Editorial

NeuroEpigenetics and Neurodevelopmental Disorders: From Molecular Mechanisms to Cell Fate Commitments of the Brain Cells and Human Disease

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Epigenetics control the gene expression program and cellular identity of individual cells in our body *via* molecular mechanisms that are not directly reflected by the genomic DNA [1]. This includes different types of DNA methylation, histone post-translational modifications (PTMs), the cross-talk of DNA methylation and histone PTMs, chromatin remodeling, and the activity of non-coding and small micro RNAs. Recent discoveries have highlighted the importance of epigenetics and neuroepigenetics in the development, function, and diseases of the central nervous system. An important feature of epigenetic mechanisms is their reversibility. In contrast to genetic mutations, which are irreversible, there is a great potential to develop therapeutic strategies that target epigenetics.

This thematic issue will cover recent advances in the field of "NeuroEpigenetics and Neurodevelopmental Disorders". In this special issue, I have gathered a collection of review articles on epigenetic mechanisms and neuroepigenetics, with a clear focus on neurodevelopmental disorders. The contributing authors have highlighted the impact of epigenetics in neuronal plasticity; as well as neural stem cell self-renewal and cell differentiation potencies in the context of neurodevelopmental disorders. The authors have further expanded the discussions on the cognitive neurodevelopmental diseases such as fetal alcohol spectrum disorders (FASD), reviewed the potential application of epigenetic drugs for neurodevelopmental disorders, discussed a well-studied neurodevelopmental disorder with genetic mutations in an epigenetic factor (Rett Syndrome), and ultimately provided an exciting series of recent discoveries in epigenetics that impact novel medicine.

In the article "Epigenetic Basis of Neuronal and Synaptic Plasticity", contributed by Nina Karpova, Amanda Sales and Sâmia Joca, at the Department of Physics and Chemistry, School of Pharmaceutical Sciences, University of São Paulo, Brazil, the authors have provided an in-depth knowledge of recent advances on the major components of the epigenetic machinery in relation to activity-dependent and long-term neural-synaptic plasticity [2]. Moreover, they have highlighted multiple regulatory layers at the transcriptional and post-transcriptional levels that include promoter activation, alternative splicing, transcript stability, and alternative polyadenylation. The authors have discussed the epigenetic basis of compromised neuronal plasticity in neurodevelopmental diseases, stress-related disorders, and additional neurological disorders. Karpova and colleagues have also provided insight into the therapeutic potential of certain epigenetic pharmacological compounds, while discussing the issues that must be addressed prior to the safe and effective application of these compounds towards neurodevelopmental disorders.

The multipotent neural stem/progenitor cells (NSPC) of the central nervous system are capable of self-renewal and differentiation into different cell types of the developing and adult brain [3]. These processes are regulated at many levels by extracellular signals and the inherent potential of NSPCs for proper response. In the contribution "Histone Methylation and microRNA-dependent Regulation of Epigenetic Activities in Neural Progenitor Self-renewal and Differentiation" by Emanuele Cacci, Rodolfo Negri, Stefano Biagioni, and Giuseppe Lupo, at the Department of Biology and Biotechnology, Sapienza University of Rome, Italy, the authors have discussed the stage-dependent response of self-renewing NSPC to extrinsic signals. These signals are coordinated through epigenetic mechanisms, and have significant implications in the pathological conditions observed in human disorders [4]. The authors have highlighted recent advances on the epigenetic basis of NSPC self-renewal, differentiation, and cell fate decisions. There is also an important discussion regarding histone PTMs and the role of protein complexes in NSPC deposition in specific regions of the brain. The role of bivalent marks is clarified at developmentally important genes at different time-points and NSPC differentiation stages. Next, Cacci *et al.,* have discussed the cross-talk between epigenetic factors and small regulatory RNAs, emphasizing the interplay between these epigenetic players in the regulation of NSPC self-renewal and cell fate commitment.

Recent discoveries have highlighted the impact of environmental insults on the genetics and epigenetics in neurodevelopmental disorders. Such disorders include fetal alcohol spectrum disorders that result from *in utero* exposure of a developing fetus to alcohol *via* drinking of the pregnant mothers. FASD are common neurodevelopmental disorders with a high economic impact on the health care services. In the article "Overview of the Genetic Basis and Epigenetic Mechanisms that Contribute to FASD Pathobiology", Vichithra Liyanage, Kyle Curtis, Robby Zachariah, Albert Chudley, and Mojgan Rastegar, from the Regenerative Medicine Program, Department of Biochemistry and Medical Genetics, University of Manitoba, Winnipeg, Canada, the authors have provided a comprehensive overview of recent research regarding the teratogenic effects of alcohol in the developing brain [5]. Since both genetic and epigenetic factors contribute to FASD pathobiology, the authors have discussed the detailed role of DNA methylation and a main DNA methyl-binding protein in the brain called "MeCP2". Genetic mutation or altered MeCP2 expression in the brain causes neurodevelopmental disorders and impaired brain function [6]. Interestingly, MeCP2 itself is controlled by DNA methylation in the brain [7, 8], and is deregulated by alcohol in differentiating embryonic brain-derived neural stem cells [9]. While FASD pathobiology is influenced by different genetic and epigenetic factors, the

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authors have focused on the detailed role of DNA methylation, different histone PTMs and noncoding regulatory RNAs in altering the gene expression program of the developing brain by alcohol. Furthermore, the authors have highlighted the association of maternal and paternal preconception alcohol consumption with possible FASD-like phenotypes in newborns. The overview of this article can elucidate the potential design of future therapeutic strategies for affected patients.

"Histone variants and composition in the developing brain: should MeCP2 care?" by Valentina Zago, Cristina Pinar-CabezaDeVaca, John Vincent, and Juan Ausió, from the Department of Biochemistry and Microbiology, University of Victoria, Victoria, Canada; and at the University of Toronto, Toronto, Canada, focused on the specific structural chromatin characteristics in neurons and the brain, which distinguish them from other tissues in the body [10]. The critical nature of such unique molecular features in brain cells is discussed in the context of cellular development and neuroplasticity. The authors have also described the significant turnover of main chromosomal proteins that include histone variants and the DNA methyl binding protein MeCP2. Such structural characteristics in brain cells is an exciting and emerging novel concept that has recently attracted much attention to the field of epigenetics, especially as it pertains to neurodevelopmental disorders. The authors have further highlighted how these epigenetic players interact and communicate, which proves to be an important area of future research in the epigenetic field.

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