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Neuroepigenomics: resources, obstacles, and opportunities

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ABSTRACT

Long-lived postmitotic cells, such as most human neurons, must respond effectively to ongoing changes in neuronal stimulation or microenvironmental cues through transcriptional and epigenomic regulation of gene expression. The role of epigenomic regulation in neuronal function is of fundamental interest to the neuroscience community, as these types of studies have transformed our understanding of gene regulation in postmitotic cells. This perspective article highlights many of the resources available to researchers interested in neuroepigenomic investigations and discusses some of the current obstacles and opportunities in neuroepigenomics.

Neuroepigenomics comes of age

Epigenetic changes are historically defined as heritable changes that alter transcription but not the underlying DNA sequence. Unlike cells in many other tissues, most neurons in the human brain are postmitotic (Gage and Temple, 2013; Lacar et al., 2014), with many individual neurons appearing to survive and function for decades. Thus, gene expression and associated synaptic changes are required to effectively respond to altered neuronal inputs, interactions with support cells, or environmental changes (e.g., nutrient levels, drugs of abuse, stress, inflammation, aging, and other microenvironmental triggers). This modulation of neuronal gene expression occurs via transcriptional and epigenomic mechanisms, which are likely to be adapted to accommodate the special requirements of neurons.

The field of epigenomics has exploded in recent years with improved assays, the generation of genome-wide epigenomic maps from multiple tissues, the identification of a host of epigenetic regulators important in numerous types of cancers, and the potential for the development of novel epigenetic therapies. Does this explosion extend to neuroepigenomics? Fig. 1A shows the exponential increase in the number of funded R01 grants related to epigenetics or epigenomics from 3 neuroscience-focused National Institutes of Health (NIH) Institutes, indicating that many researchers are working in this scientific space. Fig. 1B shows the increasing number of primary publications on topics that touch upon neuroepigenetics or neuroepigenomics, suggesting that epigenomic questions have captivated the neuroscience community.

Forays into neuroepigenetics research have led to a number of groundbreaking discoveries in substance use disorders, brain development, neurodegeneration, intellectual disability, memory, and even transgenerational inheritance of behavioral phenotypes. Because several reviews have discussed the role of epigenetic regulation in the nervous system, we will briefly highlight a few of the key discoveries below (Bellet and Sassone-Corsi, 2010; Bennett et al., 2014; Day and Sweatt, 2011; Dulac, 2010; Feng and Nestler, 2013; Haggarty and Tsai, 2011; Ma, 2010; Maze et al., 2011, 2013, 2014; Namihira et al., 2008; Nelson and Monteggia, 2011; Pena et al., 2014; Rahn et al., 2013; Rogers et al., 2011; Sweatt, 2013; Zocchi and Sassone-Corsi, 2010). For example, work from Eric Nestler's laboratory has shown that cocaine exposure leads to defined changes in histone modifications and DNA methylation of neuronal regulators in the nucleus accumbens (LaPlant et al., 2010; Nestler, 2014; Renthal et al., 2007, 2009). Investigations into autism and intellectual disability disorders indicate that epigenetic regulators (e.g., MECP2, MBD5, JARID1C, DNMT3A, ARID1B) play important roles in these disorders (Jensen et al., 2005; Moretti and Zoghbi, 2006; Santen et al., 2012; Talkowski et al., 2011; Tatton-Brown et al., 2014; Tsurusaki et al., 2012). Several lines of evidence point to an epigenetic basis underlying memory processing. Work from David Sweatt's laboratory

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suggests an essential role for epigenetic regulation in memory formation and maintenance (Day and Sweatt, 2011; Guzman-Karlsson et al., 2014; Miller et al., 2008, 2010; Zovkic et al., 2014). Marcelo Wood and colleagues have found Brg1-associated factor chromatin remodeling complexes to be necessary for memory and synaptic plasticity (Vogel-Ciernia et al., 2013). Li-Huei Tsai and colleagues have found that histone deacetylase (HDAC) inhibitors can effectively re-establish access to memories after neurodegeneration (Graff et al., 2012, 2014; Rudenko and Tsai, 2014). There is even evidence that certain exposures can lead to intergenerational inheritance of behavioral phenotypes (Byrnes et al., 2011; Dias and Ressler, 2014; Gapp et al., 2014; Szutorisz et al., 2014; Vassoler et al., 2013).

One of the most important epigenetic discoveries in the last several years is the identification of TET-mediated oxidized derivatives of 5-methylcytosine (5mC): 5-hydroxymethylcytosine (5hmC), 5-formylcytosine, and 5-carboxylcytosine in mammals (Cheng et al., 2014; Ito et al., 2011; Kriaucionis and Heintz, 2009; Mellen et al., 2012; Rudenko and Tsai, 2014; Sun et al., 2014; Tahiliani et al., 2009). 5-hydroxymethylcytosine is especially abundant in the brain with up to 10-fold higher levels compared to embryonic stem (ES) cells and other tissues. 5-hydroxymethylcytosine modification of DNA, initially discovered in Purkinje cells, is now known to play a critical role in stem cell biology and has emerging roles in other cell types and in nervous system disorders (Cheng et al., 2014; Kriaucionis and Heintz, 2009; Mellen et al., 2012; Rudenko and Tsai, 2014; Tahiliani et al., 2009). For example, analysis in specific brain cell types demonstrates that MeCP2, an epigenetic regulator known for its ability to bind 5mC of inactive gene promoters, binds 5hmC in active gene bodies in Purkinje cells, granule cells, and Bergmann glial cells (Mellen et al., 2012). In the brain, this observation is accompanied by the loss of 5mC and an increase in 5hmC in the gene body of active genes. These observations are likely to have important implications in regard to gene expression and brain plasticity.

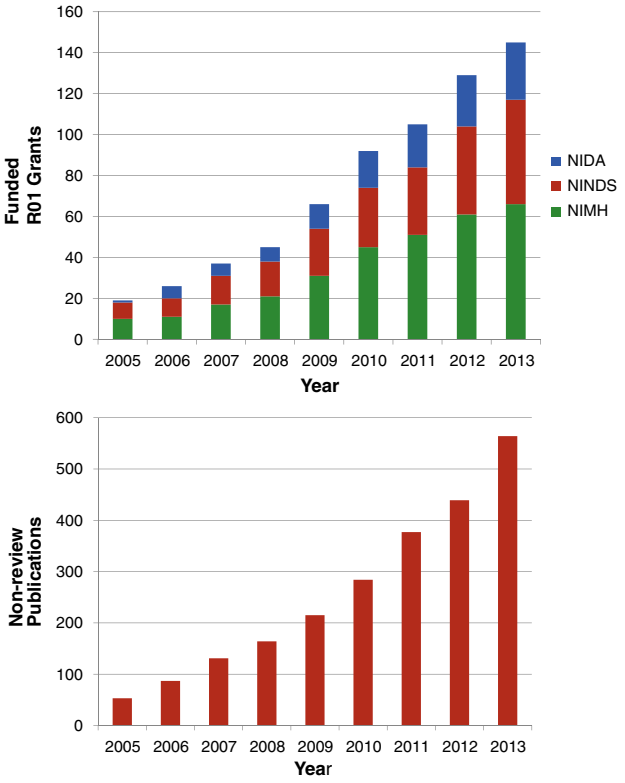

Fig. 1. (A) Increasing NIH-funded research in neuroepigenetics. The figure shows cumulative number of funded R01 epigenetic/epigenomic grants from 2005 to 2013 from 3 neuroscience-focused NIH institutes: National Institute on Drug Abuse, National Institute on Mental Health, and National Institute of Neurological Disorders and Stroke. These data were obtained by searching NIH Reporter (http://projectreporter.nih.gov/reporter.cfm) in June 2014 for funded grants that used the terms *epigenetic* or *epigenomic* in their abstract or specific aims. (B) Increasing numbers of nonreview publications in neuroepigenetics. The figure shows the increasing number of nonreview publications over time in the area of epigenetics or epigenomics in the nervous system. PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was searched in June 2014 for titles or abstracts that mention *epigen* (to capture epigenetics or epigenomics) and a nervous system term (*nervous system* or *neuro* or *brain*). The search was performed to capture only nonreview publications.

Tools and technologies for neuroscience research have improved significantly and will continue to improve through projects such as Brain Research through Advancing Innovative Neurotechnologies (BRAIN) http://www.nih.gov/science/brain/2025/index.htm. Neuroepigenomics will no doubt be an important component of many future discoveries in neuroscience. This review focuses on a few of the currently available resources that neuroepigenomics researchers might find useful, including reference epigenome maps, epigenomic assays and imaging tools, and recent key discoveries in disease research. We will also discuss several of the current obstacles and opportunities in neuroepigenomics research, including tools for single-cell analysis and epigenomic manipulation, the need for additional brain cell reference epigenome maps, a deeper understanding of the mechanisms of transgenerational epigenetic inheritance, and the further development of epigenetic biomarkers and therapeutics. These obstacles and opportunities will become increasingly important as the field of neuroepigenomics emerges from “adolescence.”

Resources and tools for neuroepigenomics

As shown in Fig. 2, the Roadmap Epigenomics Program (supported by the NIH Common Fund) consists of multiple components with different functions, including (1) development of new technologies to improve epigenome-wide assays, advance epigenetic imaging, and enable functional epigenetic manipulation; (2) identification and characterization of novel epigenetic marks; and (3) investigation of epigenomic processes underlying human disease (Satterlee et al., in press). Additionally, reference epigenome maps from normal cells and tissues were generated and uniformly processed by the Mapping Consortium and a Data Coordination Center. These data were deposited into NIH databases (Gene Expression Omnibus or database of Genotypes and Phenotypes) where they can be accessed by researchers (Bernstein et al., 2010). Most recently, a Computational Epigenomics component was added to support secondary data analysis studies using reference epigenome mapping data and other user-generated or public data sets to investigate important biological questions or diseases. Overall, 83 R01, R21, or RC1 grants were funded through the Roadmap Epigenomics Program. Below we will discuss some of the neuroepigenomic-relevant tools and resources generated by these researchers.

Reference epigenome maps for the nervous system

In the nucleus, genes are turned on and off via a sophisticated interplay of transcriptional regulators; the consequences of this elaborate dance can be monitored in part through the assay of epigenomic features. The NIH Roadmap Epigenomics Program has generated a comprehensive catalog of epigenome maps for 92 distinct normal human cells and tissues (Bernstein et al., 2010). These maps were anticipated to stimulate a variety of hypothesis-generating studies such as (1) the identification of tissue-specific functional genetic elements, (2) uncovering the breadth of epigenomic plasticity during cellular differentiation, and (3) establishing a normal reference for investigators exploring the effects of environment or disease on the