD and associated with synaptic plasticity and neural connectivity.

Deregulation of multiple interrelated epigenetic processes in ASDs may alter complex networks of gene expression and brain function including misexpression of imprinted and biallelically expressed genes without causing classical genetic lesions that are more readily detectable by linkage and association studies (Badcock and Crespi, 2006; Herbert et al., 2006; Persico and Bourgeron, 2006; Schanen, 2006; Wilkinson et al., 2007). Additional investigations suggest that the pathogenesis of ASDs, including the pronounced male gender bias, may also involve X chromosome-associated imprinted genes and intra-genomic conflicts and imbalances favoring the expression and effects of paternally versus maternally expressed genes resulting in the characteristic deficits observed in social and behavioral interactions (Badcock and Crespi, 2006). Patients with Turner's syndrome only exhibit ASDs when the maternal X chromosome is present (Schanen, 2006). In addition, ASDs are associated with microdeletions involving *FAM9B*, the human homologue of the mouse X imprinted Xlr3b gene that is maternally expressed and normally escapes X chromosome inactivation (Badcock and Crespi, 2006; Davies et al., 2006). ASDs also occur in the setting of recurrent chromosome 16p11.2 microdeletions and segmental duplications, at the genomic site of a complex interactive gene network mediating complex brain-behavior relationships (Kumar et al., 2008; Weiss et al., 2008). Moreover, a novel missense mutation in the same histone H3K4 demethylase (SMCX) that when mutated is associated with X-linked mental retardation (XLMR) results in ASD (Adegbola et al., 2008). Further, mutation in KLF14, an intronless member of the Kruppel family of transcription factors and the first example of an imprinted transcript exhibiting accelerated evolution in the human lineage, also results in ASD and the Silver-Russell imprinted syndrome. Interestingly, KLF14 acts as a transcriptional repressor by directly interacting with histone deacetylase (HDAC)-mSin3A and is imprinted through long-range chromosomal interactions, with expression dependent on a maternally methylated region that functions as an imprinting control region for the entire complex gene locus (Parker-Katiraee et al., 2007).

Prader-Willi syndrome represents a complex neurodevelopmental disorder associated with mild to moderate mental retardation, failure to thrive and hypothalamic dysfunction resulting from diverse mutations including loss of paternally inherited 15q11-13, maternal uniparental disomy and mutations of the Prader-Willi syndrome/Angelman syndrome imprinting center (Cassidy et al., 2000). Within the Prader-Willi locus is the neural imprinted gene *IPW*, a spliced and polyadenylated ncRNA (Wevrick et al., 1994). Moreover, *ZNF127* and the linked

ZNF127 antisense transcript are encoded within the *IPW* locus and display preferential expression within the nervous system (Jong et al., 1999). By contrast, Angelman syndrome results from three reciprocal mutations to those occurring in Prader-Willi syndrome, is associated with severe mental retardation, ataxia, seizures, microcephaly and sleep disturbances and exhibits cortical atrophy, cerebellar dysmyelination and loss of Purkinje neurons (Cassidy et al., 2000). *UBE3A*, the gene responsible for Angelman syndrome, exhibits biallelic expression in most tissues but preferential expression of the maternal allele in both mouse and human brains with selective imprinting in neurons throughout the nervous system (Mehler and Mattick, 2007). Loss of UBE3A function in Angelman syndrome results from deletion of the maternal *UBE3A* allele and adjacent genes (class I), the presence of duplicate chromosome 15 of paternal origin with absence of a maternal allele (class II), mutations of the imprinting center with aberrant methylation and the presence of two functional paternal alleles (class III) and mutations of the maternal *UBE3A* gene, resulting in functional inactivation without alterations in the profiles of maternal and paternal methylation (class IV) (Jedele, 2007). Moreover, there are additional patients with no known molecular genetic alterations (class V), clinical asymptomatic mothers who possess *UBE3A* mutations and severely affected offspring and unusual cases of Prader-Willi syndrome with Angelman syndrome-like methylation profiles (Jedele, 2007). There is increasing recognition of a spectrum of parent-specific epigenetic modifications at the Prader-Willi/Angelman syndrome imprinted locus that contribute to disease pathogenesis and diverse clinical presentations (Horsthemke and Wagstaff, 2008). These include changes in DNA methylation, histone and higher-order chromatin modifications, the actions of cis-acting sequences, including *UBE3A* antisense RNA associated with numerous (>70) snoRNAs, as well as the effects of trans-acting factors, including different classes of ncRNAs that interact with cis-acting sequences in both somatic and germ cells. Many of the observed imprinting defects represent epimutations that are not associated with increased risk of disease recurrence in families (Horsthemke and Wagstaff, 2008). Further, recent studies suggest that Angelman and Rett syndromes and ASDs may be etiologically linked by common alterations in gene and epigenetic effector pathways converging at the Angelman syndrome critical region (Jedele, 2007).

Fragile X syndrome, the most common hereditary form of MR, is associated with large expansions of CGG (>200) repeats in the 5’ UTR of the FMR1 gene resulting in gene silencing (Garber et al., 2008; Mirkin, 2007; Pearson et al., 2005; Warren, 2007). FMRP, the *FMR1* gene product, is an RBP involved in post-transcriptional processing and differential translation of a large subset of dendritic-associated mRNAs in concert with several distinct classes of ncRNAs required to modulate synaptic plasticity and long-term memory mechanisms (Penagarikano et al., 2007; Vanderklish and Edelman, 2005). In FXS, DNA methylation of the expanded CGG tract triggers MBD protein binding and recruitment of HDACs and other transcriptional repressors (Penagarikano et al., 2007). By contrast, pre-mutation *FMR1* carriers (CGG, 60-200 repeats) exhibit a neurodegenerative disease (FXTAS) associated with tremor and ataxia (Mirkin, 2007; Pearson et al., 2005; Sofola et al., 2007). In addition, FRAXE, which is characterized by intellectual impairment and severe language delay, is caused by significant expansion of CCG (>200) repeats in the 5’ UTR or within the body of the *FMR2* gene resulting in regional DNA hypermethylation, gene silencing and loss of FMR2 protein, a transcriptional regulator that plays a prominent role in long-term memory formation (Gu and Nelson, 2003; Mirkin, 2007; Pearson et al., 2005). Like mutations in *FMR1*, *FMR2* CCG pre-mutations result in an RNA toxicity-mediated neurodegenerative disease in animal models (Sofola et al., 2007). A rare form of severe MR in males is caused by a combined deletion of the *FMR1* and *FMR2* genes (Moore et al., 1999). Another form of MR in males is associated with a deletion that affects only the *FMR3* gene, a putative ncRNA transcribed from the opposite DNA strand to the FMR1 and FMR2 genes (Santos-Reboucas et al., 2006). In females, extensive deletion of *FMR1*, *FMR2* and *iduronate-2-sulfatase*, the gene involved in Hunter’s syndrome (mucopolysaccharoidosis, type II), combined with extensive skewing of X chromosome

inactivation (XCI) towards the normal X chromosome pattern results in MR and Hunter's syndrome, whereas incomplete skewing of XCI results in MR alone, thereby demonstrating the important roles of the X chromosome, inter-allelic communications and gene dosage effects in human cognition and the etiology of neurodevelopmental disorders (Probst et al., 2007). Interestingly, the broader *FMR* locus is rapidly emerging as a much more complex, interleaved and nested locus than originally envisioned and further functional genomics exploration will likely yield major new insights into the role of different classes of ncRNAs in neurodevelopmental as well as neurodegenerative diseases. For example, recent studies have identified *FMR4*, a primate-specific longer ncRNA that resides upstream of the *FMR1* gene and possibly both share a bidirectional promoter although each gene may be independently regulated (Khalil et al., 2008). Pathological CGG expansion in the 5' UTR of the *FMR1* gene has been shown to alter transcription in both directions, resulting in *FMR4* silencing in FXS and up regulation in permutation carriers that exhibit a neurodegenerative phenotype (FXTAS). *FMR4* exhibits cell cycle regulatory and anti-apoptotic functions and significant extraneural expression profiles particularly in cardiac tissues that are affected in FXS. Therefore, *FMR4* may contribute to significant FXS cardiac co-morbidities by virtue of its seminal cellular functions that may be mediated by integrated effects on relevant gene networks by targeting multiple involved genes in trans in ways similar to those transacted by other longer ncRNAs. Interestingly, an antisense transcript (*ASFMR1*) that encompasses the CGG repeats in the 5' UTR of the *FMR1* gene has also been described (Ladd et al., 2007). ASFMR1 possesses multiple transcription start sites, is highly spliced, exhibits a splice variant that overlaps with *FMR4* and displays profiles of transcriptional deregulation in FXS and FXTAS similar to *FMR4* (Ladd et al., 2007). Another classical lysosomal storage disease, Krabbe's disease or globoid cell leukodystrophy, associated with neurodevelopmental deficits, has recently been shown to exhibit epigenetically mediated neuronal loss and associated immune dysregulation (Galbiati et al., 2007). Werner's syndrome, a progeroid disorder associated with neurodevelopmental impairments, is caused by mutation of the gene encoding the WRN protein that is required for telomere maintenance and chromatin remodeling in association with the SIRT6 histone H3K9 deacetylase (Michishita et al., 2008). Down's syndrome causes a spectrum of neurodevelopmental deficits mediated, in part, by several epigenetic mechanisms, including abnormal DNA methylation and transcriptional dysregulation of the *DYRK1A* gene, and DYRK1A-mediated deregulation of alternative splicing, histone mRNA 3' end formation and impaired co-regulation of the calcium-dependent transcription factor, NFAT in association with the ncRNA, *NRON* (de Graaf et al., 2006; Gwack et al., 2006; Hobbs et al., 2002; Maenz et al., 2008; Old et al., 2007).

Disruption of a broad spectrum of epigenetic mechanisms is associated with both syndromic and non-syndromic forms of XLMR (Froyen et al., 2006; Ropers, 2006). One form of XLMR is associated with loss of activity of SMCX, a histone H3K4 demethylase (see above) that normally forms a transcriptional repressor complex with HDACs, a histone H3K9 methyltransferase and the key neuronal silencer factor, REST to differentially modulate the expression of a subset of REST target genes involved in neuronal maturation (Tahiliani et al., 2007). Non-syndromic XLMR also results from loss-of-function mutations that affect the FTSJ1 protein, which typically binds S-adenosyl methionine and is a major methyl donor for DNA methylation reactions that silence gene transcription (Froyen et al., 2007; Takano et al., 2008). Other forms of non-syndromic XLMR are caused by mutations in genes encoding Kruppel-type zinc finger proteins that participate in heterochromatin formation and gene silencing by recruiting HP1 in complex with HDAC3 and the histone methyltransferase, SETB1 (Froyen et al., 2006; Ropers, 2006; Schultz et al., 2002). Rett syndrome, a pervasive neurodevelopmental disorder predominantly affecting girls but also occasionally causing XLMR and severe neurological disorders in boys, is usually caused by mutations including gross deletions in MeCP2, an MDB factor with an enlarging spectrum of recognized roles in DNA methylation, alternate splicing and chromatin remodeling (Chadwick and Wade, 2007;

Froyen et al., 2006; Ropers, 2006). In terms of syndromic XLMR, the Lenz microphthalmia syndrome is associated with mutations in the Bcl6-interacting co-repressor, BCOR, a key regulator of transcription during embryogenesis with roles in histone acetylation and chromatin remodeling (Horn et al., 2005; Ng et al., 2004). At least five XLMR syndromes occur in association with distinct mutations in the gene encoding the polyglutamine binding protein-1 (PQBP1), a factor with epigenetic roles in transcription and alternate splicing and associated effects in long-term memory processing and complex behavioral repertoires (Lubs et al., 2006; Martinez-Garay et al., 2007; Yoshimura et al., 2006). There is also a family with both autism and MR that exhibits PQBP1 mutations along with skewed X chromosome inactivation (Fichera et al., 2005). Interestingly, PQBP1 may also be a central regulator of neurodegeneration in polyglutamine diseases and interacts directly with mutant ataxin-1 and huntingtin (Marubuchi et al., 2006). Mutations in ATRX, a DNA helicase involved in chromatin remodeling, DNA and histone methylation and silencing of gene expression, cause a broad spectrum of clinical phenotypes, the most severe represented by the syndrome of severe XLMR and α-thalassemia (Froyen et al., 2006; Ropers, 2006). Coffin-Lowry syndrome, associated with XLMR, is caused by mutations in the p90 ribosomal S6 kinase 2 (RSK2), a major effector of chromatin remodeling through interactions with histone methyltransferases, histone acetylases, signaling pathways mediating phosphorylation of histone proteins and mediators of long-term memory formation (Froyen et al., 2006; Ropers, 2006). Mutations in CBP, a transcriptional co-activator possessing intrinsic histone acetyltransferase activity, results in the Rubinstein-Taybi syndrome associated with MR; deregulation of CBP has also been implicated in the pathogenesis of several neurodegenerative disorders including Alzheimer's and Huntington's diseases (Froyen et al., 2006; Ropers, 2006). Mutations in CHD7, a DNA helicase involved in chromatin remodeling, cause CHARGE syndrome which is associated with developmental aberrations including MR (Froyen et al., 2006). Immunodeficiency, centromere instability and facial anomalies (ICF) syndrome causes a rare form of MR as a result of defects in DNA methylation, chromatin remodeling and transcriptional regulation due to hypomorphic germline mutations in DNMT3B (Jin et al., 2008). Finally, alterations of the gene encoding the H3K9 euchromatin histone methyltransferase 1 give rise to a developmental disorders associated with severe MR and related behavioral disturbances (Takizawa and Meshorer, 2008).

A complex spectrum of neurodevelopmental disorders arises from defects in related genes involved in different subtypes (global genomic repair [GGR] or transcription coupled repair [TCR]) of the specialized DNA repair mechanism termed nucleotide excision repair (Cleaver, 2005; Mellon, 2005). One rare disorder of GGR termed the xeroderma pigmentosum variant (XPV) syndrome is associated with MR and peripheral cancer due to deficiency of the Y-family DNA polymerase-η that may be involved in linking RNA editing and DNA recoding to promote long-term memory formation and other higher cognitive functions (Gratchev et al., 2003; Liu and Chen, 2006; Mattick and Mehler, 2008). By contrast, a disorder of TCR termed Cockayne syndrome is associated with progressive neurodevelopmental disabilities with progeroid features but without increased cancer incidence most often due to mutations in the *CSA* or *CSB* genes, the latter encoding a SWI/SNF-like ATP-dependent chromatin-remodeling enzyme (Cleaver et al., 2007; Newman et al., 2006). In addition, CSB forms a complex with the G9a histone H3K9 methyltransferase to facilitate association with the heterochromatin protein, HP1 to promote ribosomal DNA transcription, interacts with CSA in a multimeric complex to promote pre-mRNA splicing and CSA and CSB also differentially and cooperatively regulate the recruitment of distinct chromatin remodeling factors involved in histone modifications and nucleosome binding (Fousteri et al., 2006; Kuraoka et al., 2008; Yuan et al., 2007). Interestingly, recent studies have shown that a domesticated class II transposable repetitive element (*PGBD3*) residing within intron 5 of the CSB gene functions as a novel terminal exon, and that the alternatively spliced mRNA encodes a novel chimeric protein in which CSB exons 1-5 are joined in frame to the *PGBD3* transposon, encoding a transposase enzyme that binds

to and incorporates single-stranded DNA into genomic sequences, and continues to be expressed when functional CSB is lost due to the pathogenic mutation (Newman et al., 2008). The human genome contains over 600 non-autonomous *PGBD3*-related *MER85* elements, many of which are associated with genes involved in neuronal development, are regulated by CSB and may be deregulated following Cockayne syndrome-associated CSB loss-of-function mutations (Newman et al., 2008). Although congenital cerebral palsy is usually not considered genetic, a family has been described with a deletion of the *ANKRD15* gene that exhibits imprinting-like inheritance (Lerer et al., 2005). In this case, the 9p24.3 deletion is interpreted as a maternal imprinted gene expressed only from the paternal allele with the only allelic difference resulting from differential methylation in the CpG island flanking another gene (*DMRT*) located 3' of the *ANKRD15* gene (Lerer et al., 2005). Affected individuals are carriers of the paternal deletion with repression of the normal maternal allele (Lerer et al., 2005). The complex gene locus encompasses multiple promoters and diverse transcripts, and hypermethylation only occurs on the deleted chromosome when transmitted through the mother (Lerer et al., 2005). In the presence of the deletion, hypermethylation of the *DMRT1* promoter may create a longer non-coding antisense transcript that overlaps and represses *ANKRD15* expression from the normal allele or additional trans-allelic interactions (transvection or paramutation) may be operative (Lerer et al., 2005).

10. Epigenetic mechanisms underlying neurodegenerative diseases

There are many tantalizing clues suggesting that neurodegenerative diseases are mediated by aberrant epigenetic mechanisms (Anderson et al., 2008; Cattaneo, 2007; Fischer et al., 2007; Johnson et al., 2008; Kim et al., 2007a; Kim et al., 2008; Nelson et al., 2008b; Roze et al., 2007; Sadri-Vakili and Cha, 2006; Schaefer et al., 2007; Setsuie and Wada, 2007; Stack et al., 2007; Sun et al., 2005; Wang et al., 2008b; Zuccato et al., 2007). The evidence includes the absence of simple Mendelian inheritance patterns, global transcriptional dysregulation, multiple types of pathogenic RNA alterations, expansion of unstable microsatellite repeats, aberrant stimulation of developmental and mitogenic signaling pathways, the labile state of differentiation, defects in axondendritic transport, the presence of chronic stress, telomere dysfunction and genomic instability, and the importance of environmental factors and multiple distinct transition states associated with disease pathogenesis (Arendt, 2000; Bernstein et al., 2002; Cha, 2007; Chan et al., 2007; Greene et al., 2007; Gueven et al., 2007; Kovtun and McMurray, 2008; Lesnick et al., 2007; McMurray, 2005; Mirkin, 2007; Mosch et al., 2007; Pearson et al., 2005; Peng et al., 2007; Rass et al., 2007; Saxena and Caroni, 2007; Whalley et al., 2006; Zhang et al., 2007). Transcriptional dysregulation is a unifying feature of trinucleotide repeat disorders and is increasingly recognized in other subclasses of neurodegenerative diseases (Cha, 2007; Mirkin, 2007; Pearson et al., 2005; Telese et al., 2005). Independent of protein context, microsatellite repeat expansion overrides the normal program of neuronal differentiation and maintenance functions, whereas in specific trinucleotide repeat diseases there is early deregulation of genes involved in the specification and maturation of specific neuronal subtypes that later undergo physiological dysfunction and neurodegeneration (Abou-Sleymane et al., 2006; Cha, 2007; Mirkin, 2007; Pearson et al., 2005). There is also increasing evidence that microsatellite repeat sequences are essential for mediating complex cognitive functions, personality, social interactions, emotive expression and circadian rhythms (Fondon et al., 2008). Recent examination of both brain and peripheral tissues in Huntington's disease patients has identified genome-wide changes in gene expression with large domains of increased transcription and complementary regions of repressed transcription comparable to those seen in primary cancers including gliomas (Anderson et al., 2008). Huntingtin has been shown to interact with components of the basal transcriptional machinery, including direct binding to multiple transcription factors and associations with epigenetic components of both transcriptional repressor as well as activator complexes (Cha, 2007; Harjes and Wanker, 2003; Kaltenbach et al., 2007; Stack et al., 2007). Huntingtin and

other neurodegenerative disease-associated proteins, including ataxin-7, bind directly to different histone acetyltransferases, and a huntingtin-interacting protein (HYPB) represents a specific histone H3K36 methyltransferase that normally facilitates active transcription (Helmlinger et al., 2004; Sun et al., 2005). In addition, disrupted interactions of mutant huntingtin with a Bmi1-associated E3 ubiquitin ligase histone-modifying complex increase the monoubiquitylation of histone H2A and decrease the analogous modification of histone H2B resulting in complex profiles of transcriptional dysregulation associated with complementary alterations in histone acetylation and methylation, respectively, through complex epigenetic crosstalk (Kim et al., 2008). Furthermore, the cytoplasmic domain of amyloid precursor protein mediates direct binding of an additional histone acetyltransferase and indirectly associates with a nucleosome assembly factor (Telese et al., 2005). Neurodegenerative disease-associated proteins such as huntingtin also promote chromatin modifications by complex interactions with developmental and adult cytokine and neuromodulatory receptors and intracellular signaling pathways that promote selective post-translational modifications of histone proteins as well as non-histone proteins involved in all aspects of normal CNS cellular functions (Bennett et al., 2007; Cattaneo, 2007; Harjes and Wanker, 2003; Hayakawa-Yano et al., 2007; Kaltenbach et al., 2007; Li et al., 2007b; Liu et al., 1997; Roze et al., 2007; Taniura et al., 2007). Huntington's disease and associated animal models exhibit intricate abnormalities in histone acetylation, methylation and phosphorylation, impaired nucleosome remodeling, selective striatal deficiency of a downstream nuclear component (MSK1) of the MAPK pathway and associated alterations in cell cycle regulation, protein degradation, DNA repair, axodendritic transport, telomere maintenance, senescence pathway activation, stress and metabolic responses, genomic stability and cell viability (Anderson et al., 2008; Bennett et al., 2007; Cho et al., 2007; Harjes and Wanker, 2003; Kaltenbach et al., 2007; Li et al., 2007b; Roze et al., 2007; Sadri-Vakili and Cha, 2006; Stack et al., 2007). Interestingly, the SIRT1 NAD-dependent HDAC is deregulated in several neurodegenerative disease mouse models associated with dysfunction of seminal non-histone transcriptional regulators (Kim et al., 2007a). In addition, multiple components of the MAPK pathway are impaired in vulnerable neurons in neuropathological specimens of Alzheimer's disease associated with the establishment of a labile state of neuronal differentiation (Arendt, 2000). Treatment with HDAC inhibitors and DNA/RNA-binding anthracyclines that affect nucleosome positioning have shown positive effects on behavioral measures, neuroprotection, nucleosome remodeling and associated chromatin dynamics and transcriptional profiling in various Huntington's disease and also additional neurodegenerative disease animal models (Abel and Zukin, 2008; Stack et al., 2007). By contrast, over expression of HDAC6 suppresses the neurodegenerative phenotype associated with ubiquitin proteasomal system dysfunction, in selective trinucleotide repeat disorders and in animal models associated with Alzheimer's disease pathology (Pandey et al., 2007). Moreover, huntingtin represents a nucleocytoplasmic chaperone for the neuronal gene silencer, REST/NRSF, and mutant huntingtin is impaired in its ability to sequester REST in the cytoplasm (Zuccato et al., 2003). In Huntington's disease cells, animal models and human post-mortem specimens, there is increased binding of REST at multiple RE1 consensus sequences and genomic loci resulting in significantly reduced transcription of REST-related genes associated with diverse impairments in cellular specification and maturation both within and outside of the nervous system without corresponding changes in overall cellular levels of REST expression (Zuccato et al., 2007). Ectopic nuclear expression of REST in Huntington's disease models also leads to deregulation of an integrated miRNA pathway regulating neuronal cell identity and neural connectivity (Johnson et al., 2008). These findings suggest that an additional mechanism underlying transcriptional and post-transcriptional dysregulation and complex chromatin abnormalities in Huntington's disease is impairment in the genome-wide deployment of higher-order macromolecular REST-associated chromatin remodeling complexes and pervasive but selective alterations in gene regulation as well as global cellular homeostasis (Ballas and Mandel, 2005; Otto et al., 2007). These overall observations suggest that complex but selective profiles of alterations in chromatin dynamics and post-

transcriptional processing occur in individual neurodegenerative diseases through a diverse array of pathogenic mechanisms and therefore give rise to a broad spectrum of progressive cellular abnormalities culminating in selective neurodegeneration.

Alterations in RNA regulatory circuitry have also recently been identified as important mechanisms in the pathogenesis of neurodegenerative diseases (Hebert and De Strooper, 2007; Mehler and Mattick, 2007; Mirkin, 2007; Nelson et al., 2008b; Osborne and Thornton, 2006; Pearson et al., 2005). In *Drosophila*, a specific miRNA (*ban*) exerts neuroprotective actions (Bilen et al., 2006). Ablation of miRNA biosynthesis pathways in Dicer deficient mouse models results in neurodegeneration of cerebellar Purkinje cells, concomitant loss of cerebellar granule neurons and associated ataxia, without immediate and earlier effects on cellular physiology (Schaefer et al., 2007). miRNA deficiencies have also been associated with spinocerebellar ataxia type 3 (SCA3)- and microtubule-associated protein tau (MAPT)-related neurodegeneration (Bilen et al., 2006; Nelson et al., 2008b). *MiR-133b* is normally enriched in the midbrain and suppresses full differentiation of dopaminergic neurons in vitro, participates with the transcriptional regulator, Pitx3 in a negative feedback loop regulating the maturation of dopaminergic neurons, and *miR-133b* is selectively down regulated in neuropathological specimens in Parkinson's disease (Kim et al., 2007b). In Tourette's syndrome, there is sequence variation in the binding site for *miR-189* in the 3' UTR of the neuronal SLIT and Trk-like family member 1 (*SLITRK1*) gene (Abelson et al., 2005). Moreover, there is a sequence variation in the 3' UTR of the fibroblast growth factor 20 (*FGF 20*) gene causing disruption of the binding site for *miR-433*, enhanced translation of FGF 20 and associated increased expression of α-synuclein, thereby conferring greater susceptibility to Parkinson's disease (Wang et al., 2008a). Amyloid precursor protein (*APP*) and *α-synuclein* genes that are mutated in familial forms of Alzheimer's and Parkinson's disease, respectively, both have 3' UTRs that are targeted by a spectrum of diverse miRNAs that participate in complex gene and neural regulatory pathways (Nelson et al., 2008b). Similarly, the 3' UTR of the β-amyloid precursor protein-cleaving enzyme 1 (*BACE1*) gene has at least five distinct miRNA target sites, and early down regulation of expression of *miR-107* in cortical lamina associated with pathological changes in Alzheimer's disease may accelerate disease progression through modulation of BACE1 actions (Wang et al., 2008b). Additional miRNAs that are deregulated in Alzheimer's disease are normally associated with complex regional patterns of expression associated with areas underlying learning and memory and complex cognitive functions, target synaptic plasticity genes and recapitulate neurodevelopmental profiles of expression (Cogswell et al., 2008; Kim et al., 2004; Kosik, 2006; Krichevsky et al., 2003). MiRNAs have intricate and unique roles in stress adaptations that are central pathogenic components of all neurodegenerative diseases and they also participate in a broad array of epigenetic regulatory events including multiple interrelated components of post-transcriptional processing that are known to be deregulated in different subclasses of neurodegenerative diseases (Nelson et al., 2008b). In sporadic amyotrophic lateral sclerosis (ALS), but not in familial ALS with superoxide dismutase 1 (*SOD1*) mutations or in spinal bulbar muscular atrophy, there is selective impairment within motor neurons of RNA editing at the Q/R site of the ionotropic glutamate AMPA receptor subunit, GluR2 resulting in enhanced calcium permeability and excitotoxicity culminating in neurodegeneration (Kawahara et al., 2006).

Microsatellite expansion diseases, particularly those harboring certain sequence repeats, have a propensity to form intramolecular DNA and RNA hairpin structures that cause genomic instability and novel RNA gain-of-toxic-function effects, respectively (Kovtun et al., 2007; Legendre et al., 2007; Li et al., 2008b; Lim et al., 2008; Mirkin, 2007; Osborne and Thornton, 2006; Pearson et al., 2005). These unusual and previous unrecognized aberrant structural features disrupt DNA replication, repair and recombination as well as diverse post-transcriptional regulatory events including alternate splicing mediated by different classes of ncRNAs (Kelkar et al., 2008; Kovtun and McMurray, 2008; Mirkin, 2007; Osborne and

Thornton, 2006; Pearson et al., 2005). The expansion of repetitive elements may serve as a sink to sequester RBPs and their cargo as well as additional proteins and protein complexes, thereby disrupting the stoichiometric balance between specific gene transcripts and related binding proteins and other disease-associated proteins (Li et al., 2008b; Lim et al., 2008; Mirkin, 2007; Osborne and Thornton, 2006). The ensuing microaggregates may display complex profiles of subcellular distribution, particularly if the mutations create or eliminate recognition elements for RBPs or miRNAs (Mirkin, 2007; Osborne and Thornton, 2006). This, in turn, alters the localization of key regulatory factors, such as splicing factors, in selected disorders including myotonic dystrophy and causes a reversion to the splicing profiles normally observed only in more immature tissues (Osborne and Thornton, 2006). Changes in the balance of native protein complexes associated with the normal and the expanded repeat-containing proteins may modify their functional roles in promoting or deregulating seminal cellular processes (Kovtun and McMurray, 2008; Li et al., 2008b; Lim et al., 2008; Mirkin, 2007; Pearson et al., 2005). The different types of repeat expansions as well as their genomic coordinates within coding regions, 5'/ 3' UTRs, introns and promoter/enhancer elements play a major role in the dynamic profiles of repeat expansion occurring during specific developmental and proliferative states, in the context of intergenerational and somatic transmission, following exposure to potentially deleterious environmental agents and with respect to the types of RNA gain-of-toxic-functional states exhibited (Kovtun and McMurray, 2008; Mirkin, 2007; Osborne and Thornton, 2006; Pearson et al., 2005). The unusual RNA structural features present in these diseases result in abnormal profiles of protein sequestration, RNA degradation and chromatin silencing, the latter through the process of RNA-induced gene silencing mediated by antisense transcription and interactive histone modifications (Mirkin, 2007; Osborne and Thornton, 2006; Pandey et al., 2007; Pearson et al., 2005). In post-mitotic neurons, age-dependent repeat expansion is facilitated by attempts to repair oxidative DNA damage, resulting in escalating cycles of DNA excision repair and dependent on a single base excision repair enzyme (8-oxoguanine DNA glycosylase 1: OGG1) (Kovtun et al., 2007). This aberrant DNA repair process occurs in Huntington's disease, thereby establishing direct molecular links between oxidative damage, DNA repair pathways and neurodegeneration (Kovtun et al., 2007). Repeat expansion disorders exhibit very heterogeneous clinical and pathological profiles including those encompassing a spectrum of neurodegenerative, neuromuscular and neurodevelopmental disorders (Mirkin, 2007; Osborne and Thornton, 2006; Pearson et al., 2005). While trinucleotide repeat disorders comprise the largest disease category, there are also examples of larger repeat expansions including tetranucleotides (myotonic dystrophy, type 2), pentanucleotides (spinocerebellar ataxia 10), minisatellites (progressive myoclonic epilepsy 1) and megasatellites (fascioscapulohumeral muscular dystrophy, type 1A) (Legendre et al., 2007; Mirkin, 2007; Sposito et al., 2005). These repeat expansion disorders also display complex maternal and paternal forms of transmission and minimal and alternate neurological symptoms/signs and disease manifestations due to the progressive effects of repeat length expansions on disease threshold through the expression of pre-mutations and proto-mutations, respectively (Kovtun and McMurray, 2008; Medica et al., 2007; Mirkin, 2007; Pearson et al., 2005). RNA-mediated dysfunction may also be prominent in different forms of ataxia with oculomotor apraxia (AOA), early-onset forms of autosomal recessive spinocerebellar ataxias due to mutations in aprataxin, a HIT superfamily DNA/RNA binding and nucleotide hydrolase (AOA1) and senataxin, a DNA/RNA helicase (AOA2) that is also associated with familial juvenile ALS (Chen et al., 2006b; Gueven et al., 2007; Kijas et al., 2006; Schols et al., 2008). Moreover, alterations in axodendritic transport that are prominent features of Huntington's disease and associated disorders may further alter the fidelity of axonal growth cone and mature synaptic terminal RNA editing and RNA-directed DNA recoding, thereby predisposing to neurodegeneration through alterations in developmental neuronal wiring, increased susceptibility to synergistic environmental risk factors as well as disruptions to synaptic plasticity and progressive memory formation (Harjes

and Wanker, 2003; Kaltenbach et al., 2007; Mattick and Mehler, 2008; Rong et al., 2007; Truant et al., 2006; Truant et al., 2007; van Dellen et al., 2005).

11. Epigenetic principles underlying cellular transformation and neurooncology

Systemic cancers are associated with a spectrum of genome-wide epigenetic alterations that promote tumor initiation, progression, invasion, metastasis, drug resistance, subversion of immunosurveillance and progressive genomic instability (Calin and Croce, 2007; Esteller, 2008; Koebel et al., 2007; Ting et al., 2006). In addition, recent studies suggest that cell transformation requires intricate and cooperative modulation of downstream oncogenic signaling pathways through synergistic modulation of hierarchies of cell and gene regulation involving a limited number of “cooperation response genes” and the employment of a subset of “cancer-initiating cells” with aberrant stem and progenitor cell properties that are in a relatively quiescent state and are responsible for tumor maintenance (Ito et al., 2008; McMurray et al., 2008). The cancer epigenome is central to these interrelated pathogenic processes and is characterized by complex alterations in DNA methylation, histone code modifications, nucleosome and chromatin remodeling, expression and function of ncRNAs particularly miRNA biogenesis and function, RNA editing and DNA recoding, post-transcriptional RNA processing and long-range epigenetic silencing (Calin and Croce, 2007; Clark, 2007; Esteller, 2007a; b; Nicoloso and Calin, 2008; Paz et al., 2007; Scholzova et al., 2007; Ting et al., 2006; Vartanian et al., 2008; Wang et al., 2007a; b). These progressive and self-sustaining epigenetic lesions promote silencing of tumor suppressor genes, activation of oncogenes and deregulation of genes and genomic loci involved in stem cell self renewal and clonal and polyclonal expansion (tumor progenitor genes), cell cycle progression, cell survival and apoptosis, growth suppression and senescence, tissue-selective lineage specification and differentiation, angiogenesis, maintenance of germ-line integrity, genomic imprinting, DNA damage sensing and repair, telomere maintenance, cellular stress responses, control of parasitic repetitive elements and prevention of non-instructive recombination events (Calin and Croce, 2007; Clark, 2007; Esteller, 2007a; b; Nicoloso and Calin, 2008; Paz et al., 2007; Postovit et al., 2007; Scholzova et al., 2007; Ting et al., 2006; Vartanian et al., 2008; Wang et al., 2007a; b). Recent studies have utilized these enormous conceptual and experimental advances in tumor biology to begin defining epigenetic alterations associated with specific types of neural tumors and thus to begin to define disease pathogenesis and to identify novel molecular targets as early biomarkers and for innovative therapeutic applications.

Glioblastomas have recently been shown to exhibit complex alterations in gene expression profiles associated with inactivation of tumor suppressor genes, aberrant activation of protooncogenes and selective or sequential alterations in the expression and function of other classes of genes involved in tumor initiation and progression (Esteller, 2007a; 2008; Hesson et al., 2004; Kim et al., 2006b). Aberrant epigenetic silencing in these CNS tumors is frequently mediated by hypermethylation of promoter-associated CpG islands, by repressive histone modifications, by imprinting-associated gene allele inactivation (LOH: “loss of heterozygosity”) and by additional epigenetic mechanisms (Calin and Croce, 2007; Esteller, 2007a; 2008; Hesson et al., 2004; Kim et al., 2006b; Nicoloso and Calin, 2008; Paz et al., 2007). Mutations in genes encoding epigenetic modifying machinery (HDACs, nucleosome assembly factors and histone chaperones) are also seen in gliomas and may predict responses to certain classes of epigenetic therapeutic agents (Esteller, 2007a; 2008; Hesson et al., 2004; Kim et al., 2006b). The profiles of epigenetically mediated changes in gene expression may evolve over time and may therefore reflect both the earliest initiating pathogenic events as well as increasing degrees of dedifferentiation and invasiveness (Hesson et al., 2004; Kim et al., 2006b; van den Boom et al., 2006; Waha et al., 2005). Moreover, changes in expression of multiple deregulated genes may reflect both independent and linked as well as evolving

epigenetic processes (Hesson et al., 2004; Kim et al., 2006b; van den Boom et al., 2006). Glioblastoma tumor-initiating cells (TICs) have been identified with properties resembling neural stem cells (Lee et al., 2008; Nakano and Kornblum, 2006; Nakano et al., 2008; Vescovi et al., 2006). A subset of these TICs (type II) exhibit down regulation of expression of the bone morphogenetic protein receptor, type 1B (BMPR1B), normally associated with inhibition of proliferation and promotion of astroglial differentiation, through BMPR1B promoter hypermethylation and additional epigenetic silencing mediated by the H3K27 methyltransferase, EZH2, a component of the PcG2/3 repressor chromatin remodeling complex (Lee et al., 2008). Over expression of the glial lineage transcriptional regulator, Olig2 also promotes the elaboration of glioblastoma stem cells, in part, by repression of the $p21^{WAF1}$ tumor suppressor gene (Ligon et al., 2007). Tumor-initiating cells with stem cell properties have also been identified in oligodendrogliomas, medulloblastomas and ependymomas and may be fostered by complex epigenetic alterations that impair the normal signaling interactions between regional neural stem cells and their vascular niches to create a fertile tumor microenvironment through age-related deterioration of the stem cell niche and epigenetic “rewiring” of TIC signal transduction pathways to promote multi-drug resistance (Gilbertson and Rich, 2007; Vescovi et al., 2006). NcRNAs, particularly miRNAs, are also deregulated in glioblastomas and exhibit specific miRNA “fingerprints” (Calin and Croce, 2007; Nicoloso and Calin, 2008). *miR-21*, *miR-221* and *miR-222* are all over expressed in glioblastomas and associated cell lines, whereas the brain-enriched *miR-128* and *miR-181a-c* are down regulated (Nicoloso and Calin, 2008). *MiR-21* represents an oncogenic miRNA that functions in association with constitutively active signal transducer and activator of transcription (STAT3) intracellular signaling, targets several tumor suppressor genes and blocks expression of apoptosis-associated genes (Chan et al., 2005; Nicoloso and Calin, 2008). By contrast, over expression of *miR-221/222* promotes the development of glioblastomas by direct suppression of $p27^{KIP1}$ through cell cycle deregulation with associated G1 arrest (Nicoloso and Calin, 2008).

Recent novel combination epigenetic therapeutic strategies using locked-nucleic-acid (LNA)-modified oligonucleotides to silence *miR-21* in concert with neural progenitor cell-secretable variants of the cytotoxic tumor necrosis factor-related apoptosis inducible ligand (TRAIL), combined anti-*miR-21/221-222* oligonucleotides and targeting of ultraconserved genomic loci associated with these miRNA clusters have shown promising results in glioblastomas (Nicoloso and Calin, 2008). There is significant global RNA hypoediting of *Alu* repetitive elements in glioblastomas with cancer gene-specific editing profiles (Paz et al., 2007). These findings correlate with down regulation of ADAR1-3 gene expression levels, and with corresponding profound reductions in ADAR3 transcript expression that are linked to enhanced tumor aggressiveness (Paz et al., 2007). In addition, hypoediting of the glutamatergic AMPA receptor, GluR2 is observed in high-grade glioblastoma multiforme but not in low-grade astrocytomas (Paz et al., 2007). Moreover, down regulation of ADAR2-mediated RNA editing is a feature of pediatric astrocytomas and correlates with the grade of malignancy (Cenci et al., 2008). Interestingly, in these childhood tumors ADAR 2 exhibits normal expression whereas ADAR1 and 3 exhibit enhanced expression profiles, and selective deregulation of ADAR1/3 expression is thought to interfere with ADAR2 specific editing activity (Cenci et al., 2008). By contrast, down regulation of ADAR1-3 expression is seen in oligodendrogliomas, with the selective targeting of ADAR3 revealing novel roles for this unusual RNA editing enzyme in translational regulation through modulation of double-stranded RNA-activated protein kinase (PKR) and the translational initiation factor, eIF2a (Paz et al., 2007). Recent studies suggest additional roles for single- and double-stranded RBPs in glioma formation by competing with RNA editing and related enzymes (Paz et al., 2007). Over expression of ADAR1 and ADAR2 in a glioblastoma multiforme cell line reduces cellular proliferation, indicating a direct role for RNA editing in neural tumor pathogenesis (Paz et al., 2007).

Epigenetic inactivation of multiple tumor suppressor genes is observed in a large proportion of medulloblastomas due, in large part, to promoter and associated 5' UTR hypermethylation (Lindsey et al., 2005; Lindsey et al., 2004; Waha et al., 2007; Waha et al., 2003). The profiles of aberrant methylation are complex and reflect multiple epigenetic mechanisms that differentially target specific classes of genes involved in the establishment and progression of this childhood tumor derived from cerebellar granule precursor cells (Fogarty et al., 2005; Leung et al., 2004).

Treatment with DNA methyltransferase inhibitors frequently reverses the epigenetic-mediated silencing observed in meduloblastoma cells (Lindsey et al., 2004; Waha et al., 2007; Waha et al., 2003). In medulloblastomas, there is also epigenetic deregulation of multiple *S100* gene family members, involved in cell growth, cell cycle regulation, differentiation, transcription and cell motility, with differential hypo- and hyper-methylation within their promoter CpG islands (Lindsey et al., 2007). Some of the methylation changes observed in these genes in medulloblastomas reflect alterations of the normal epigenetic developmental program of methylation, whereas others appear to reflect de novo alterations associated with the appearance of aggressive anaplastic tumors (*S100A6* hypermethylation) or progression to metastasis (*S100A4* hypomethylation) (Lindsey et al., 2007). A wide variety of epigenetically mediated recombination events are also prominent features of medulloblastomas and result in complex profiles of deregulated gene expression and function (Ellison, 2002; Lindsey et al., 2004). The PcG transcriptional repressor, Bmi1, involved in stem cell self-renewal, is over expressed in medulloblastomas as are the developmental sonic hedgehog (Shh) transcriptional modulators, Gli1-3, whereas the Shh receptor subunits are differentially impaired: smoothened (Smo) is activated while patched (Ptc) is either over expressed or inactivated due to loss of heterozygosity (Fogarty et al., 2005; Leung et al., 2004). During early development of the cerebellum, Shh is essential for up regulating expression of Bmi1 with resultant expansion of the pool of cerebellar granule cell precursor cells, and Shh signals through intricate feedback regulation of Ptc and Smo and also complex engagement of dual activator/repressor functions of Gli proteins (Fogarty et al., 2005; Leung et al., 2004). Therefore, epigenetic promotion of medulloblastoma initiation and progression appears to subvert the normal cerebellar stem and progenitor cell developmental program (Fogarty et al., 2005). The more aggressive supratentorial primitive neuroectodermal tumors (PNETs) but not medulloblastomas exhibit high frequencies of promoter hypermethylation of the cyclin-dependent kinase inhibitors, $p14^{ARF}$ and $P16^{INK4}$, both encoded at the *CDKN2A* locus, and also selective epigenetic inactivation of the tumor suppressor gene, *DLC-1* that is involved in Ras-mediated cell transformation, growth, migration, apoptosis and cytoskeletal organization (Inda et al., 2006; Pang et al., 2005). Although CpG promoter hypermethylation is important in epigenetic silencing of *DLC-1*, there is recent evidence that histone deacetylation precedes DNA methylation, thereby illustrating the complex epigenetic crosstalk that occurs in brain tumor initiation and progression (Kim et al., 2003). In rhabdoid tumors of the brain, there is biallelic loss of the *SNF5* gene, encoding an ATP-dependent chromatin remodeling factor normally involved in regulating cellular proliferation, cell cycle progression, DNA damage repair and maintenance of genomic stability (Versteege et al., 1998; Wang et al., 2007b).

In meningiomas, there is evidence of altered genomic imprinting of the fetal growth factor, IGF2 and the tumor suppressor ncRNA, *H19*, as well as chromosomal translocation involving the *MN1* gene, encoding a transcriptional co-activator, which may inactivate MN1 functions and those of adjacent miRNAs such as *miR-180* (Calin and Croce, 2007; Muller et al., 2000). The pathogenesis of meningiomas also involves biallelic inactivation of the neurofibromatosis type 2 (*NF2*) tumor suppressor gene with higher frequency in fibroblastic as compared to meningothelial subtypes, and loss of expression of the *NDRG2* tumor suppressor gene associated with hypermethylation of the *NDRG2* promoter in both high grade (WHO grade III) and lower grade (grade II) but more aggressive tumors (Hansson et al., 2007; Kalamarides et

al., 2002; Lusis et al., 2005). Neuroblastoma, an embryonic tumor originating from the neural crest with complex profiles of spontaneous tumor regression and rapid malignant acceleration, is associated with promoter hypermethylation and down regulation of expression of several potential tumor suppressor genes involved in apoptosis signaling pathways, including TRAIL, caspase 8 and the TRAIL decoy receptors, DCR1-4 (Clark, 2007; Tonini and Romani, 2003). In addition, neuroblastoma has been linked to aberrant promoter methylation and loss of heterozygosity of the *PHOX2B* gene that is associated with dysautonomia syndromes and may cause impaired differentiation of sympathetic neuroblasts from neural crest precursor cells (de Pontual et al., 2007). The *PHOX2B* epigenotype in neuroblastoma is also associated with impairments in p53/MDM2/$p14^{ARF}$ pathways that may, in part, mediate the complex molecular and cellular aberrations observed in this neural tumor type (de Pontual et al., 2007). Further, neuroblastoma is associated with considerable epigenetically mediated genomic instability including gain of chromosome 17 regions differentially associated with tumor pathogenesis and progression (Chen et al., 2006a). Candidate genes on restricted regions of chromosome 17 that may contribute to the pathogenesis and the intricate clinicopathological phenotypes associated with neuroblastoma include *WSB1*, encoding a hedgehog-inducible ubiquitin ligase subunit, PPM1D, a negative regulator of the p53 neuronal survival pathway, survivin, an inhibitor of apoptosis factor, and NME1/2, two metastasis suppressor factors (Chen et al., 2006a). Moreover, neuroblastomas are associated with pathogenic alterations in RNA editing in relation to ADAR enzymatic activity profiles and substrate preferences (Scholzova et al., 2007). In pituitary adenomas, the most common CNS tumor, there is evidence of complex deregulation of multiple miRNAs involved in modulating cell proliferation and apoptosis, often as a result of microdeletions that form predictive signatures and help to delineate histiotypes, microadenomas from macroadenomas and differential response to treatment (Nicoloso and Calin, 2008). In primary CNS lymphoma (PCNSL), miRNA deregulation occurs by a different epigenetic mechanism through chromosomal translocation resulting in fusion of the *Bcl-6* oncogene to regulatory elements of *miR-28* (Calin and Croce, 2007). Moreover, PCNSL is associated with promoter hypermethylation of up to 14 distinct tumor suppressor genes resulting in intricate profiles of epigenetic gene silencing (Chu et al., 2006). Interestingly, although PCNSLs are predominantly high-grade non-Hodgkin lymphomas of diffuse large B-cell type, the profiles of epigenetic gene deregulation exhibit only incomplete overlap with those of their systemic counterparts despite the presence of significant genomic instability in both cases, thereby identifying unique biomarkers that define epigenetically mediated gene networks selective to PCNSL pathogenesis as well as potential selective epigenetic therapeutic targets (Chu et al., 2006).

12. Epigenetics and neuroimmunological disorders

The nervous system is under continuous immune surveillance by the innate and adaptive immune systems throughout development and adult life to detect and respond to changes in cell identity and neural connectivity that underlie the pathogenesis of diverse classes of neurological disorders (Bailey et al., 2006; Hanisch et al., 2008; Hickey, 2001). Moreover, deregulation of both adaptive and acquired immune responses, impairment of crosstalk between these systems as well as alterations in the deployment of innate immune mechanisms and the development of adaptive immune repertoires can predispose to CNS autoimmunity and neurodegeneration, including diseases such as multiple sclerosis (MS) that encompass features of both interrelated pathological processes (Hauser and Oksenberg, 2006; McFarland and Martin, 2007). Dynamic gene-environmental interactions are essential for appropriate immune modulation (Hauser and Oksenberg, 2006). It is therefore not surprising that increasing evidence suggests that the development and deployment of the innate and acquired immune systems in response to a spectrum of challenges to cellular and systems level functional integrity and also in the evolution of autoimmunity are mediated by sophisticated and nuanced epigenetic mechanisms including DNA methylation, histone modifications, nucleosome and

higher-order chromatin remodeling, ncRNAs particularly miRNAs, RNA editing, DNA recoding and dynamic nuclear reorganization (Akimzhanov et al., 2007; Ballestar et al., 2006; Brooks, 2005; Gantier et al., 2007; Kleinman et al., 2008; Knudsen et al., 2007; Lodish et al., 2008; Lu et al., 2008; Parseghian and Luhrs, 2006; Sawalha, 2008; Wilson and Merkenschlager, 2006). For example, miRNAs play fundamental roles in the development of the immune system, in mediating innate and adaptive immune responses, in modulating proinflammatory and immunomodulatory cytokines, in promoting regulatory interactions between innate and adaptive immune systems and between B and T lymphocyte developmental as well as mature species (Lodish et al., 2008). Moreover, through employment of diverse post-transcriptional mechanisms miRNAs fine-tune levels of gene expression and integrated gene networks to regulate T cell sensitivity to antigens necessary to orchestrate both tolerance and immunity and to differentially modulate Toll-like receptors (TLRs) and associated innate immune responses to control the behavior of diverse infectious agents, including mediating viral tropism and co-regulation of viral and host RNAs (Hanisch et al., 2008; Lodish et al., 2008). Both DNA recoding as well as RNA editing enzymes are involved in the elaboration and diversification of the B cell antibody repertoire through the processes of somatic hypermutation, class switch recombination and gene conversion (Franklin et al., 2004; Honjo et al., 2005). The specification, maturation and deployment of specialized T cell subsets, particularly those involved in the initiation (T_H1) and propagation (T_H17) of immune-mediated CNS injury in MS, are modulated by dynamic epigenetic remodeling of gene regulatory regions and by long-distant intra- and inter-chromosomal interactions controlling the expression profiles of an interrelated spectrum of immunoeffector cytokines through the mediation of DNA methylation, histone modifications, nucleosome and chromatin remodeling and multiple classes of ncRNAs (Akimzhanov et al., 2007; Brooks, 2005; Gray and Dangond, 2006; Lodish et al., 2008; Lu et al., 2008; Mameli et al., 2007; Sawalha, 2008; Shi et al., 2007a; Steinman, 2007; Wilson and Merkenschlager, 2006). Moreover, diverse environmental toxins acting through a promiscuous environmental sensor, the ligand-activated aryl hydrocarbon receptor, differentially promote the maturation of T_H17 versus T_{reg} cells, the latter involved in immune tolerance, to exacerbate or suppress animal models of MS, respectively (Quintana et al., 2008; Veldhoen et al., 2008). Recent evidence suggests that extracellular trafficking of ncRNAs, particularly small interfering RNAs, can selectively modulate features of the innate immune system through direct interactions with TLRs (Kleinman et al., 2008). Moreover, additional components of the innate immune system, such as the complement cascade, as well as those of the adaptive immune system, including MHC class I molecules expressed on neurons, individually and collectively mediate CNS synapse elimination and developmental synapse refinement (Huh et al., 2000; Stevens et al., 2007). These seminal immune-associated neural developmental processes may be regulated by distinct epigenetic mechanisms whose deregulation could play an important role in the pathogenesis of the primary neurodegenerative features seen in MS (Kumar et al., 2007; Lodish et al., 2008; Stevens and Bradfield, 2008).

Autoimmunity has been increasingly linked to targeted deregulation of a spectrum of these diverse and interrelated epigenetic mechanisms, and use of epigenetic therapeutic agents including DNA methylation and HDAC inhibitors in humans and RNA-mediated interference in experimental animal models may help to reverse these complex pathogenic processes (Gray and Dangond, 2006; Kaiko et al., 2008; Love et al., 2008; Lu, 2006; Lu et al., 2007). Moreover, MS encompasses the interrelated features of CNS inflammation, immune-mediated demyelination and neurodegeneration, and additional etiological clues suggest that it may well represent an emerging class of epigenetic disorders because of the presence of intricate gene-environmental interactions and developmental critical periods, gender differences, phenotypic diversity, modest risk heritability, changing incidence patterns, pathological thresholds, complex profiles of deregulation of gene networks in neuropathological specimens and multiple genomic variants of interest (Brooks, 2005; Fontaine and Barcellos, 2008; Gray and Dangond, 2006; Hauser and Oksenberg, 2006; Knudsen et al., 2007; Maier et al., 2007; Mameli

et al., 2007; Mycko et al., 2004; Scarisbrick, 2008; Shi et al., 2007a). Studies of HDAC inhibitors in animal models of MS suggest that these epigenetic modifiers may be protective through multiple interrelated and independent mechanisms that promote anti-inflammatory, immmunomodulatory and neuroprotective effects by altering the gene expression profiles of key signal transduction effectors, pro-inflammatory and immunomodulatory cytokines, MHC class II proteins, T cell receptor co-stimulatory molecules, matrix remodeling agents, and neuronal differentiating and pro- and anti-apoptotic factors (Gray and Dangond, 2006). Recent association studies have identified significant MS risk alleles including those that code for cytokine receptor subunits known to be under epigenetic control and to be essential for neuronal development, thereby underscoring the potential importance of immune-mediated injury acting on an abnormal nervous system, possibly due to neural developmental alterations established in concert with environmental triggers during a critical period of heightened vulnerability in susceptible individuals (Begovich et al., 2007; Hafler et al., 2007; Mehler and Kessler, 1997). Interestingly, allelic variants of T cell receptor genes with polymorphisms in their 3' UTRs, representing molecular platforms for mediating the actions of ncRNAs including miRNAs and their post-transcriptional regulatory circuitry, display altered signaling thresholds and responsiveness to T cell receptor stimuli that may underlie increased susceptibility to autoimmune diseases such as MS (Maier et al., 2007; Sandberg et al., 2008). Interestingly, after activation of CD4+ T lymphocytes there is a proliferation-associated increase in the profiles of expression of mRNAs with shortened 3' UTRs, suggesting dynamic epigenetically-mediated reorganization of miR-associated signaling networks that orchestrate cell cycle progression (Sandberg et al., 2008). Deregulation of expression of β-arrestin-1, a multifunctional adapter protein that regulates the survival of activated CD4+ T cells through modulation of histone H4 acetylation at the bcl2 anti-apoptotic gene is associated with increased susceptibility to autoimmune diseases including MS (Shi et al., 2007a). There is also accumulating evidence that MS may be associated with excess DNA damage and impaired DNA repair resulting in loss of genomic stability and epigenetic control, with tissue-specific consequences including the development of auto-antigens and an evolving autoimmune response profile (Brooks, 2005). Regions of the X chromosome, particularly Xp22.1 that contain genes mediating the spermine synthase and polyamine synthesis pathway have the potential to become deregulated (Brooks, 2005). Further exacerbation of these molecular lesions by stress and environmental triggers including viruses may result in: altered DNA methylation and histone code modifications, inappropriate activation of parasitic repetitive elements (*Alu*, *LINE-1* and *HERV-W*), associated genomic instability and improper gene activation and deployment of diverse gene regulatory networks, altered DNA and RNA conformational profiles with impaired functioning of ncRNAs and RNA editing and DNA recoding and spermine-mediated disruption of the integrity of the blood-brain-barrier, and impaired myelin formation and neuronal excitability and cell viability (Brooks, 2005). Interestingly, HERV-W expression is increased in MS patients and may occur through deregulation of the expression and function of sense/antisense regulatory ncRNAs (Mehler and Mattick, 2007; Perron et al., 2005). Moreover, *syncytin-1*, a gene present at an MS susceptibility locus, encodes an envelope glycoprotein of a member of the W family of *HERV* repetitive elements (Mameli et al., 2007). Proinflammatory cytokines that promote MS progression activate whereas immunomodulatory cytokines that are protective against MS progression inhibit the activation of the relevant *HERV-W* promoter (Mameli et al., 2007). Furthermore, skewing of X-chromosome inactivation may be the result of an imbalance of longer ncRNAs and has been observed in female MS patients who have primary or secondary progressive but not relapsing and remitting disease profiles; this epigenetic phenomenon may be linked to loss of immunological tolerance to X-linked self-antigens (Knudsen et al., 2007; Mehler and Mattick, 2007).

13. Epigenetic mechanisms underlying cerebrovascular disorders

The predisposition to and the development of cerebrovascular diseases involve the dynamic interplay between environmental and intrinsic vascular, systemic and CNS risk factors. Increasing evidence suggests that disruption of these homeostatic and plasticity events involves an array of deregulated epigenetic processes including DNA methylation, histone modifications and chromatin remodeling, ncRNAs, RNA editing, transcriptional dysregulation, inappropriate allelic expression (LOI: “loss of imprinting”), microsatellite and genomic instability and aberrant telomere attrition (Formisano et al., 2007; Jover-Mengual et al., 2007; Kittler, 2006; Peng et al., 2006; Stenvinkel et al., 2008; Takami et al., 2007). Transient global cerebral ischemia (TGCI) following systemic hypoperfusion is associated with selective and delayed death of hippocampal CA1 pyramidal neurons through the mediation of a series of parallel epigenetic processes (Abel and Zukin, 2008; Formisano et al., 2007; Jover-Mengual et al., 2007; Peng et al., 2006). Within vulnerable neurons, there is selective down regulation of ADAR2 and defective Q/R site editing of the ionotropic glutamatergic AMPA, GluR2 receptor subunit, resulting in the expression of the death-promoting calcium permeable GluR2 isoform and associated impairment in GluR2 mRNA and protein expression, receptor assembly, membrane trafficking and synaptic targeting (Peng et al., 2006). Heterogeneity in ADAR2-mediated GluR2 Q/R site editing enhances the vulnerability of hippocampal CA1 pyramidal neurons to global ischemia-associated neurodegeneration (Peng et al., 2006). In parallel, TGCI induces the selective expression of REST within these vulnerable neurons with associated suppression of GluR2 and the CA1-selective μ-opioid receptor 1 (MOR1) in inhibitory interneurons through a series of histone modifications, including MOR1 promoter H3/4 deacetylation, H3K9 dimethylation and associated recruitment of the G9a histone methyltransferase (Formisano et al., 2007). This has been postulated to represent a failed attempt of inhibitory interneurons to dampen the excitotoxicity of CA1 pyramidal neurons by disinhibiting GABA release (Formisano et al., 2007). Ischemia-induced alterations in the histone code may be the result of early dephosphorylation and inactivation of components of the neuronal ERK1 and CREB1 signal transduction pathways that simultaneously reduce expression of the anti-apoptotic, bcl2 gene and activate expression of the pro-apoptotic, caspase 3 effector pathway (Jose and Hunter, 2007). There is also evidence that the more common type of focal stroke syndrome due to occlusion of the middle cerebral artery is associated with aberrant DNA methylation and histone H3 deacetylation, and that systemic administration of a potent HDAC inhibitor reduces the volume of the ischemic infarction whereas concurrent application of an HDAC inhibitor with a DNA demethylating agent confers neuroprotection against mild but not severe ischemic injury (Endres et al., 2000; Faraco et al., 2006). Increasing evidence suggests that intricate epigenetic processes may also operate to modulate pre-morbid vascular pathology and responses to agents that attenuate ischemic risk factors. For example, a novel deubiquinating enzyme, ubiquitin carboxyl-terminal hydrolase L1 (UCHL1), mutated in a rare inherited form of Parkinson’s disease, is normally present in vascular endothelial cells of atherosclerotic lesions of human carotid arteries and attenuates pathological vascular remodeling by inhibiting tumor necrosis factor α-induced NF-κB activation (Takami et al., 2007). Interestingly, the normal balance of transcriptional activity and associated histone acetylation and methylation that is disrupted in cerebral ischemia depends, in part, on maintenance of the balance of histone H2A and H2B mono-ubiquitylation that is mediated through the actions of UCHL1 (Setsuie and Wada, 2007). Moreover, statins have recently been shown to act through inhibition of HDAC activity and associated enhancement of histone H3 acetylation (Lin et al., 2008).

14. Epigenetics and neuropsychiatric diseases

A broad range of epigenetic alterations has recently been identified in diverse neuropsychiatric conditions (Abdolmaleky et al., 2005; Canli et al., 2006; Colvis et al., 2005; Kan et al., 2004;

Mill and Petronis, 2007; Mill et al., 2008; Perkins et al., 2005; Renthal et al., 2007; Tamura et al., 2007; Tsankova et al., 2007). Down regulation of transcript and protein levels of reelin, an extracellular matrix protein important in neural development and synaptic plasticity, is observed in inhibitory interneurons of the prefrontal cortex, hippocampus and cerebellum in bipolar illness and in schizophrenia associated with enhanced promoter methylation and increased levels of the maintenance DNA methyltransferase, DNMT1 (Levenson et al., 2008; Tamura et al., 2007). The exact nature of the psychiatric disorder appears to be determined by the type of derangement in DNMT1 expression (Levenson et al., 2008; Tamura et al., 2007). Recent studies have indicated the presence of genome-wide psychosis-associated methylation abnormalities in the frontal cortex affecting numerous genomic loci involved in glutamatergic and GABAergic neurotransmission, brain development, mitochondrial function and stress responses (Mill et al., 2008). Mutations in MeCP2 may also lead to schizophrenia through related epigenetic mechanisms (Burmistrova et al., 2007; Cohen et al., 2002; Shibayama et al., 2004). Treatment with valproate, a mood stabilizer and HDAC inhibitor, results in enhanced reelin expression, reduced reelin promoter methylation and attenuation of schizophrenia-associated behaviors in methionine-induced epigenetic model systems (Dong et al., 2005). The observation of similar effects using other HDAC inhibitor compounds suggests that histone hypoacetylation may regulate DNMT1 accessibility to promoter regions or enhance putative DNA demethylase activity (Abel and Zukin, 2008; Levenson et al., 2008; Tamura et al., 2007; Tsankova et al., 2007). These findings suggest that hypermethylation, mediated by DNMT1 and additional chromatin-related remodeling complexes, down regulate multiple genes in GABAergic inhibitory neurons and cause dysfunction of GABA-mediated neuronal circuitry resulting in alterations in neuronal oscillatory synchrony and associated neural network dysfunction in schizophrenia (Blatow et al., 2003; Costa et al., 2007; Ruzicka et al., 2007; Uhlhaas et al., 2008). Both DNMT1 and HDAC inhibitors have been employed to treat schizophrenia, and the combined use of valproate and anti-psychotic agents are known to accelerate the anti-psychotic effects (Tremolizzo et al., 2005). Interestingly, reductions in *GAD1* GABAergic gene expression and promoter histone H3K4 trimethylation, normally associated with gene activation, occur predominantly in females with schizophrenia in association with a risk haplotype at the 5' regulatory region of the *GAD1* gene (Huang et al., 2007a). The presence of heterozygosity for mixed-lineage leukemia 1 (Mll1), a H3K4 methyltransferase expressed in cortical GABAergic neurons, results in reduced H3K4 methylation at GABAergic gene promoters, whereas *GAD1* H3K4 trimethylation and Mll1 gene occupancy is observed in the cerebral cortex of mice treated with clozapine, an atypical antipsychotic (Huang et al., 2007a). Reversal of the normal developmental program for prefrontal GABAergic neuronal chromatin remodeling in schizophrenia and the reestablishment of this molecular hierarchy by antipsychotic treatment establishes important mechanistic links between epigenetic and developmental dysregulation of GABAergic neuronal circuitry, alterations of neuronal oscillatory synchrony and neural network integrity and cognitive impairments in the pathogenesis of schizophrenia (Costa et al., 2007; Uhlhaas et al., 2008).

Additional epigenetic mechanisms have also been implicated in the pathogenesis of schizophrenia. Schizophrenia disease genes may encompass abnormal transcriptional units that disrupt the expression or function of multiple classes of ncRNAs including miRNA biogenesis, alter post-transcriptional gene processing, promote gene conversion and impair RNA tertiary conformation (Mehler and Mattick, 2007; Perkins et al., 2005; St Laurent and Wahlestedt, 2007); (Stark et al., 2008). The effects of these complex changes in RNA regulatory circuitry in schizophrenia include developmental deregulation in the timing, location and expression levels of genes within integrated gene networks, associated changes in relevant metabolic pathways and responsiveness of multiple neurotransmitters, neuromodulators and their associated receptor subtypes, alterations of neural network and synaptic connectivity and impairment in environmental influences on gene expression, function and associated epigenetic

modulation (Mehler and Mattick, 2007; Perkins et al., 2005; St Laurent and Wahlestedt, 2007). There is increasing interest in the Disrupted-in-Schizophrenia-1 (*DISC1*) gene product that represents a hub protein mediating a diverse spectrum of functions involved in neural development, adult neurogenesis, synaptic function and plasticity, epigenetic regulatory pathways, neural network integration and higher order cognitive and behavioral traits (Chubb et al., 2008; Duan et al., 2007; Leliveld et al., 2008). DISC1 is involved in the overall functions of the *DISC* locus, a genetic hotspot for susceptibility to schizophrenia, schizoaffective disorder, bipolar illness and major depressive disorders as well as the elaboration of complex cognitive traits (Chubb et al., 2008; Leliveld et al., 2008). Within the *DISC* locus is the natural antisense transcript, *DISC2*, the ncRNA that partially overlaps *DISC1* and may regulate its expression and multifunctional activities through intricate epigenetic regulatory mechanisms (Chubb et al., 2008). Interestingly, epigenetic-mediated changes to a broad spectrum of neurotransmitter and neuromodulatory molecules confer susceptibility to schizophrenia and related disorders (Abdolmaleky et al., 2005). Recently, it was shown that molecular switches integrating serotonin (5HT[2A]R) and glutamate (mGluR2) receptor signaling pathways that regulate neocortical sensory gating and are the targets of atypical neuroleptic agents are differentially altered in major psychosis, including post-mortem brains of untreated schizophrenics (Gonzalez-Maeso et al., 2008; Snyder, 2008). Additional studies suggest that complex alterations in parasitic repetitive elements, particularly primate-specific *Alu* sequences, result in many of these genome-wide impairments that may underlie the major psychoses (Kan et al., 2004). These overall observations suggest that schizophrenia and related disorders may be orchestrated by deregulation of a spectrum of epigenetic mechanisms resulting in alterations in large numbers of integrated gene networks involved in the development and elaboration of higher-order cognitive and behavioral functions.

Bipolar disease exhibits overlaps in genetic susceptibility with schizophrenia and associated disorders and is characterized by profound changes in circadian rhythms and by neural circuit instability and enhanced sensitivity to minor environmental and homeostatic cues indicative of a chaotic system (Berns and Nemeroff, 2003; Newberg et al., 2008; Schloesser et al., 2008). Risk genes for bipolar disease include a host of receptor genes for serotonin, dopamine and GABA neurotransmission, glutamate signaling pathways, circadian rhythms and direct targets of front-line therapeutic agents, namely lithium and valproate (Berns and Nemeroff, 2003; Newberg et al., 2008; Schloesser et al., 2008). These therapeutic agents are synergistic in regulating the development and deployment of signaling pathways mediating state transitions associated with dynamic genome-wide alterations in transcriptional regulation, histone code modifications and chromatin remodeling, neural development, synaptic function and plasticity, neuroprotection and circadian rhythms (Leng et al., 2008; Newberg et al., 2008; Schloesser et al., 2008). Interestingly, state-dependent switching in bipolar disease may be mediated, in part, by environmental-sensitive epigenetically mediated imbalances in norepinephrine and serotonin within the locus coeruleus, a master regulator of higher-order cognitive and behavioral functions through massive noradrenergic innervation of the neocortex, hippocampus, thalamus, hypothalamus and the cerebellum (Berridge and Waterhouse, 2003; Seager et al., 2005; Wiste et al., 2008). Furthermore, the regulation of circadian physiology involves the interplay of interrelated transcriptional and translational autoregulatory feedback loops contained within the suprachiasmatic nucleus of the hypothalamus and entrained by environmental cues (Belden et al., 2006; Nakahata et al., 2007). Peripheral tissues contain a multitude of complementary circadian clocks regulated by the suprachiasmatic nucleus through dynamic changes in chromatin transitions (Belden et al., 2006; Nakahata et al., 2007). The CLOCK-BMAL1 complex activates clock-associated genes including cryptochromes (*CRYs*) whose gene products act as repressors by direct CLOCK-BMAL1 interactions (Belden et al., 2006; Hirayama et al., 2007; Nakahata et al., 2007). This negative feedback loop is facilitated by CLOCK H3K14 acetyltransferase activity that creates a transcriptionally permissive state for the activation of *PER1, 2* and *CRY1, 2* genes that

promote feedback inhibition of CLOCK-BMAL1 expression through the mediation of HDAC1/2 activities (Belden et al., 2006). Circadian control of chromatin remodeling by CLOCK involves the dynamic assembly of multimeric protein regulatory complexes through the influence of metabolic, nutritional, additional environmental and homeostatic signals that modulate the CLOCK positive feedback limb via intracellular signaling pathways that promote complementary histone code modifications (Belden et al., 2006; Hirayama et al., 2007; Nakahata et al., 2007); (Shimba et al., 2005; Yin et al., 2007). BMAL1, in turn, coordinates and integrates central and peripheral circadian-associated signal transduction pathways through activation of additional tissue-specific factors that orchestrate parallel circadian pathways through complementary positive and negative factor feedback loops regulated by similar histone modifications and chromatin remodeling (Shimba et al., 2005; Yin et al., 2007). Moreover, the MAPK/ERK signaling pathway appears to link circadian neuronal activity rhythms to clock gene expression, with activity-dependent activation of MAPK signaling likely promoting circadian gene expression through histone code modifications (Akashi et al., 2008). Bipolar disease risk genes include these global regulators of circadian transitions through signaling pathways that are modulated by lithium and valproate (Leng et al., 2008; Newberg et al., 2008; Schloesser et al., 2008).

The effects of life stress on depression are moderated by repeat length variations in the transcription control region of the serotonin transporter gene, with carriers of the short variant associated with reduced serotonin uptake and enhanced vulnerability to depressive symptomatology and suicidal ideation (Canli et al., 2006). This epigenotype modulates amgdala-prefrontal cortex functional connectivity, thereby suggesting continuing roles in cognitive processing beyond those mediating affective cues (Canli et al., 2006). Chronic electroconvulsive therapy (ECT) is associated with chromatin remodeling including enhanced histone H3 acetylation at selective gene promoters including brain-derived neurotrophic factor (BDNF) with corresponding increased BDNF transcript and protein expression (Tsankova et al., 2007; Tsankova et al., 2004). These observations stand in contrast to the epigenetic modifications mediated by acute ECT that includes histone H4 rather than H3 acetylation (Tsankova et al., 2007; Tsankova et al., 2004). Chronic social defeat stress results in sustained down regulation of expression of two *BDNF* splice variants associated with repressive histone modifications (H3K27 dimethylation) at the *BDNF* promoter (Berton et al., 2006; Tsankova et al., 2007; Tsankova et al., 2006). Interestingly, chronic imipramine antidepressant treatment reverses the BDNF gene repression by promoting two activating histone modifications (H3 acetylation, H3K4 methylation) rather than by modifying the repressive histone signature, thereby demonstrating the complex histone crosstalk occurring in response to targeted therapeutic strategies (Berton et al., 2006; Tsankova et al., 2007; Tsankova et al., 2006). By contrast, over expression of HDAC5 in the hippocampus of experimental animals prevents the imipramine-mediated restoration of BDNF expression levels and the associated behavioral improvements, whereas systemic administration of a non-specific HDAC inhibitor restores the antidepressant effects (Schroeder et al., 2007; Tsankova et al., 2007; Tsankova et al., 2006). It is of note that H3K4 demethylation is normally catalyzed by BHC110/LSD1 that is homologous to monoamine oxidases (MAOs), and application of an MAO inhibitor results in global H3K4 methylation and transcriptional derepression (Lee et al., 2006; Tsankova et al., 2007). These observations suggest that antidepressant therapeutic efficacy involves the complex interplay of several seminal histone modifications at targeted gene loci (Kouzarides, 2007). Offspring of high-nurturing mothers are less behaviorally anxious with attenuated glucocorticoid responses to stress compared to offspring of low-nurturing mothers and exhibit evidence of over expression of the glucocorticoid receptor gene in the prefrontal cortex and the hippocampus associated with a splice variant (*GRI7*) in the brain-specific promoter containing the *NGFI-A* binding site with enhanced NGFI-A expression (Champagne et al., 2003; Meaney and Szyf, 2005b; Tsankova et al., 2007). Further, in offspring of low-nurturing mothers increased DNA methylation is already present during the first week of life at the *NGFI-*

A-associated *GRI7* site and persists in the absence of application of a HDAC inhibitor that promotes DNA cytosine demethylation and increased H3 acetylation with enhanced NGFI-A binding to the *GRI7* promoter site (Meaney and Szyf, 2005a; b; Weaver et al., 2004). Cross-fostering also reverses the deleterious effects of improper maternal nurturing and the epigenetic therapeutic effects suggest that significant crosstalk between the processes of DNA methylation and histone code modifications are of central importance in mediating the maternal influences on stress adaptations as well as the therapeutic responses to early maladaptive influences at the molecular level (Szyf et al., 2007; Weaver et al., 2004). Additional evidence suggests that major depressive disorder is mediated, in large part, by a spectrum of epigenetic processes, exemplified by the presence of discordance between monozygotic twins, strong environmental influences and pronounced gene-environmental interactions, high female prevalence (skewed X-chromosome inactivation), parent-of-origin effects (impaired genomic imprinting) and the presence of epialleles and epi-haplotypes (see below), including characteristic DNA methylation profiles associated with specific alleles in genes linked to mood disorders (Mill and Petronis, 2007).

Recent studies suggest that HDAC5 is a fundamental molecular switch mediating drug addiction, depression and stress adaptations (Renthal et al., 2007). Chronic but not acute cocaine exposure and stress results in reduced HDAC5 function in the nucleus accumbens, a central component of brain reward pathways, in association with increased histone acetylation and transcription of HDAC5 target genes (Renthal et al., 2007). In chronic cocaine addiction, drug exposure results in rapid and transient HDAC5 phosphorylation and nuclear export associated with acute gene activation and histone acetylation that is rapidly reversed within 24 hours by HDAC5 nuclear redeployment and limitation of the expression of cocaine-induced genes (Renthal et al., 2007). Loss of HDAC5 promotes hypersensitive responses to stress and to chronic but not acute cocaine exposure (Renthal et al., 2007). Interestingly, chronic but not acute social defeat stress causes reductions in HDAC5 functions in the nucleus accumbens by a mechanism distinct from that seen with cocaine addiction (Renthal et al., 2007). Chronic administration of imipramine selectively increases HDAC5 expression in the nucleus accumbens but decreases its expression in the hippocampus and reduces stress-associated maladaptive responses (Renthal et al., 2007). Additional studies further reveal that distinct epigenetic modifications are associated with acute versus chronic drug addiction (Colvis et al., 2005; Tsankova et al., 2007). Acute cocaine administration increases striatal early-immediate gene expression in concert with CBP-mediated H4 acetylation at activated gene promoters and MAPK/ERK1/MSK1-mediated H3 phosphoacetylation only at the *c-Fos* promoter (Brami-Cherrier et al., 2005; Kumar et al., 2005; Levine et al., 2005; Taniura et al., 2007). By contrast, chronic cocaine use promotes H3 rather than H4 acetylation at the *FosB* promoter associated with increased FosB expression, and also enhances H3 acetylation at the promoters of distinct effector genes involved in the maintenance of the chronic state of addiction (Kumar et al., 2005; Tsankova et al., 2007). Genome-wide analysis confirms that chronic cocaine addiction is associated with deregulated acetylation of several hundred genes (Kumar et al., 2005; Tsankova et al., 2007). Chronic cocaine addiction is also associated with increased MeCP2 and MBD1 expression in the adult brain (Cassel et al., 2006). Chronic alcoholism is further linked to a diverse array of chromatin remodeling events that involve changes in both DNA methylation as well as histone acetylation (Bonsch et al., 2005; Mahadev and Vemuri, 1998; Tsankova et al., 2007). These observations suggest that the differential modulation of DNA methylation and histone acetylation at selected target genes within specific brain reward and memory circuits is a sensitive mediator of specific forms of stimulus saliency, and that disruption of these interrelated epigenetic modifications promotes the transition from acute adaptive responses to chronic neuropsychiatric disease states (Colvis et al., 2005; Maurice et al., 2008; Renthal et al., 2007; Tsankova et al., 2007).

15. Environmental epigenomics: gene-environmental interactions, neural critical periods across the lifespan and multigenerational inheritance

The epigenome exhibits unusual degrees of both plasticity as well as heritability, especially within the mammalian brain, and may represent the long sought after molecular interface mediating dynamic gene-environmental interactions throughout the life cycle (Feinberg, 2007; Jirtle and Skinner, 2007; Santos-Reboucas and Pimentel, 2007; van Vliet et al., 2007). In fact, components of the epigenome are particularly susceptible to disruption during gestation, the neonatal period, puberty and old age (Feinberg, 2007; Jirtle and Skinner, 2007). Environmental influences can impact the epigenetic hierarchy at all levels, including DNA methylation, histone modifications, nucleosome and higher-order chromatin remodeling, ncRNAs, RNA editing and DNA recoding, and are associated with effects on genomic architecture, nuclear reorganization and intracellular transport of diverse RNA species and RBPs (Jirtle and Skinner, 2007; Mattick and Mehler, 2008; Mehler and Mattick, 2007; Santos-Reboucas and Pimentel, 2007; van Vliet et al., 2007). These dynamic processes translate into short- and long-term phenotypic effects based on the timing and nature of the environmental influences, the degrees of cellular responsiveness and the nature and durability of the epigenetic modifications at individual gene loci and through genome-wide effects (Burdge et al., 2007; Feinberg, 2007; Jirtle and Skinner, 2007; Santos-Reboucas and Pimentel, 2007; van Vliet et al., 2007). Metastable epialleles are alleles that exhibit variable expression due to epigenetic influences early in development and are particularly susceptible to environmental influences that enhance susceptibility to late-onset diseases (Dolinoy et al., 2007; Jirtle and Skinner, 2007). Susceptible targets for epigenetically mediated environmental influences include parasitic repetitive elements, cis-acting regulatory regions of imprinted genes, promoter elements of common (“house-keeping”) genes and associated CpG islands (Burdge et al., 2007; Dolinoy et al., 2007; Feinberg, 2007; Jirtle and Skinner, 2007; Santos-Reboucas and Pimentel, 2007; van Vliet et al., 2007). Extensive epigenetic reprogramming occurs during gametogenesis and in pre-implantation embryos, with less extensive modifications occurring at fertilization (Anway et al., 2008; Groth et al., 2007; Hajkova et al., 2008; Sasaki and Matsui, 2008). These processes are essential to clear acquired epigenetic marks as a result of genetic factors, environmental exposures and pathological conditions including disease states (Anway et al., 2008; Feinberg, 2007; Groth et al., 2007; Hajkova et al., 2008; Jirtle and Skinner, 2007; Sasaki and Matsui, 2008). Certain genomic sequences are partially protected from developmental epigenetic reprogramming such as imprinted genes and loci, heterochromatic regions near centromeres and more recently acquired and active repetitive elements that may participate in the dynamic sculpting of neurodevelopmental processes such as neural connectivity whose deregulation is involved in the pathogenesis of neurological disorders with complex cognitive phenotypes (Hajkova et al., 2008; Jirtle and Skinner, 2007; Kishino, 2006; Lane et al., 2003; Mehler and Mattick, 2007; Sasaki and Matsui, 2008). Imprinted genes are overly represented at susceptibility loci for complex neuropsychiatric diseases and are particularly problematic in terms of heritability and environmental influences (Dolinoy et al., 2007; Kishino, 2006; Mehler and Mattick, 2007; Sasaki and Matsui, 2008; Schanen, 2006). Imprinted genes provide no buffer against the pernicious effects of recessive mutations, increase susceptibility to developmental aberrations and disease and are deregulated by non-genotoxic or by specific combinations of normally benign environmental agents that can cause LOH or LOI (Dolinoy et al., 2007). Classical epigenetic processes including DNA methylation, histone modifications, nucleosome packing and higher-order chromatin folding, and associated attachments to nuclear subdomains and matrix components can enhance these and other potentially heritable changes (Ahmed and Brickner, 2007; Akhtar and Gasser, 2007; Burdge et al., 2007; Dolinoy et al., 2007; Feinberg, 2007; Santos-Reboucas and Pimentel, 2007; van Vliet et al., 2007). Recent studies also suggest that DNA recoding in somatic cells, including post-mitotic neurons, and intercellular and germline transmission of somatic mRNAs and

ncRNAs derived from these and from other genomic sequences may also represent novel genomic loci resistant to epigenetic reprogramming because of the absence of classical “epigenetic signatures” (Dinger et al., 2008; Mattick and Mehler, 2008).

Environmental epigenetics has radically changed the definition of heritability to include environmentally mediated changes to the epigenome that are retained following mitosis, meiosis, single generation inheritance as well as multigenerational transmission despite the absence of direct inciting environmental events (Burdge et al., 2007; Dolinoy et al., 2007; Feinberg, 2007; Groth et al., 2007; Jirtle and Skinner, 2007; Santos-Reboucas and Pimentel, 2007; van Vliet et al., 2007). Our increasing ability to decipher components of the epigenome within individual cells, tissues and particularly within neural stem and developmental species, neural networks and their dynamic evolution, in concert with both environmental as well as homeostatic influences, will soon allow us to identify novel, fine-grained, subtle and complex “neurotoxic” environmental factors and features that have not been amenable to interrogation by classical genetic epidemiological studies (Feinberg, 2007; Jirtle and Skinner, 2007; Mehler and Mattick, 2007; Santos-Reboucas and Pimentel, 2007; Sathyan et al., 2007; van Vliet et al., 2007). Environmental epigenomic initiatives will also promote the development of advanced epigenetic detection systems to identify more sensitive biomarkers, signatures of pre-clinical phases of neurological diseases, disease progression and responses to therapeutic interventions to allow the development of new generations of pharmacoepigenomic agents to promote targeted epigenetic reprogramming (Feinberg, 2007; Jirtle and Skinner, 2007; Santos-Reboucas and Pimentel, 2007; van Vliet et al., 2007).

16. Pharmacoepigenomics: novel therapeutic strategies, epigenetic reprogramming and future directions

The central nervous system is unique in its requirement for appropriate degrees of cellular differentiation, organizational integrity and neural network connectivity and activity-dependent synaptic plasticity and emergent properties that define environmental receptivity, hierarchical multimodal sensory processing, integration and intentionality of behavioral outputs (Abrous et al., 2005; Mehler, 2002a; b; Mehler and Mattick, 2007). These operational features of the brain likely reflect apparent as well as hidden layers of informational signals that may be difficult to identify and to recapitulate following significant disease associated perturbations or may encompass self-organizing principles that respond to less elaborate but well defined molecular “hub” molecules or master regulators (Alcamo et al., 2008; Han et al., 2008; Ptak and Petronis, 2008; St Laurent and Wahlestedt, 2007). Recent studies have shown that complex disease traits may be related to highly interconnected gene networks and core network modules that are deregulated by susceptibility loci, and that the clinical manifestations of specific disease states may therefore represent emergent properties of these networks (Chen et al., 2008b; Emilsson et al., 2008). Moreover, additional investigations suggest that “rewiring” of discrete portions of the architecture of gene networks deregulated in specific neurological diseases may allow restoration of function or even improvements of function reflective of whole network operations rather than regional feedforward or feedback regulation, thus illustrating the principles of system robustness, evolvability and emergent properties (Isalan et al., 2008; Mehler and Mattick, 2007; Muotri and Gage, 2006). These network properties are reminiscent of the features of epigenome biology and the advent of RNA regulatory circuitry and post-transcriptional processing for promoting innovations in human brain form, function and adaptability (Amaral et al., 2008; Mattick and Mehler, 2008; Mehler and Mattick, 2007; St Laurent and Wahlestedt, 2007). In the final analysis, the challenge of epigenetic therapies lies in the nature of the injury or disease state (unifocal, multifocal, cell types and connections involved, acuteness or chronicity of the pathological state), the stage of the life-cycle (development, adult, senescence), the molecular lesions (component[s] of the epigenome affected, consequences for single allele or gene expression/function, integrated

gene networks, genomic architecture/output, intracellular transport, nuclear organization), the unique epigenetic profiles contained within each neural cell as well as the potential for stem cell-mediated regenerative responses and dynamic tissue remodeling (Chan et al., 2007; Cho et al., 2007; Fischer et al., 2007; Lesnick et al., 2007; Mattick and Mehler, 2008; Mehler and Mattick, 2007; St Laurent and Wahlestedt, 2007). Moreover, recent experimental reports suggest that evolving epigenomic therapies will soon allow us to "recover" seemingly lost memories and cognitive functions and to both "rejuvenate" as well as actively regenerate dysfunctional and dying neurons and impaired neural network connections in complex neurological disorders such as neurodegenerative diseases (Chan et al., 2007; Chang et al., 2008; Cho et al., 2007; Efroni et al., 2008; Fischer et al., 2007; Mattick and Mehler, 2008; Mehler and Mattick, 2007; Muotri and Gage, 2006).

There are currently three classes of epigenetic therapies that have been utilized in both animal models of disease as well as in human clinical trials: DNA methylation inhibitors, HDAC inhibitors and RNA-based approaches (Bhindi et al., 2007; Ptak and Petronis, 2008; Wood et al., 2007). DNA methylation inhibitors exist as nucleoside and non-nucleoside analogues whose aim is to reactivate pathologically silenced genes (Mund et al., 2006; Ptak and Petronis, 2008; Sigalotti et al., 2007). Nucleoside analogues act either by demethylation or by deletion of DNMTs, whereas non-nucleoside analogues act by binding to the active sites of DNMTs or preventing their expression without direct DNA incorporation, with the latter class exhibiting less cytotoxicity (Mund et al., 2006; Ptak and Petronis, 2008; Sigalotti et al., 2007). Histone deacetylase inhibitors include a broad spectrum of functional classes each containing distinct biochemical modifications: short-chain fatty acids (SCFA), hydroxamic acids (HXA), benzamides (BZM) and cyclic tetrapeptides (CTP). SCFAs are limited by lack of potency, low specificity and bioavailability; HXAs exhibit higher potency, less toxicity, a broader spectrum of actions, effects on DNA demethylation and synergy with other therapeutic agents; BZMs display higher bioavailability including efficacy by the oral route and synergy with multiple other therapeutic agents; CTPs directly inhibit the HDAC catalytic pocket, and hybrids containing BZMs called cyclic hydroxamic acid-containing peptides (CHAPs) reversibly inhibit HDACs at low nanomolar concentrations, and by changing methylene chain length can create numerous independent molecular species with unique functional properties (Ptak and Petronis, 2008).

Interestingly, multiple classes of psychotropic drugs, including mood stabilizers, tricyclic antidepressants and selective serotonin reuptake inhibitors act by modifying HDAC activity and the actions of DNA methylation-associated enzymes (Ptak and Petronis, 2008). Interestingly, alleviation of the silencing of the *FMR1* gene due to microsatellite expansion in the 5' UTR in fragile X syndrome requires the use of a class III-selective HDAC, SIRT1 that promotes histone acetylation at multiple sites on different histone proteins without altering DNA methylation profiles that are normally linked to the therapeutic effects of less selective HDAC inhibitors and would require combined use of a DNA methylation inhibitor only active in dividing cells (Biacsi et al., 2008). These observations suggest that SIRT1 may be particularly efficacious for gene reactivation in post-mitotic neurons with epigenetic lesions resulting in specific types of neurological disorders (Kim et al., 2007a). The use of transcription factors such as engineered zinc finger proteins which target individual gene promoters can greatly increase the specificity of both DNA methylation and HDAC inhibitors and thereby avoid adverse effects associated with a lack of specificity of these reagents (Ptak and Petronis, 2008). These epigenetic agents can be utilized in concert and have the potential to target not only a spectrum of protein-coding genes but also multiple classes of ncRNAs (Verschure et al., 2006). Additional classes of DNA methylation and histone-modifying enzymes are increasingly being targeted using small molecule libraries, high-resolution structural analysis, virtual screening technologies, ligand motif-based libraries and fragment-based pharmaceutical design techniques (Ptak and Petronis, 2008).

Several additional approaches targeting RNA species using short oligonucleotides acting on diverse gene transcripts under endogenous regulation have the potential to begin to address the complex underlying disease mechanisms particularly in neurodevelopmental, neuromuscular and neurodegenerative diseases (Bhindi et al., 2007; Wood et al., 2007). The strategy of using of antisense oligonucleotides with newer biochemical modifications to enhance stability, specificity and efficacy is being applied to diseases caused by epigenetic alterations of pre-mRNA splicing (Wood et al., 2007). RNA trans-splicing to form a composite of two separately transcribed mRNAs using spliceosome-mediated trans-splicing (SMaRT) or ribozyme-associated trans-splicing is being applied to epigenetic diseases caused by aberrant isoform switching, deregulation of specific enzymatic components of the epigenome or even to promote RNA repair particularly in situations in which conformational changes subtly alter substrate/target specificities for the actions of epigenetic enzymes, ncRNAs or diverse associated DNA: RNA: protein interactions (Wood et al., 2007). RNA interference (RNAi) using double-stranded small interfering RNAs (siRNAs) is being applied to numerous pathogenic lesions including promoting the silencing of selective mRNA isoforms and mutant alleles deregulated by a spectrum of epigenetic aberrations (Bhindi et al., 2007; Wood et al., 2007). While these therapeutic approaches represent major biological advances, they are still limited by issues of inefficient tissue and cell site delivery, non-specific biological effects, lack of appropriate regulatory elements for precise spatial and temporal resolution of expression and inappropriate induction of inflammatory and immunological reactions (Wood et al., 2007). Additional modifications and associated molecular variants including LNAs, decoys (short, double-stranded DNA molecules containing binding elements for a range of protein targets that competitively inhibit promoter binding) and aptamers (synthetic oligonucleotide ligands derived by selection from a combinatorial library of nucleic acid sequences that bind target proteins with high affinity and specificity) have the potential and are increasing being applied to combat complex and aberrant arrays of epigenetic targets such as multiple ncRNAs, including miRNAs, RNA/DNA editing enzymes and nucleosome and chromatin remodeling complexes (Akhtar and Benter, 2007; Bhindi et al., 2007; Elmen et al., 2008; Sigalotti et al., 2007).

While these epigenetic approaches hold great promise for achieving unprecedented therapeutic successes, emerging concepts concerning the complexity and versatility of the epigenome are beginning to suggest new directions for identifying and targeting of seminal molecular master regulators and genome-wide and complementary cellular processes. The massive epigenetic reprogramming that occurs during gametogenesis, fertilization and in the pre-implantation embryo has emphasized the importance of gradations of epigenetic modifications, unique roles of histone variants, linker proteins and chaperones and the ability of epigenetic changes initiated in gametes to influence gene expression and functional integration at sensitive epialleles in the offspring (Bronner et al., 2007; Chong et al., 2007; Ciliberti et al., 2007; Godde and Ura, 2008; Ng and Gurdon, 2008; Raisner and Madhani, 2006; Sandovici et al., 2005; Sasaki and Matsui, 2008). Our evolving understanding of the nature of regional genomic organization and complex transcriptional units has uncovered novel mechanisms of nucleosome modulation to allow uncoupling of the threshold for gene activation from its dynamic range of expression, multilayered and interrelated epigenetic memory systems, the hierarchy, overlap and context-selectivity of epigenetic processes and their dynamic modulation by mechanisms regulating genomic architecture and other fundamental cellular processes such as DNA repair and senescence responses (Blasco, 2007; Bronner et al., 2007; Lam et al., 2008; Narita et al., 2006; Schneider and Grosschedl, 2007). Emerging insights into genome-wide organization, regulation and communications have revealed intricate mechanisms underlying higher-order chromatin states governing regulatory effects on remote promoters and enhancers, allelic communications, dosage effects and epigenetic marking, and regulators and dynamic switching of somatic as well as totipotency (germline) developmental, maturational and maintenance programs (Bejerano et al., 2006; Grummt, 2007; Kapranov et

al., 2007b; Kleinjan and van Heyningen, 2005; Mikkelsen et al., 2008; Misteli, 2007). Recent studies have suggested that stem cell reprogramming may be greatly facilitated by RNA inhibition of lineage-specifying transcription factors and by concurrent application of DNA methyltransferase inhibitors (Mikkelsen et al., 2008). These scientific advances have also identified cascades of epigenetic and associated regulatory factors involved in coordinated environmentally mediated inter- and intra-chromosomal interactions, dramatic reorganization of nuclear territories and the transient creation of hubs of transcriptional supercomplexes to promote integrated genome-wide expression profiles, functional outcomes and potentially flexible and evolving gene and neural network programs (Nunez et al., 2008). For example, members of the SATB family of genomic organizers mediate these flexible genome-wide regulatory functions through direct DNA binding and interactions with chromatin remodeling molecules (Han et al., 2008). Moreover, SATB2 imparts cell identity and functional connectivity to neocortical neurons, is regulated by conserved non-coding elements derived from transposable elements in the mammalian genome that also modulate forebrain patterning centers, and is derived from a complex bidirectional locus containing a ncRNA that exhibits congruent neocortical expression (Alcamo et al., 2008; Gyorgy et al., 2008; Mercer et al., 2008). These overall observations suggest that therapeutic targeting of master epigenetic regulators such as SATB2 may have profound genomic regulatory effects through actions on multiple complementary epigenetic regulatory mechanisms relevant to molecular reprogramming of neural cell identity and remodeling of neural network connectivity (Alcamo et al., 2008; Gyorgy et al., 2008). Finally, increasing recognition of the computational power, flexibility and intra-and extra-cellular transport routes of diverse RNA species has clarified the seminal importance of RNA regulatory networks for environmentally mediated and activity-dependent nervous system processes, in the diversity of alternative splicing activities and processing events, and in RNA-directed DNA rearrangements, methylation events, site editing and DNA/RNA stereoisomer formation and function (Amaral et al., 2008; Dinger et al., 2008; Matthews et al., 2007; Mattick and Mehler, 2008; Nowacki et al., 2008; Placido et al., 2007; St Laurent and Wahlestedt, 2007; Wang and Cooper, 2007; Wang et al., 2008c; Wong et al., 2007). Newer genome-wide high throughput technologies, when combined with advances in imaging modalities such as in vivo optical imaging and nanotechnology, will allow us to examine both local as well as global alterations of the epigenome and associated changes to genomic architecture, nuclear organization, cellular microdomains and activated neural network to greatly enhance disease risk stratification and to identify disease-associated epimutations that represent more robust, selective and sophisticated biomarkers and therapeutic targets than current translational approaches that are limited by our current abilities of defining pathogenic alterations of specific epigenetic enzymes or associated molecular species (Barski et al., 2007; Catez et al., 2006; Darzacq et al., 2007; Feinberg, 2007; Mikkelsen et al., 2007; Rauch et al., 2008; Tan et al., 2007).

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Abbreviations

ADARs

adenosine deaminases acting on RNAs

ADATs
adenosine deaminases acting on tRNAs

AID
activation-induced cytidine deaminase

ALS
amyotrophic lateral sclerosis

AOA
ataxia with oculomotor apraxia

APOBECs
apolipoprotein B editing catalytic subunit family

ASDs
autism spectrum disorders

BACE1
β-amyloid precursor protein-cleaving enzyme 1

BCOR
Bcl6- interacting corepressor

BDNF
brain-derived neurotrophic factor

BMPR
bone morphogenetic protein receptor

BZM
benzamides

CBP
CREB binding protein

C/EBP
CCAAT/enhancer binding protein

CHAPs
cyclic hydroxamic acid-containing peptides

CoREST
corepressor for REST

CpG
cytosine dinucleotide

CREB
cAMP response element binding protein

CRYs
cryptochromes

CTP
cyclic tetrapeptides

DISC1
disrupted in schizophrenia 1

DMR
differentially methylated region

dsNRSE
double-stranded neuron-restrictive silencing element

E
glutamate

ECT
electroconvulsive therapy

endo-siRNAS
endogenous small interfering RNAs

ENOR
long expressed non-coding region

ERK
extracellular signal-regulated kinase

FMRP
fragile X mental retardation protein

FRAXE
fragile X mental retardation syndrome with FMR2 repeat expansion

FXS
fragile X syndrome

FXTAS
fragile X tremor and ataxia syndrome

GABA
gamma-amino butyric acid

GABAR
GABA receptor

GGR
global genomic repair

HARs
human accelerated regions

HDAC
histone deacetylase

HERV
human endogenous retrovirus

HP1
heterochromatin protein 1

HXA
hydroxamic acids

HYP
huntingtin-interacting protein

ICCs
imprinting control regions

ICF
immunodeficiency, centromere instability and facial anomalies syndrome

K
lysine

LCRs
locus control regions

LINE
long interspersed nuclear elements

LNA
locked-nucleic acid

LOH
loss of heterozygosity

LOI
loss of imprinting

LTP
long-term potentiation

MAOs
monoamine oxidases

MAPK
mitogen-activated protein kinase

MBDs
methyl CpG binding proteins

miRNAs
microRNAs

Mll1
mixed-lineage leukemia 1

MOR1
μ-opioid receptor 1

MS
multiple sclerosis

MSK
mitogen- and stress-activated protein kinase

ncRNAs
non-coding RNAs

NF
neurofibromatosis

NPCs
nuclear pore complexes

NRSF/REST
neuron-restrictive silencing factor/RE-1 silencing transcription factor

OGG1
8-oxoguanine DNA glycosylase 1

PARPs
polyADP ribose polymerases

PcG
polycomb

PCNSL
primary CNS lymphoma

piRNAs
piwi protein-interacting RNAs

PKMzeta
protein kinase Mzeta

PKR
RNA-activated protein kinase

PNETs
primitive neuroectodermal tumors

PQBP1
polyglutamine binding protein 1

PRE
PcG-response element

PTB
polypyrimidine tract binding protein

PTC
patched

R
arginine

Rag-1/2
recombination-activating gene-1/2

RBPs
RNA binding proteins

RNAi
RNA interference

rRNA
ribosomal RNA

RSK2
p90 ribosomal S6 kinase isozyme

S
serine

SAHF
senescence-activated heterochromatic foci

SCFA
short chain fatty acids

Shh
sonic hedgehog

SINE
short interspersed nuclear elements

Sir
silent information regulators

SLITRK1
neuronal SLIT and Trk-like family member 1

SMaRT
spliceosome-mediated trans-splicing

Smo
smoothened

sniRNAs
small nucleolar interfering RNAs

snoRNAs
small nucleolar RNAs

SOD1
superoxide dismutase 1

STAT3
signal transducer and activator of transcription 3

T
threonine

TCR
transcription coupled repair

TGCI
transient global cerebral ischemia

TICs
tumor-initiating cells

tiRNAs
transcription initiation RNAs

TLRs
Toll-like receptors

TRAIL
tumor necrosis factor-related apoptosis inducible ligand

TRE
: TrxG-response element

TrxG
: trithorax

UCHL1
: ubiquitin carboxyl-terminal hydrolase L1

UTR
: untranslated region

XCI
: X chromosome inactivation

Xi
: inactive X chromosome

Xic
: X chromosome inactivation centers

XLMR
: X linked mental retardation