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Keystone Symposia on Neuroepigenetics—bridging the gap between genome and behavior

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ABSTRACT

The Keystone Symposium on Neuroepigenetics (Santa Fe, NM, USA, February 22–26, 2015) brought together outstanding researchers to discuss their latest findings in the field of epigenetic regulation of gene expression in the nervous system. This has been the first conference entirely devoted to the integration of the fields of epigenetics and neuroscience. The goal of the symposium was to raise new challenging questions and to stimulate innovative ideas fostered by the provocative results presented by experts working in a wide array of epigenetic systems and generated by a variety of experimental approaches in many model systems. This report will discuss a number of groundbreaking discoveries presented at the symposium encompassing studies of human evolution, nervous system development, adult brain plasticity, transgenerational inheritance, mental disorders, and large-scale efforts to generate detailed reference epigenomes. The outcome of the symposium provided new exciting perspectives and the framework for expanding the frontiers of neuroscience research.

Introduction

In recent years, epigenetics has emerged as one of the most rapidly expanding and dynamic research areas in biology that investigates the genome function in the regulation of an impressive diversity of cellular processes in homeostasis and disease (Sweatt, 2013). Although the genomic sequence of many organisms has been completed, understanding how DNA sequences are deciphered in the context of individual cell types or specific environmental conditions represents the fundamental question of epigenetics. Tremendous advances in massively parallel sequencing techniques have revolutionized the field of epigenetics, and large-scale epigenomic projects, such as the Encyclopedia of DNA Elements (Stamatoyannopoulos, 2012) and the NIH Epigenomic Roadmap (Bernstein et al., 2010), have been instrumental in identifying the functional elements of the genome and their contribution to human diseases by generating detailed maps of chromatin states of distinct cell types and tissues. Because epigenetic mechanisms play central roles in many neuronal processes, a deeper understanding of distinct epigenetic signatures of the neuronal genome also has the potential to tackle their deregulation into a broad spectrum of brain diseases (Telese et al., 2013). These and other aspects of epigenetics research were addressed at the Keystone Symposia on Neuroepigenetics. The conference featured a diverse group of outstanding scientists, including plenary speakers and junior researchers, reporting their latest findings during an exciting 3-day agenda. The symposia was a tremendous success supported by NIH Director's Fund and organized by Hongjun Song (Johns Hopkins University, USA) and Li-Huei Tsai (Massachusetts Institute of Technology, USA); the program that these 2 leading researchers developed and their selection of presenters were key to meet the goal of pushing the boundaries in the emerging field of neuroepigenetics.

Keynote session

Two leading pioneers of the field delivered the first keynote session: Fred H. Gage (The Salk Institute for Biological Studies, USA) and Micheal E. Greenberg (Harvard Medical School, USA). Fred Gage described his journey in studying the role of transposable elements in human evolution by identifying the molecular differences between human and nonhuman primates based on cutting-edge techniques that incorporate high-throughput sequencing epigenomic approaches with the establishment of induced pluripotent stem cells (iPSCs) from human, chimpanzee, and bonobo. Comparative gene expression analysis of specie-specific iPSCs revealed differences in the regulation of long interspersed element 1 (LINE-1) transposons, which are the only known active transposons in the human genome (Marchetto et al., 2013). Recent findings from Gage's laboratory and others indicated that those elements are expressed not only in the germ line but also in the brain, challenging the dogma that the genome of postmitotic neurons is static and suggesting that they drive genetic heterogeneity across neurons in the same

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individual and, therefore, they might have a role in dictating individual behavior and contributing to vulnerability to disease (Guffanti et al., 2014; Kazazian, 2004; Muotri et al., 2005). In his inspiring talk, Fred Gage presented sequencing data to identify novel nonreference L1 insertions and provided evidence that LINE-1 repeats exhibit different mobility in nonprimate compared to humans, supporting the hypothesis that LINE-1 transposition could be considered as potential driver of genomic innovation underlying adaptive changes in evolution. Given that epigenetic mechanisms, such as DNA methylation, are crucial to control the mobilization of transposable elements in the genome, the study of epigenetic regulation of their mobility has major implications in all areas of neuroscience (Erwin et al., 2014).

The second lecture by Michael Greenberg focused on his career-long research interest regarding the function of gene expression programs activated by neuronal activity at the level of synapses and transduced into the nucleus by signaling molecules that ultimately target transcription factors and chromatin regulators (West and Greenberg, 2011). The most intriguing aspect of his presentation was his recent work on the misregulation of long gene expression in the brain when MECP2 is mutated in human or mouse models of Rett syndrome (Gabel et al., 2015). Combining genomic profiling of MeCP2 and genome-wide base pair resolution DNA methylation assays, it emerged that MECP2 represses long genes by binding to a form of methylated DNA enriched in the brain. Because the long genes repressed by MeCP2 are enriched in functional annotation of neuronal functions, Michael Greenberg proposed the idea that disruption of long gene expression might be a general mechanism underlying the neurological dysfunctions in Rett syndrome. It was exciting to hear how the inhibition of topoisomerases with topotecan, a drug commonly used as a chemotherapeutic agent, leads to a dose-dependent reversal of long gene expression, which inspired novel ideas for developing methods to rebalance long gene expression as a strategy to correct neural dysfunction in neurodevelopmental disorders.

Epigenetic mechanisms in reprogramming

Induced pluripotent stem cell technology represents one of the major advances in modeling of neurological disorders in vitro (Nityanandam and Baldwin, 2015). iPSC-derived neurons represent a powerful strategy for elucidating disease pathogenesis for drug discovery and development, for personalized medicine, and eventually for regenerative cell therapy, as suggested by many talks and posters presented at this meeting. However, the standard transdifferentiation protocol, which relies on the forced expression of neural lineage–specific transcription factors, is a long process with multiple steps that might increase the heterogeneity of the final neuronal population. In this context, Xiang-Dong Fu (University of California, San Diego, CA, USA), a leader in the research area of RNA splicing, presented his recent work on an innovative and fast method for direct conversion of somatic cells to functional neurons based on repressing the expression of a single RNA binding protein, PTB (Xue et al., 2013). Researchers led by Xiang-Dong Fu elucidated the molecular feedback loops that modulate the repression of PTB during neuronal differentiation when a microRNA-regulated splicing event causes the switch to the neuronal-specific isoform of PTB.

Many discussions at this meeting pivoted on the urgent need of efficient protocols for transdifferentiation to specific neuronal subtypes and supported the notion that the epigenomic profiling of these cells is a crucial strategy for mechanistic characterization of these cells and for developing novel protocols.

Epigenetic mechanisms in regulating synapse formation, plasticity, and behavior

Long-standing themes such as regulation of synaptic plasticity were included in the program, and various talks proposed novel viewpoints in the molecular mechanisms underlying cognitive functions. A novel perspective was offered by Li-Huei Tsai, who has dedicated her career to elucidate molecular and cellular mechanisms of cognition with particular emphasis on models of Alzheimer disease. She presented her latest findings in the regulation of immediate early genes, which involves generation of DNA double strand breaks within their promoters to relieve a topological constraint that imposes another layer of regulation in the fast response of neurons to experience-dependent changes. This provocative finding inspired questions regarding mechanisms of DNA repair in postmitotic neurons and might have major implications in the study of neurodegenerative pathways.

David Sweatt (University of Alabama at Birmingham, USA) presented his recent work on novel mechanisms of epigenetic regulation of associative conditioning that involve recently identified extracoding RNAs, suggesting that neuronal activity-dependent transcription modulates DNA methylation (Di Ruscio et al., 2013). Those noncoding RNA molecules are generated from coding genes and have the ability to block DNA methylation events by forming secondary structures that interact with the methyltransferase DNMT1. By using deep sequencing approaches to profile the transcriptome and methylome of neuronal cultures, it emerged that the presence of extracoding RNAs may predict gene-specific methylation status. This epigenetic mechanism is involved in the regulation of associative conditioning in the hippocampus, as demonstrated by altered learning behaviors of mice previously injected with antisense oligos interfering with specific extracoding RNAs.

In addition, this session highlighted novel groundbreaking discoveries in the epigenetic regulation of synaptic and behavioral plasticity mediated by methylation events that dynamically target both DNA and RNA. Particularly, Hongjun Song covered the mechanisms of neuronal activity-induced active DNA demethylation pathways that involve TET enzymatic machineries to convert 5-methylcytosine to 5-hydroxylmethylcytosine. Tet3 expression is dynamically regulated by synaptic activity and in turn effects excitatory glutamatergic transmission by modulating the amount of surface GluR1 at a transcriptional level (Yu et al., 2015). Timothy Bredy (Queensland Brain Institute, Australia) talked about RNA modifications, such as N6-methyladenosine, as a crucial epigenetic mechanism in the fine tuning of gene expression related to adaptation.

The increasing amount of epigenetic modifications associated to experience-dependent changes in the brain and linking epigenetic alterations to development of neurological disorders provoked fertile discussions regarding epigenetic modifications as potential targets for drug treatment. Jeffrey S. Ney (Janssen R&D/Johnson and Johnson Innovation, Cambridge, MA, USA) portrayed the latest advances in the translational use of neuroepigenetic discoveries as epigenetic therapies for brain disorders. It emerged that combining genomic sequencing and expression data might represent a critical strategy to better define the druggable epigenomes. Although many of the epigenetic drugs hold great promises, such as HDAC inhibitors as treatment for cognitive impairments, many challenges are still unsolved, such as efficient delivery through the blood-brain barrier, safety, and tolerability for chronic treatments.

Molecular mechanisms

Experts in the field of epigenetics presented their overview of how diverse signaling transduction pathways affect behavioral