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Introduction: Epigenetics and neuropsychiatric diseases

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Introduction

I am delighted to introduce and to serve as Guest Editor of this Special Issue of *Neurobiology of Disease* on Epigenetics and Neuropsychiatric Diseases. The fields of epigenetics and epigenomic medicine represent rapidly emerging disciplines of translational neuroscience that are already furnishing unique insights and perspectives regarding evolutionary innovations in brain form and function, nervous system development, emergent properties of neural stem cells and neural fate decisions, neural cell diversity and connectivity, neuronal and neural network homeostasis and plasticity, the pathogenesis of diverse classes of nervous system diseases and innovative therapeutic strategies.

Epigenetic processes include the interrelated mechanisms of DNA methylation, histone modifications, nucleosome positioning, higher order chromatin remodeling, deployment of numerous classes of short and long non-protein-coding RNAs, RNA editing and DNA recoding. The unusual biophysical properties and associated informational versatility of RNA molecules are essential for directing and integrating these local as well as genome-wide processes and for orchestrating the transcriptional state of the cell, multiple complex pathways of post-transcriptional processing and epigenetic memory states. These cellular and systems biological transitional and homeostatic states can be modulated by cell intrinsic as well as environmental signals and by RNA and DNA editing events operating via activity-dependent intracellular transport and modification of RNAs and RNA regulatory complexes as well as through extracellular, systemic and even germ-line trafficking of distinct RNA subclasses. This continuum of epigenetic events, in turn, promotes the dynamic reorganization of functional nuclear microdomains and the overall genomic architecture to orchestrate the expression and function of individual neural genes and integrated gene networks with sophisticated spatial and temporal trajectories required to facilitate evolving brain processes and to thereby mediate higher order cognitive, behavioral and sensorimotor functions in health and disease. There is increasing evidence that epigenetics thus represents the dynamic molecular interface mediating gene-environmental interactions during critical periods through the lifespan as well as through multigenerational inheritance of complex neuropsychological traits.

As revealed by the compelling evidence presented in the individual contributions of this Special Issue, epigenetics and epigenomic medicine have already begun to revolutionize our

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understanding of nervous system disease latency, onset and progression, the underlying molecular basis of major classes of neuropsychiatric diseases as well as more efficacious responses to newer therapeutic modalities based on these novel neurogenetic principles. These articles also stress the point that emerging classes of pharmacoepigenomic agents have the potential to truly revolutionize neurological therapeutic strategies and to significantly enhance recovery of impaired and even seemingly lost neurological functions through epigenetic reprogramming of endogenous neural stem cells and more mature neural cell subtypes and by dynamic remodeling of neural network connections and reorganization of associated synaptic and neural network-wide plasticity programs.

In this Special Issue:

- Van Bokhoven and Kramer examine the roles of alterations in direct and indirect modifiers of chromatin structure and function in altering specific neural genes, functional gene networks and associated neuronal processes involved in mediating specific subclasses of intellectual and developmental disabilities with a synopsis of the prospects for developing innovative therapeutic interventions.
- Chamberlain and Lalande explore the complex epigenetic basis underlying neural developmental disorders associated with genomic imprinting at human chromosome 15q11-13, including Prader-Willi, Angelman and 15q duplication syndromes, with incisive analysis of epigenotype/phenotype correlations and future perspectives for innovative experimental investigations and novel therapeutic applications.
- Nakamori and Thornton discuss evolving principles underlying the pathogenesis of a subset of expansion repeat disorders that give rise to distinct neurodevelopmental, neurodegenerative and neuromuscular disorders through the effects of heterochromatin-mediated gene repression and RNA dominance/toxic gain-of-function mechanisms and explain why these epigenetically-mediated disorders may be unusually responsiveness to a diverse repertoire of evolving therapeutic strategies.
- Buckley's and Cattaneo's groups illustrate the interrelated mechanisms by which deregulation of the dynamic epigenetic and transcriptional modulatory REST supercomplex may promote Huntington's disease pathogenesis through transcriptional dysregulation, aberrant post-transcriptional processing and impairment of associated epigenetic processes, including DNA methylation, histone and chromatin modifications, and deployment and function of microRNAs and long non-coding RNAs, with implications for the development of robust biomarkers and diverse modes of therapeutic interventions.
- Martinez and Esteller examine the role of deregulation of key epigenetic processes in the pathogenesis of different types of glioblastoma multiforme, including alterations in DNA methylation, histone and chromatin modifications and in the expression and function of microRNAs, and the importance of these seminal advances in identifying novel biomarkers, cancer-initiating/stem cells and in devising innovative therapeutic approaches that would help to restore epigenetically altered cell regulatory pathways involved in these currently refractory and highly invasive primary CNS tumors.
- Huynh and Casaccia explore the deregulated chromatin landscape underlying demyelinating disorders and mediated through the actions of specific epigenetic processes involved in oligodendrocyte progenitor cell differentiation during development, remyelination and senescence, including the emerging roles of novel histone post-translational modifications and histone variants, microRNAs and DNA methylation, with a complementary examination of their relevance to other neuropsychiatric disorders.

- Qureshi and Mehler discuss the diverse roles of epigenetic mechanisms, including DNA methylation, histone and chromatin modifications, non-coding RNAs and RNA editing, in the pathogenesis of human epilepsy syndromes and in the process of epileptogenesis, with novel insights with regard to cell type specific and environmentally responsive deployment of genes and functional gene networks that underlie disease onset, epilepsy subtypes, associated co-morbidities and targeted epigenetic therapeutic reprogramming strategies.
- Franklin and Mansuy illustrate a spectrum of epigenetic mechanisms involved in orchestrating environmentally mediated transgenerational inheritance of complex cognitive and behavioral traits that predispose to adult-onset neuropsychiatric diseases with an emphasis on DNA methylation and its emerging roles in mediating gene-environmental interactions and neural plasticity in the mature nervous system.
- McGowan and Szyf examine epigenetic processes involved in mediating social adversity during early life and the long lasting impact of deregulation of DNA methylation, histone, nucleosome and chromatin modifications and deployment of non-coding RNAs on the activities and functions of specific neural genes, with important implications for the development of innovative pharmacoepigenomic as well as social interventions for the major classes of neuropsychiatric diseases associated with developmental antecedents.
- Hsieh and Eisch define the emerging roles of diverse epigenetic mechanisms in stem cell- and neurogenic niche-mediated adult constitutive hippocampal neurogenesis and in encoding environmental inputs into stable and behaviorally salient changes in gene expression, and of evolving links between adult neurogenesis, epigenetic processes and neuropsychiatric disorders, with important implications for the development of new classes of psychotropic agents based on relevant epigenetic principles and stem cell-mediated neural protective and regenerative mechanisms.

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