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Editorial

Neuroepigenetics: Introduction to the special issue on epigenetics in neurodevelopment and neurological diseases

Gene expression profile represents the molecular state of a cell at a given time and is dynamically regulated and precisely controlled in response to external stimuli. While the DNA sequences are the ultimate templates for gene transcription, epigenetic features of the genome, including modifications of histones, methylation of cytosine nucleotides of the genomic DNA, 3-dimensional interaction of genomic regions, and the expression of various forms of non-coding RNAs, regulate the accessibility and processability of the genomic loci and add another layer of regulation of gene expression beyond the heritable DNA sequences. For decades, some epigenetic properties of the genome, such as DNA methylation, have been considered as stable and inheritable marks. The functional role of dynamic epigenome and subsequent gene expression regulation in the nervous system, is only recently being appreciated. Significance progress has been made in the last few years, which has revealed special features of epigenetic regulation in the nervous system that are different from those in previous heavily studied fields, for example cancer, and neuroepigenetics is emerging as a new field of investigation.

In this special issue of Experimental Neurology on Epigenetics in Neurodevelopment and Neurological diseases, we aim to introduce the readers of this exciting new field and discuss the potential role of neuroepigenetic mechanisms in neurodevelopment, synaptic plasticity as well as how dysregulation of neuroepigenetics contributes to neurological diseases.

Our genome is coded by only four nucleobases: A (adenine), T (thymine), G (guanine) and C (cytosine). Methylation at the 5th position of cytosine base (5mC) was previously thought to be the only epigenetic modification directly on genomic DNA and functions to ensure transcriptional gene silencing to maintain cell type identity in differentiated cells. Recent studies, however, provide strong evidence that DNA methylation and demethylation are active, dynamic processes, which can be induced by stress or neuronal activity in post-mitotic neurons. Furthermore, it is now clear that 5mC is not the only form of DNA modification. There are several intermediate products during active DNA demethylation process, including 5-hydroxymethylcytosine (5hmC), an oxidized product of 5-methycytosine that is present at much higher level in the brain than other tissues. In the first article, Cheng and colleagues review the role of 5hmC as a new player in neuroepigenetics, and discuss how 5hmC level is dysregulated in various neurodevelopmental disorders, neurodegenerative diseases and neuropsychiatric diseases. In the second article, Provencal and Binder review how early life stress, occurring either in utero or during early postnatal stages, leads to long-term effects on the mental state in the adulthood or even transgeneration via epigenetic remodeling of the DNA methylation status in the nervous system.

The structural unit of the chromatin is nucleosome, which is comprised of DNA chains wrapping around histone proteins. Nucleosomes can be either loosely or densely packed, which is associated with active or suppressed gene transcription, respectively. The chemical modifications of the histone tail, most commonly acetylation, methylation and phosphorylation, are one of the determinants of the structural status of the chromatin. Histone acetylation is in general correlates with loose chromatin and active gene expression. On the other hand, Histone-3 lysine-4 trimethylation (H3K4Me3) plays both positive and negative roles in regulating gene expression, depending on the combination of other histone modifications. The article by Shen and colleagues describes the genome-wide, differential distribution of H3K4Me3 in male and female brains and discuss how epigenetic regulation, including both DNA and histone modifications, plays an important role in the development and maintenance of sex differentiation. The molecular underpinning of long-lasting memory formation has long been hypothesized by Francis Crick to be the relatively stable changes of epigenome. Guan and colleagues review the current knowledge on the memory formation, which is now shown at least in part mediated through conformational change of chromatin at specific genomic loci induced by neuronal activity, which results in subsequent gene expression changes. They also discuss the potential role of epigenetic histone and DNA modifications in the maintenance of long-term memory. The role of epigenetic regulation in neural plasticity after injury is further elaborated in the Felling and Song review. They also discuss that epigenetic machinery might be a target for developing new interventions for promoting recovery after ischemic stroke.

Non-coding RNAs, including microRNAs, siRNAs, piRNAs and snoRNAs, are RNA molecules not translated into proteins. The functional importance of these non-coding RNAs is still largely unknown. Among these non-coding RNAs, microRNA is a family of small RNA with 20–25 nucleotides in length and probably the most studied non-coding RNAs in the last decade. Function analyses of microRNAs support a role in post-transcriptional regulation of gene expression. In the review by Sun and Shi, they summarize the role of brain specific microRNAs in neurodevelopment and discuss the implication of aberrant microRNA expression in various neurodevelopmental disorders, including schizophrenia and bipolar disorders.

Neuroepigenetics is a rapidly expanding new field that shed new light onto our understanding in the molecular determination of the neural developmental events and plasticity and our quest on delineating mechanisms of the pathological events in neurological diseases. Newly developed technologies, such as next generation sequencing, enable us to detect and document the epigenetic changes in the nervous system in response to environmental and pathological stimuli. It is clear,

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however, at this stage, much of the evidence for a role of neuroepigenetics in neurobiology and neurological diseases is still in its infancy, and is mostly descriptive and correlative. There are also emerging new areas that remain to be fully explored, for example, non-CpG methylation and long non-coding RNAs in neurons, and epigenetics in glia cells. Nevertheless, we hope this special issue will introduce this new exciting field of epigenetic regulation on the molecular state of neurons, the building block of our brain to readers.

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