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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.

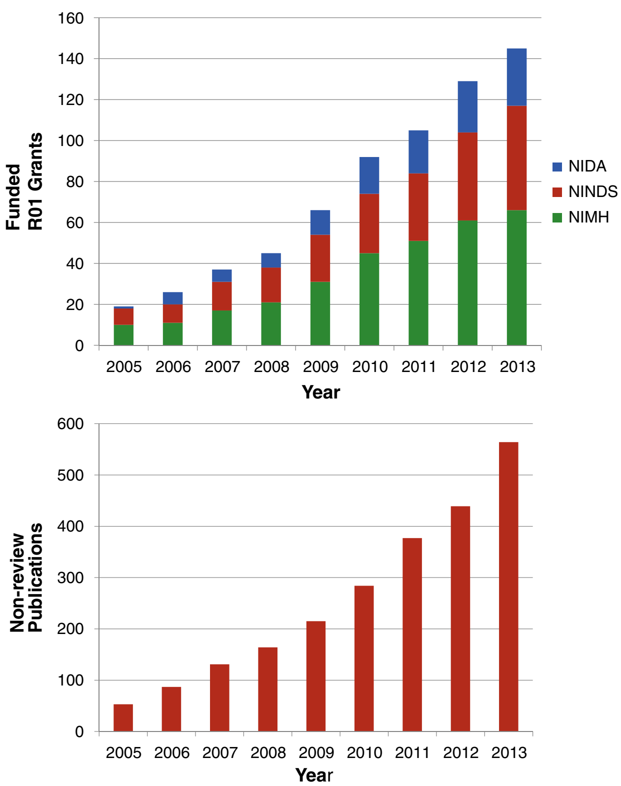

Fig. 1. (A) Increasing NIH-funded research in neuroepigenetics. The figure shows cumulative number of funded R01 epigenetic/epigenomic grants from 2005 to 2013 from 3 neuroscience-focused NIH institutes: National Institute on Drug Abuse, National Institute on Mental Health, and National Institute of 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 epigenome (Bernstein et al., 2010; Pollock et al., 2014; Satterlee et al., in press).

These reference epigenomes (http://www.roadmapepigenomics.org) are available to the research community, and prior publications have outlined how to access and visualize the data (Chadwick, 2012; Satterlee et al., in press). The reference data sets typically include DNA methylation assays, chromatin immunoprecipitation followed by sequencing for a core set of 6 post-translational histone modifications, and messenger RNA (mRNA) expression analysis. In some cases, tissues were also assayed for chromatin accessibility using DNAse I hypersensitivity assays. As indicated in Table 1, these assays can be used to help identify gene promoters, tissue-specific enhancers, or actively transcribed or repressed regions of the genome (Rada-Iglesias et al., 2011; Guenther et al., 2007; Kimura, 2013; Barski et al., 2007; Creyghton et al., 2010; Wagner and Carpenter, 2012; Grewal and Jia, 2007; ENCODE Project Consortium, 2012). Table 1 shows the assays used to interrogate a variety of neuroscience-relevant cells and tissues, including ES cells, ES-derived cells including neural progenitor cells, induced pluripotent stem (iPS) cells, postmortem fetal tissues (brain and spinal cord), and postmortem adult brain (angular gyrus, anterior caudate, cingulate gyrus, hippocampus, inferior temporal lobe, midfrontal lobe, and substantia nigra). The Human Epigenome Browser (http://epigenomegateway.wustl.edu/info/) provides an Ensembl-like visualization of these epigenomic data and can even display long-range genomic interactions (Zhou et al., 2011, 2013). The Roadmap Epigenomics Mapping Consortium has also developed a set of experimental protocols, assay standards, and data quality standards to aid researchers who wish to perform these types of assays in their own laboratories (http://www.roadmapepigenomics.org/protocols).

Additional data sets relevant for the neuroscience community have been generated by the International Human Epigenome Consortium (IHEC), Encyclopedia of DNA Elements (ENCODE), MethylomeDB, Brain Cloud, and Brainspan projects. As shown in Table 1, the IHEC is generating similar epigenomic data sets for several additional human brain samples including prefrontal cortex, glioblastoma, and malignant glioma (http://ihec-epigenomes.org/outcomes/datasets/). Similarly, the ENCODE project has data for several human postmortem brain regions (https://www.encodedcc.org) (Bernstein et al., 2012). As a part of the mouse ENCODE project, epigenomic and gene expression assays have been performed on forebrain, midbrain, hindbrain, and a number of other brain regions. MethylomeDB provides genome-wide DNA methylation data for selected mouse and human brain regions (http://www.neuroepigenomics.org/methylomedb/) (Xin et al., 2012). Two projects have collected longitudinal data that include fetal development. The Brain Cloud project showcases gene expression and DNA methylation data for postmortem human prefrontal cortices from fetal development through the aging adult (http://braincloud.jhmi.edu/) (Colantuoni et al., 2011), whereas BrainSpan provides transcriptome data for the developing human brain from prenatal through postnatal development (http://www.brainspan.org/). See Table 1 for details about these selected resources for neuroepigenomics.

These data sets can be exploited for a variety of scientific investigations. For example, epigenomic data have enhanced the analysis of Genome Wide Association Study (GWAS) (Ernst et al., 2011; Karczewski et al., 2013; Maurano et al., 2012; Pasquali et al., 2014; Trynka et al., 2013). In one study, researchers found that a significant percentage of disease-associated single nucleotide polymorphisms from GWAS occur in DNAse I–hypersensitive sites that are frequently associated with transcription factor binding (Maurano et al., 2012). This combined epigenomic and GWAS analysis can enable researchers to mine GWAS data sets for relevant gene variants that were not statistically nominated using standard analysis methods. Aberrant gene silencing or activation could explain some of the variability in GWAS findings and underscores the value of integrating epigenomic data with gene expression and genotype information. Remarkably, epigenomic and GWAS analyses can also be useful for predicting the cell types or tissues most likely to be impacted by a human disease phenotype (Maurano et al., 2012). For human brain

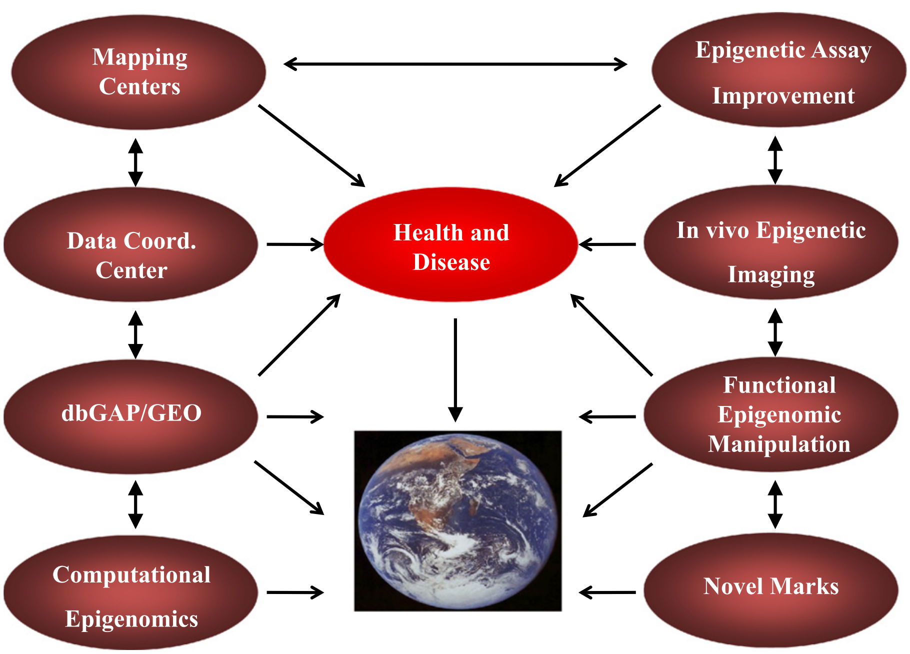

Fig. 2. NIH Common Fund (Roadmap) Epigenomics Program components. The reference epigenome mapping components included Mapping Centers, a Data Coordination Center, and databases where scientists can obtain this information (Gene Expression Omnibus and database of Genotypes and Phenotypes). A Computational Epigenomics component was recently funded to support computational investigations into important biological questions or diseases using reference epigenome mapping data. Three technology development initiatives endeavored to improve epigenome-wide assays, improve epigenetic imaging, and enable functional epigenetic manipulation. Two additional components included identification and characterization of novel epigenetic marks as well as investigations into epigenomic processes in human disease.

disorders, a comprehensive set of cell type and brain region–specific epigenomic data sets could enhance our ability to identify new gene variants involved in disease and help corroborate or even predict cell types or brain regions disrupted in human brain disorders.

Epigenomic assay and imaging tools

Some of the technologies developed through the NIH Roadmap Epigenomics Program have contributed greatly to our ability to perform epigenetics research. For example, the MethylC-seq whole genome bisulfite sequencing assay developed in the Ecker laboratory can be used to characterize *methylomes*, which are defined as all of the methylated and nonmethylated DNA cytosine residues in a cell type or tissue (Lister et al., 2009). This assay was used to pioneer the exploration of mammalian methylomes, and the publication describing it has been cited more than 1082 times as of June 2014. These researchers found that a significant fraction of DNA methylation occurred in a non-CG context in human ES cells and later revealed important DNA methylation differences between human ES cells and iPS cells (Lister et al., 2009, 2011). MethylC-seq and related methylome assays have been applied to a variety of mammalian cell and tissue types, including the brain, by the Roadmap Mapping Consortium (Table 1) as well as other researchers (Guo et al., 2014; Hovestadt et al., 2014; Varley et al., 2013). For example, during mammalian brain development, 5-methylcytosine and 5-hydroxymethylcytosine undergo profound reconfiguration (Lister et al., 2013). The development or improvement of other epigenomic assays has also significantly enhanced our ability to interrogate the epigenome. For example, padlock probes allow the interrogation of DNA methylation at investigator-selected specific regions of the genome without the need for expensive whole genome sequencing (Deng et al., 2009; Diep et al., 2012), whereas nanofluidic approaches have been used to investigate the epigenomic state of single molecules (Cipriany et al., 2010, 2012).

Epigenomic assays have been improving steadily; however, they typically provide measurements for only a single point in time. Our ability to observe chromatin features dynamically and in vivo has been quite limited. Researchers in the Lomvardas and Larabell laboratories are using soft x-ray tomography to investigate chromatin domains in mouse olfactory neurons. Each neuron expresses only 1 olfactory receptor; the remaining ones are silenced. These studies show that reductions in lamin b receptor levels lead to the aggregation of the silenced olfactory receptors in the nuclear periphery, whereas the active receptors lie within an active transcriptional zone (Clowney et al., 2012). In the future, soft x-ray tomography could be combined with a fluorescence complementation strategy to enable visualization of epigenetic regulators in vivo. Using this strategy, a fluorescent signal is only observed following interaction of 2 proteins labeled with partial complementary fluorescent domains. As these and related approaches improve our ability to image chromatin features in vivo (including noncoding RNAs, DNA binding proteins, and modified histones), it is hoped that neuroscientists will be able to use these tools to better investigate how chromatin territories are associated with gene regulation in the nervous system.

A critical consideration for brain researchers is our almost complete inability to obtain brain specimens from living humans for epigenomic analysis. Each mammalian cell type is believed to exhibit a distinct epigenome; thus, interrogation of the brain epigenomes of specific cell types may be essential for disease diagnosis. Some researchers funded through the Roadmap Epigenomic Program have been exploring methods for in vivo imaging of epigenetic enzymes to begin to overcome this obstacle. Specifically, these researchers are developing positron emission tomography (PET) radiotracers for class I and class III HDACs (Schroeder et al., 2013; Wang et al., 2013; Yeh et al., 2013). Development and pharmacokinetic optimization of these in vivo brain permeable PET ligands that monitor HDAC levels or activity in humans could improve accuracy of disease diagnosis, enable monitoring of the efficacy of epigenetic therapeutics, or enhance our ability to explore the effects of environmental factors such as psychosocial stress or substance abuse.

Disease investigations

Historically, cancer researchers have been the most strenuous pursuers of epigenetic studies. However, many scientists have wondered about the potential role of epigenetic regulation in other diseases and chronic conditions including those that impact the nervous system. To encourage work in this area, the Roadmap Epigenomics Program supported research projects that investigated potential epigenetic changes that underlie a number of diseases including autism, Alzheimer's disease (AD), schizophrenia, bipolar disorder, and substance use disorders. Some of the publications associated with these investigations can be found at the following Web site: http://www.roadmapepigenomics.org/publications.

Of particular interest are 2 recent epigenome-wide association studies that profile alterations in CpG methylation in postmortem brain regions of patients with AD. The investigators independently converged on several loci including CpG dinucleotides near *ANK1*, *RPL13*, *CDH23*, and *RHBDF2* (De Jager et al., 2014; Lord and Cruchaga, 2014; Lunnon et al., 2014). Interestingly, calculations by one group suggested that the 71 CpG variants they identified explained 28.7% of the variance in neuritic amyloid plaque burden, whereas all known AD gene variants from GWAS studies explained only 13.9% of the variance (De Jager et al., 2014; Lord and Cruchaga, 2014). Thus, epigenomic studies can reveal new candidate loci involved in brain diseases and suggest that DNA methylation may play a role in the onset or progression of AD.

Technology, tool, and research needs for neuroepigenomics

Although the field of neuroepigenomics has made great strides, it is clear that even greater progress has been hampered by specific obstacles that must be overcome. Briefly, we will describe some of the technology needs for neuroepigenomics, such as tools for epigenomic manipulation and robust single-cell assays. Similarly, resource and data set needs in neuroepigenomics include: expanding neuroepigenomic data sets, exploration of human neuroepigenomics using imaging technologies and postmortem brain resources, as well as the exploration and development of neuroepigenomic surrogates and biomarkers. Finally, there are some very exciting opportunities in neuroepigenomics research that should not be overlooked including exploration of the 4-dimensional (4D) structure of neuronal genomes, somatic mosaicism in neuronal cells, environmental epigenomics, investigation of mechanisms of intergenerational inheritance of behavioral phenotypes, and further development of epigenetic neurotherapeutics.

Technology needs for neuroepigenomics

Tools for cell-type–specific, locus-specific, and temporal manipulation of neuronal epigenomes

In the nervous system, optogenetic and chemogenetic strategies have been instrumental in enabling neuroscientists to explore questions regarding neuronal function (Chow et al., 2012; Dong et al., 2010; Fenno et al., 2011; Wess et al., 2013). However, long-term changes in neuronal function are associated with concomitant changes in gene expression via transcription factor and epigenomic

Table 1
Selected neuroepigenomics data resources.

DATA RESOURCE (tissue)	MOLECULAR FEATURE													
	DNA Methylation				Histone Tail Modifications							Expression		Chromatin Accessibility
	Context dependent repression or activation				Active		Active Promoter/TSS		Enhancer	Repressive		RNA transcripts		Regulatory DNA
	WGBS	MeDIP	MRE	RRBS	H3K36me3	H3K27Ac	H3K4me3	H3K9Ac	H3K4me1	H3K27me3	H3K9me3	RNA-seq	smRNA-seq	DNAse I HS
NIH Roadmap Epigenomics Program														
ES and iPS (cultured cells)														
H1 ES Cells														
H9 ES Cells														
Other ES Cells														
H1 Derived Neural Progenitors														
H9 Derived Neural Progenitors														
H9 Derived Neural Cultures														
iPS Cells (16 lines; Each line varies)														
Neurospheres (cultured cells)														
Cortex derived														
Ganglionic eminence derived														
Post-mortem Tissues														
Fetal brain 122 Days														
Fetal spinal cord														
Brain														
Angular gyrus														
Anterior caudate														
Cingulate gyrus														
Hippocampus														
Inferior temporal lobe														
Mid-frontal lobe														
Germinal matrix														
Substantia nigra														
International Human Epigenome Consortium														
Human Post-mortem Brain Tissues														
Glioblastoma														
Prefrontal cortex														
Malignant glioma														
ENCODE: Encyclopedia of DNA Elements														
Human														
Frontal cortex														
Cerebellum														
Astrocytes (cerebellum)														
Astrocytes (hippocampus)														
Occipital lobe														
Parietal lobe														
Diencephalon														
Choroid plexus epithelial cells	Methylarray and RRBS													
Temporal lobe														
Cerebellar granule cell														
Brain (age 66)	Methylarray and RRBS													
Mouse														
Forebrain														
Midbrain														
Hindbrain														
Brain														
Cerebellum														
Cortical plate														
Frontal cortex														
Telencephalon														
Olfactory bulb														
MethylomeDB														
Tissues														
Human prefrontal and auditory cortices	Methyl-MAPS													
Mouse forebrain	Methyl-MAPS													
Brain Cloud Project														
Tissues														
Longitudinal post-mortem human dorsal lateral prefrontal cortex (fetal through adult)	Methylation beadchip											Microarrays		
BrainSpan														
Tissues														
Longitudinal post-mortem developing human brain (prenatal through postnatal)														

regulation. Our ability to investigate long-term gene expression changes in the nervous system via manipulation of the epigenome and the associated expression of genes has lagged in comparison; most strategies use small-molecule modulators (e.g., HDAC inhibitors) or RNA silencing methods. These approaches provide limited temporal control and impact many cell types and genomic loci. The ability to conduct spatiotemporal manipulation in vivo would enable researchers to probe the effects of locus-specific changes to the epigenome in neuronal or glial cells in a reversible manner. Some researchers are already making important strides in this direction. For example, Feng Zhang and colleagues have developed first-generation genetic tools called *LITES* (light-inducible transcriptional effectors) that enable researchers to optically control transcriptional and epigenetic states (Konermann et al., 2013).

To address this critical technology gap, the Roadmap Epigenomics Program is supporting the development of a variety of robust tools and technologies in this area. These include manipulating the epigenome at specific loci using genome editing technologies (e.g., transcription activator-like effectors (TALES), clustered regularly interspaced short palindromic repeats (CRISPR)), temporally regulating the epigenome via opto-epigenetic or chemo-epigenetic strategies, and exploiting available genetic tools to achieve cell-type specificity in key model organisms. It will be of great interest to see what fundamental questions in neuronal gene regulation can be answered using these platforms.

Single-cell analyses

During normal growth and differentiation, cells must tightly control if, when, and where gene expression occurs. Epigenetic marks are critical in ensuring that the correct gene expression patterns are maintained and transmitted to the next generation of cells. Each type of cell displays a distinct epigenomic profile that reflects its past experiences and developmental potential (Gifford et al., 2013; Zhu et al., 2013). This epigenetic profile is read by the transcriptional machinery, creating a unique gene expression signature. Current technologies permit epigenetic marks to be studied in extracts from large populations of cells, yet epigenetic gene regulation occurs within single living cells (Wills et al., 2013). Distinct microenvironments within cellular niches likely influence the molecular and cellular phenotypes of different cell types. Induced pluripotent stem (iPS) cells provide a striking example of this cellular diversity, because only some of the precursor cells have the necessary plasticity to de-differentiate into a pluripotent state (Smith et al., 2010). This ability to transform from a differentiated state to an iPS cell may reflect the individual epigenomes of these cells. Unfortunately, current technologies do not permit analysis of a given epigenomic modification in a single cell at a global scale. This challenge is especially acute in learning and memory studies, where epigenomic changes may occur in response to neural activity (Zovkic et al., 2013). Although improvements have allowed glimpses into the DNA methylation and gene expression profiles at the single-cell level, more work must be done to enable assay of histone modifications and other chromatin features at the single-cell level (Hayashi-Takanaka et al., 2011; Iourov et al., 2012; Patel et al., 2014; Shalek et al., 2014; Smallwood et al., 2014). There is great hope that the Common Fund Single Cell Analysis program (https://commonfund.nih.gov/Singlecell) will facilitate the development of platforms with the capability of studying the epigenomes and gene expression profiles of individual cells.

Resource and data set needs for neuroepigenomics

Expanded neuroepigenomic data sets

Although the Roadmap Epigenomics Program and other projects have generated valuable epigenomic data sets, systematic efforts to apply molecular phenotyping strategies to the nervous system are lacking. A comprehensive atlas of molecular phenotypes that spans a wide variety of brain regions, brain cell types, and developmental stages for both human and mouse is crucial for understanding the molecular etiology and ontology of neurological diseases. Key molecular phenotypes should encompass chromatin features (e.g., histone or DNA modifications), transcription factor binding sites, and mRNA or binding sites, and RNA expression whenever possible. The histone variant H2A.Z was recently shown to play a role in memory consolidation, suggesting that histone variants would be an important molecular feature to assay (Zovkic et al., 2014). Secondary molecular phenotypes that could be assayed include modified RNAs, circular RNAs, and higher-order chromatin structure. Ideally, these molecular phenotypes will be connected whenever possible to brain cell morphology, connectivity, and electrophysiological measures. In addition to helping elucidate the ontology of disease, molecular phenotypes will aid in the interpretation of GWAS and other data sets that investigate psychiatric diseases, as well as help to delineate candidate cell-type–specific molecular targets for the development of small-molecule therapeutics.

Human brain disease epigenomics: postmortem and imaging resources

Investigation of the human brain epigenome is a necessary step to understanding long-term changes in gene regulation and gene expression that may be associated with neurodevelopmental or neuropsychiatric disorders. It is also important to determine the extent to which the molecular pathways that regulate brain phenotypes in rodent and non-human primate models are recapitulated in humans. For studies exploring the mechanisms of disease processes, it is of critical importance to study the epigenomic changes that occur in the tissue and cell types specifically associated with that disease. Yet unlike diseases involving blood or skin, epigenomic assay of the human brain is particularly problematic. It is uncommon to obtain fresh surgical specimens, and, even when available, these brain samples are typically associated with a pre-existing disease state.

Post-mortem human studies are therefore essential for investigating epigenomic changes associated with brain diseases. However, alterations occurring at or near the time of death (e.g., changes in oxygen levels or brain pH) can negatively impact the stability and levels of molecular brain phenotypes. Minimization of the interval between death and brain collection is essential for maximal preservation of

This table highlights resources generated by several large-scale projects of relevance to neuroepigenomics researchers as of September 2014. Cell or tissue types are shown on the left, whereas epigenomic modifications, putative functions, and assay type are shown at the top (see text for further details). The upper section of the table describes resources generated by the NIH Roadmap Epigenomics Program (www.roadmapepigenetics.org) (Bernstein et al., 2010). This is followed by data from the IHEC (http://ihec-epigenomes.org/research/cell-types) as well as the ENCODE project (https://www.encodedcc.org) (Bernstein et al., 2012). Please note that the Roadmap Epigenomics Program and ENCODE are both IHEC members, so the IHEC data sets shown in this table were generated by the other IHEC members. Data from the MethylomeDB (http://www.neuroepigenomics.org/methylomedb/), Brain Cloud (http://braincloud.jhmi.edu/), and BrainSpan (http://www.brainspan.org) projects are also shown (Colantuoni et al., 2011; Miller et al., 2014; Xin et al., 2012). A blue square indicates the data are currently available, a green square indicates assays are in progress, whereas a white square indicates no data are available for a given assay for this cell or tissue type. Histone modifications (e.g., H3K36me3) were assayed by chromatin immunoprecipitation followed by sequencing.

Key: DNase I HS, DNase I hypersensitivity assay; MeDIP, methylated DNA immunoprecipitation sequencing;, Methyl-MAPS, methylation mapping analysis by paired-end sequencing; MRE, methylation-sensitive restriction enzyme sequencing; RRBS, reduced representation bisulfite sequencing; smRNA-seq, small RNA sequencing; TSS, transcription start site.

molecular phenotypes (Birdsill et al., 2011). In general, DNA methylation marks can be fairly well preserved in postmortem brain samples, and mRNA profiling has been performed successfully (Colantuoni et al., 2011; Ernst et al., 2008; Kang et al., 2011; Twine et al., 2011). However, histone modifications and other chromatin features may be less stable, and some classes or subsets of RNAs may have differential sensitivity to the postmortem interval (Barrachina et al., 2012). Animal studies have been used to examine alterations in mRNA expression associated with the interval between postdissection and tissue preservation. Depending on the length of the interval, clear gene expression signatures emerge both temporally and functionally (e.g., hypoxia inducible genes, heat shock proteins, stress-response genes etc.) (Catts et al., 2005; Durrenberger et al., 2010; Sanoudou et al., 2004; Trotter et al., 2002; Zhao et al., 2006). To better address the extent to which fresh and postmortem human tissues differ, freshly resected normal or diseased tissue with minimal time to preservation can be compared to more widely available postmortem human brain tissue. Comparisons of gene expression profiles for these 2 conditions are currently under way for human non-brain tissue in the Common Fund Genes, Tissue, and Expression (GTEx) program (http://www.gtexportal.org/home/). One confounding issue is the lack of appropriate controls with human postmortem research due to unique genotypes and environmental exposures. However, postmortem brain studies have been successful for helping understand human brain function and disorders such as autism and AD (Colantuoni et al., 2011; Davies et al., 2012; De Jager et al., 2014; Kang et al., 2011; Lunnon et al., 2014; Mill et al., 2008; Twine et al., 2011; Voineagu et al., 2011).

An alternative possibility for exploring the human brain epigenome is the use of in vivo imaging approaches. As described earlier, PET ligands can be used to measure the amount and activity of certain HDACs. Although this does not reveal epigenomic information at the single-gene level or for an individual cell type, these approaches may have value for disease diagnosis and measurement of therapeutic efficacy. The development of in vivo molecular imaging approaches to monitor a greater variety of epigenomic readers, writers, and erasers as well as approaches that enable more refined measurement of epigenomic features would revolutionize neuroscience research.

Neuroepigenomic surrogates and biomarkers

Given our inability to obtain human brain samples from living patients, another approach of great potential clinical utility is to identify robust peripheral indicators that closely reflect both the phenotypic and epigenomic changes identified in disease-relevant brain cells. These peripheral indicators could include accessible cell types such as blood cells, skin, buccal samples, olfactory epithelia, or even body fluids. Both animal and human studies could be used to advance our knowledge in this area. Animal studies would enable experimental control of genotype and environment and would provide a more detailed understanding of how epigenomic events in the brain are correlated with molecular phenotypes in more accessible cell types. Parallel human experiments could be carried out using postmortem brain and peripheral tissues from the same donor. The Common Fund Genes, Tissue, Expression (GTEx) program (http://www.gtexportal.org/home/) will in part address the latter scientific question, because one goal of this program is to capture genotype and RNA-seq information for 50 tissues from each individual donor. When the GTEx program is completed, it is expected that data for 900 individual donors will be available. Epigenomic and other molecular phenotype assays will be added to the GTEx data sets for some tissues, which may help to identify the surrogate tissues most salient for brain investigations (Lonsdale et al., 2013). However, a surrogate tissue strategy may not yield useful biomarkers for all neurological disorders. A recent AD epigenome-wide association study reports that the DNA methylation state of surrogate tissues (cerebellum and whole blood) does not recapitulate disease-relevant DNA methylation differences in brain tissues impacted by AD (superior temporal gyrus and prefrontal cortex) (Lunnon et al., 2014).

Body fluids are another potential source for generation of informative biomarkers. Extracellular vesicles and proteins associated with extracellular RNAs, exRNAs, appear to move through the body and act in ways analogous to the endocrine system (Christianson et al., 2014; Lai and Breakefield, 2012; Yang et al., 2011). The best current candidates to test for extracellular RNA content include cerebral spinal fluid (CSF) and blood serum, although other bodily fluids could provide additional informative biomarkers (Revenfeld et al., 2014; Saman et al., 2012). Studies aimed at generating methods to purify extracellular vesicles derived solely from the brain could, theoretically, prove an exceptionally useful source of biomarkers for brain disorders.

Additional opportunities in neuroepigenomic research

The neuronal genome: 4D structure

Evidence from imaging, as well as genome conformation assays, indicates that cellular genomes have complex and dynamic 3-dimensional structures (Clowney et al., 2012; Fullwood et al., 2009; Lieberman-Aiden et al., 2009; Mitchell et al., 2014). Although our knowledge of the structure of neuronal or glial genomes is poorly understood, recent studies demonstrate that olfactory neurons display a complex genomic architecture that differs between olfactory neuron types depending upon the gene expression status of individual olfactory receptors (Clowney et al., 2012). Furthermore, adenosine triphosphate–dependent chromatin remodeling proteins such as Brg1-associated factor 53b (BAF53b) have neurodevelopmental, synaptic plasticity, and memory functions, suggesting that genome conformation plays an important role in the nervous system (Staahl and Crabtree, 2013; Vogel-Ciernia et al., 2013; Yoo et al., 2009). However, a systematic investigation of the 4D structure of the genome conformation of distinct neuronal cell types is needed to understand the extent of the relationship between genome conformation and neuronal function. The recently launched Common Fund 4D-Nucleome program will begin to address some of the scientific questions in this area (http://commonfund.nih.gov/4Dnucleome/index). Studies aimed at gaining a deeper understanding of how transcription factor binding, epigenomic modifications, and 4D nuclear architecture correlate with gene expression would yield important insights into the complexities and dynamics of gene regulation in normal tissues and during disease processes.

Brain somatic mosaicism and epigenomic regulation

It is often assumed that the genomes of all of our cells are identical. However, this is always the case. For example each haploid germ cell contains a distinct genome, whereas every B cell and T cell undergoes a unique recombination event that generates a repertoire of immune cells that are poised to attack different types of antigens (Alt and Baltimore, 1982; Roth et al., 1992). It is becoming increasingly clear that as cells in the nervous system differentiate, they may undergo genomic rearrangements or acquire copy number or other structural variations, which ultimately can lead to significant levels of somatic mosaicism in the brain. For example, Jerold Chun and colleagues demonstrated that distinct cells from the nervous system differ dramatically in their complement of chromosomes (Bushman and Chun, 2013; Rehen et al., 2005; Westra et al., 2010). Furthermore, L1 retrotransposons can become active, jumping into different chromosomal locations within the brain (Erwin et al., 2014; Muotri et al., 2010; Reilly et al., 2013; Singer et al., 2010). In some organisms, epigenomic regulation modulates transposon activity (Creasey et al., 2014; Lorenz et al., 2012). Interestingly, MeCP2, which is mutated in patients with Rett syndrome (an autism spectrum disorder), can regulate L1 transposition (Amir et al., 1999; Muotri et al., 2010). MeCP2 is known for its role in regulating epigenetic processes; it binds 5mC residues, as well as the oxidized derivative, 5hmC. 5-hydroxymethylcytosine levels are higher in the brain than any other tissue (Kriaucionis and Heintz, 2009), and it would be intriguing to understand the potential roles that 5mC and 5hmC may play in retrotransposon activation.

In addition to somatic mosaicism on the genomic level, females display partial somatic mosaicism on an epigenetic level due to X-chromosome inactivation. X-inactivation is apparently random and leads to clustering of daughter cells; some will inactivate the maternal X chromosome, whereas others will inactivate the paternal X chromosome. DNA methylation, histone code changes, and expression of ncRNAs mediate this process (Gendrel and Heard, 2014). X-inactivation can contribute to disease phenotypes in Rett syndrome (Braunschweig *et al.*, 2004) and other neurobehavioral disorders (Lasalle and Yasui, 2009), where the males are often more highly affected than the females. In addition, regions subject to genomic imprinting also display localized somatic mosaicism at the epigenetic level, as the epigenotypes on the maternal alleles differ from the paternal alleles. Mistakes in this process lead to several imprinted disorders, including Prader-Willi syndrome and Angelman syndrome (Horsthemke and Wagstaff, 2008; Reis et al., 1994). Individuals affected by Prader-Willi syndrome exhibit specific behavioral phenotypes that include hyperphagia and obsessive-compulsive disorder (Saitoh *et al.*, 1997), whereas those affected by Angelman syndrome display severe developmental delay, an easily excitable personality with an inappropriately happy affect, profound movement and balance deficits, as well as seizures (Lossie *et al.*, 2001). One important area for future research is to explore the extent to which somatic mosaicism, at the genomic and epigenomic levels, occurs in the brain and whether or not it underlies neurodevelopmental, neuropsychiatric, or substance abuse disorders.

Environmental epigenomics investigations

Environmental exposures such as prenatal environment, early childhood or adult trauma, psychiatric medications, or exposure to substances of abuse are associated with epigenomic alterations in particular brain cell types (McGowan et al., 2009; Miller et al., 2010; Nestler, 2014; Pena et al., 2014; Rutten and Mill, 2009; Satterlee, 2013; Toffoli et al., 2014; Zhang et al., 2013). Although several studies have documented these changes, they have not been systematically investigated. In most cases, it is unclear how long these presumed environmental epimutations perdure and what molecular pathways are involved in maintaining or reversing these changes (Berger et al., 2009; Guerrero-Bosagna et al., 2013; Robison and Nestler, 2011; Zhang et al., 2013). One approach to address these questions would be to perform tightly controlled, systematic experiments in which genetically identical animals are quantitatively exposed to environmental stressors, such as psychosocial stress or substances of abuse, and then phenotyped for a suite of epigenomic brain features at different time points. These studies would determine the long-term plasticity and persistence (days, weeks, months) of brain epigenome changes and enable researchers to begin to functionally characterize the biological processes involved in formation, maintenance, or erasure of brain epigenome features resulting from environmental exposures.

Mechanisms of intergenerational inheritance

There is evidence that exposure to certain chemical toxins, social environments, or nutrient levels can, in some cases, lead to persistence of particular phenotypes in subsequent generations. These phenotypes appear to be transmitted without an apparent DNA mutation and can be transmitted even when subsequent generations have not been exposed to the environmental factor (Carone et al., 2010; Champagne, 2008; Crews et al., 2012; Skinner et al., 2008; Weaver et al., 2004; Youngson and Whitelaw, 2008). For example, endocrine disruptor (bisphenol A) exposure can lead to behavioral effects on social recognition in subsequent generations (Rissman and Adli, 2014). Work from Chris Pierce and colleagues showed that male rats that self-administered cocaine had sons, but not daughters, that were resistant to the acquisition of cocaine self-administration and that this phenotype was correlated with *Bdnf* promoter histone-3 acetylation in sperm from cocaine-exposed fathers (Vassoler and Sadri-Vakili, 2014; Vassoler et al., 2013). Exposure to tetrahydrocannabinol (THC), morphine, nicotine, or methamphetamine also appears to impact phenotypes in subsequent generations (e.g., heroin seeking, anxiety), although the mechanisms by which this occurs remain to be elucidated (Byrnes et al., 2011; Itzhak et al., 2014; Rehan et al., 2013; Szutorisz et al., 2014; Zhu et al., 2014). Chronic stress exposure can lead to increased anxiety and other behavioral phenotypes in subsequent generations (Saavedra-Rodriguez and Feig, 2013), whereas early life trauma in mice impacts metabolic and behavioral phenotypes in the next generation and may be transmitted through sperm RNAs (Gapp et al., 2014). There has even been a report that a parental olfactory experience (fear conditioning paired with the odorant acetophenone) is associated with increased DNA methylation of the acetophenone odorant receptor in sperm. The resulting progeny exhibited increased sensitivity to acetophenone (Dias and Ressler, 2014).

Future studies aimed at validating claims of intergenerational inheritance are critical to ensure that any reported findings are robust and reproducible in different laboratories. It will also be crucial to identify the molecular mechanisms by which changes or risk factors are transmitted to and manifested in subsequent generations. It is often hypothesized that germline transmission of epigenetic features accounts for the persistence of some phenotypes over multiple generations, so it will be important to investigate the association of germline epigenetic modifications (and any RNAs that might influence these modifications) with offspring phenotype. It will also be critical to explore alternate hypotheses, including neurobehavioral or societal transmission or transmission through infectious agents such as viruses or the parental microbiome (Youngson and Whitelaw, 2008). Despite these caveats, this area of research has great relevance to disease prevention, because knowledge that a particular environmental exposure could lead to phenotypes in subsequent generations would have profound public health implications.

Epigenetic neurotherapeutics

If a disease is caused by the presence of a particular gene variant or mutation, then gene therapy approaches may ultimately be necessary to correct the disorder. However, epigenetic changes are inherently more plastic than DNA-based mutations and thus should be more readily impacted by small-molecule therapeutics (Haberland et al., 2009; Haggarty and Tsai, 2011). We will briefly touch on 2 areas of epigenetic neurotherapeutic investigation: HDAC inhibitors and histone acetylation readers such as BRD4. Histone deacetylase inhibitors (HDACis) have been used to treat T-cell lymphoma as well as bipolar disorder, migraines, and seizures (Bialer and Yagen, 2007; Mack, 2006; Sharma et al., 2010). In animal models, HDACis can positively influence depression as well as cognitive defects in an AD model (Fischer et al., 2007; Kilgore et al., 2010). For substance abuse, prolonged inhibition of class I HDACs with MS-275 blocks cocaine locomotor sensitization (Kennedy et al., 2013). The HDAC inhibitor sodium butyrate has been shown by Marcelo Wood and colleagues to facilitate extinction of cocaine-associated cues (Malvaez et al., 2010), suggesting that HDACis or perhaps other epigenetic therapeutics could be particularly efficacious if used in concert with behavioral therapies.

One limitation of HDACis is that they are pleiotropic and can impact many different cells and genetic loci. It is known that certain epigenetic "reader" proteins can bind to a subset of histone modifications. Thus, researchers targeted BRD4, which can bind to a subset of acetylated lysines, in an attempt to generate therapeutics with more specificity than HDACis (Dey et al., 2003). JQ1, a small-molecule inhibitor of BRD4, has promise as a potential treatment for acute myeloid leukemia (AML) (Filippakopoulos et al., 2010; Zuber et al., 2011). Researchers are also beginning to target histone methylation enzymes as well as other epigenetic "readers, writers, and erasers" to treat a variety of diseases including nervous system disorders (Fiskus et al., 2009; Grant, 2009; Hamada et al., 2010). It would be of great value to systematically develop small-molecule modulators of epigenetic readers, writers, and erasers to (1) to serve as chemical probes to investigate the functions of these enzymes, (2) for development into ligands for in vivo imaging studies, and (3) as potential lead compounds for future therapeutic development (Arrowsmith et al., 2012). Some work in this area is currently being pursued by the Structural Genomics Consortium http://www.thesgc.org/epigenetics.

Summary

As the field of neuroepigenomics matures, it is likely to produce revolutionary new insights into the regulation of gene expression in neurodevelopmental and neuroplastic processes in cells that can persist for decades. It will also likely yield new and perhaps paradigm-shifting opportunities for the diagnosis, treatment, and prevention of diseases of the nervous system. In this review, we described a few of the tools and technologies available to neuroepigenomics researchers currently, including reference epigenome maps for nervous system cells and tissues, improved epigenomic assays, improved ways to monitor epigenetic enzymes and changes in vivo, and a deeper understanding of epigenetic mechanisms in nervous system disorders.

We have also delineated some of the obstacles and opportunities in this area including: improved tools for manipulating epigenetic processes, additional reference epigenomes for the nervous system, improved technologies for single-cell analyses, validation of animal epigenetic studies using human postmortem tissue, investigation into the potential of surrogate tissues and body fluids as biomarkers, and exploration of the 4-D chromatin structure of nervous system–relevant cell types. Another important area for future work is to better understand how acute or chronic environmental exposures (e.g., early life stress, drugs of abuse, environmental toxins, diet, inflammation, aging) impact the brain epigenome both somatically (including the somatic genome) as well as in subsequent generations.

There are 3 additional gaps and opportunities in neuroepigenomics that should be mentioned briefly. The first is that the computational needs for neuroepigenomic research are challenging, and it will be important to develop user-friendly computational tools to enable researchers to mine and exploit epigenomic information effectively. Secondly, the typical graduate or postdoctoral training program for neuroscientists differs greatly from that of epigenomicists. The development of explicit training programs in neuroepigenomics would help researchers be able to move more seamlessly between these 2 scientific "worlds" and better train the next generation of neuroepigenomicists. Finally, as neuroepigenomic tools and resources improve, it is essential that individual researchers continue to initiate cutting-edge explorations into the epigenetic mechanisms of nervous system disorders. Without an understanding of these mechanisms at a deep level, it will be impossible to improve the prevention, diagnosis, and treatment of nervous system disorders due to epigenetic dysregulation.

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