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Chromatin in nervous system development and disease

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Abstract

Epigenetic regulation of gene expression is critical during development of the central nervous system. Pathogenic variants in genes encoding epigenetic factors have been found to cause a wide variety of neurodevelopmental disorders including Autism spectrum disorder, intellectual disability, and epilepsy. Cancers affecting neuronal and glial cells in the brain have also been shown to exhibit somatic mutations in epigenetic regulators, suggesting chromatin-based links between regulated and dysregulated cellular proliferation and differentiation. In this special issue, six articles review recent discoveries implicating epigenetic modifiers in normal and disease states affecting the nervous system, and the underlying mechanisms by which these modifiers function. Two articles present new information about roles for chromatin regulators in nervous system development and cancer. Together, these manuscripts provide a concise overview of this rapidly growing field. In this introduction, we briefly summarize themes presented in the issue, and pose questions for ongoing research and discovery.

1. Introduction and historical comments

Developmental disabilities including Autism Spectrum Disorder and Intellectual Disability affect 1 in 7 children in the United States (Boyle et al., 2011). In the brain, a wide variety of neuronal and non-neuronal cell types must be accurately formed and connected in order for organisms to adapt their behavior to an ever-changing environment. These various cell types have to be generated at the proper time and in the right place for normal motor, sensory, and cognitive abilities. First, self-renewal/proliferation of progenitor pools during embryogenesis ensures an adequate supply of stem cells, and these cells then migrate to specific destinations while they undergo differentiation. Once the neurons and glia are placed in their respective niches and proper connections are made, the brain can begin to integrate sensory inputs. These sensory inputs, i.e. experiences, help generate neuronal networks through neurite/synaptic organization and remodeling, ultimately leading to appropriate wiring and brain connectivity. Even subtle impairments in these developmental processes can lead to poor outcomes, such as neurodevelopmental disorders and brain tumors. Impaired gene

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regulation due to abnormalities in chromatin has emerged as a primary factor in neurodevelopmental disorders, and is therefore the focus of this special issue.

At every step of the intricate process of brain morphogenesis, exquisite spatio-temporal control of gene expression is crucial. Transcriptional regulation in eukaryotes occurs on chromatin, not on naked DNA. The term chromatin, ‘stainable material’, was coined in the late 19th century to describe the thread-like cytological structures that are divided into the two daughter nuclei during cell division (Paweletz, 2001). The basic unit of chromatin is the nucleosome, which consists of two copies of each core histone protein H2A, H2B, H3, and H4, wrapped with approximately 146 bp of DNA into a disc-like structure (Luger et al., 1997). Nucleosomes are connected through linker DNA and/or linker histone H1 in a bead-on-string fashion and folded into higher-order structures such as 30-nm fibers (Andrews and Luger, 2011). Both DNA and histone proteins are subjected to a variety of post-translational modifications (methylation, acetylation, ubiquitination, sumoylation, etc.), thereby serving as a signaling platform for nuclear events such as transcription, DNA repair, and chromosome segregation. Complex signaling on DNA and histones culminates in recruitment of ATP-dependent chromatin remodelers that alter and/or maintain higher order chromatin compaction and relaxation. Non-coding RNAs, such as long-noncoding RNAs, enhancer RNAs, and microRNAs are also increasingly recognized as integral elements for chromatin and gene regulation. Notably, brain cells are not exempt from this basic architecture and regulatory chromatin mechanism; instead, chromatin is the essential platform upon which the intricate temporal dynamics and spatial diversity of gene expression are generated during brain development.

Chromatin regulatory proteins are involved in most, if not all, key phases of brain development, from neural progenitor proliferation to experience-driven synaptic organization in both neurons and non-neuronal cells. In this issue, six review articles and two original research articles comprehensively illustrate how specific classes of chromatin regulators and chromatin regulatory pathways contribute to brain development, and how pathogenic variants in genes encoding chromatin modifiers lead to disrupt brain development and cancers.

2. Chromatin in neuronal and glial development

Proper development of neurons and glia involves a highly regulated series of cellular lineage decisions in discrete areas of the nervous system. In the central nervous system, neural stem cells first give rise to neurons through coordinated activities of pioneer and proneural transcription factors. Neurogenesis is followed by gliogenesis and formation of astrocytes and oligodendrocytes. Wijayatunge et al. (in this issue) provide new research on the histone H3 lysine 27 (H3K27) demethylase Kdm6b (Jmjd3), which was previously shown to promote cellular differentiation. Their study shows that loss of Kdm6b impairs late, but not early, events in cerebellar granule neuron differentiation. Koreman et al. (in this issue) review oligodendrocyte maturation and the epigenetic mechanisms that regulate oligodendrocyte specification, differentiation and myelination, including histone methylation, acetylation, chromatin remodeling, microRNAs, and noncoding RNAs.

Neural plasticity, learning, and memory all involve changes in synaptic architecture and neurotransmission, and have been shown to be associated with changes in RNA transcript and protein abundance (Leighton et al., 2017). Madabhushi and Kim (in this issue) provide a historical overview of major developments in the discovery of immediate-early genes, cis-acting elements within immediate-early gene promoters, signaling pathways that govern gene induction, and chromatin remodeling enzyme functions in these processes. They also highlight neuronal activity-dependent gene expression controls, and roles for enhancer RNAs (eRNAs), pausing of RNA polymerase II (RNAPII), enhancer-promoter communication, and activity-induced DNA breaks. These activity- and transcription-dependent processes give rise to dynamic RNA and proteins states in neurons, and often involve changes in splicing or use of micro-exons. Porter et al. (in this issue) provide a comprehensive overview of neuron-specific splicing events, including microexon usage, and describe several examples of human neurodevelopmental disorders that are caused by aberrant alternative splicing.

3. Human phenotypes related to chromatin dysregulation

Impaired chromatin regulation is not a new concept in the pathophysiology of developmental brain disorders. In 1999, pathogenic variants in *MECP2*, which encodes Methyl-CpG binding protein, were identified as responsible for Rett syndrome (Wan et al., 1999), which presents with severe cognitive deficits accompanied with regressive motor coordination. In 1995, Alpha-thalassemia/mental retardation syndrome, X-linked (ATR-X syndrome), was found to be caused by pathogenic variants in the *ATRX* gene, encoding an ATP-dependent chromatin remodeler (Gibbons et al., 1995). Both *MECP2* and *ATRX* were identified by classic linkage analyses in relatively rare families. In the past 10 years, clinical genetics has experienced rapid growth in the number of newly identified genes that contribute to neurodevelopmental disorders. The availability of chromosomal microarray and next-generation sequencing technologies, including whole exome and whole genome sequencing, has identified many additional developmental brain disorders caused by pathogenic variants in genes encoding chromatin regulatory genes. There are now hundreds of known Mendelian forms of autism spectrum disorder, intellectual disability, and epilepsy, and more yet to be discovered.

Chromatin remodelers (see the articles by Moccia and Martin, and Goodwin and Picketts, in this issue) comprise a large fraction of genes mutated in neurodevelopmental disorders, likely due to their early and broad roles in establishment of cellular lineage and fate decisions. These same genes are also being implicated in brain cancers. Yi and Wu (in this issue) review recent data showing that medulloblastoma, the most common brain malignancy of childhood, is associated with somatic mutations in epigenetic regulators. Patterns of gene expression dictate cellular identity, and must be both dynamic during cellular differentiation and resistant to change during mitosis. Histones and their associated post-translational modifications are attractive candidates for mediating gene expression changes, since they are readily and accurately replaced after cell division and also correlate with active or repressive states at promoters and enhancers. Thus, enzymes that modify (add or remove) histone marks, remodel chromatin, regulate transcriptional states, control splicing, or modulate enhancers have all been associated with neurodevelopmental disorders.

Two classes of chromatin remodelers, the ISWI (Imitation SWItch) and Chromodomain Helicase DNA binding protein family (CHD) are of particular interest given their broad roles in regulating neural stem cell proliferation and differentiation. Goodwin and Picketts (in this issue) provide a comprehensive review of ISWI chromatin remodelers including SNF2H and SNF2L, both of which are implicated in neurodevelopmental disorders. In addition, they highlight SWI/SNF related, Matrix associated, Actin dependent Regulator of Chromatin, subfamily A (SMARCA) proteins and their functions in neurodevelopment. SMARCA proteins have helicase and ATPase activities which target nucleosomes and lead to their displacement or repositioning on chromatin. Moccia and Martin (in this issue) discuss chromatin remodelers in general, with a focus on Trithorax proteins. Trithorax proteins, originally described in *Drosophila*, counteract Polycomb repressors and generally act as transcriptional activators. Included in the broad class of Trithorax proteins are several CHD proteins which, in mammals, are divided into 3 separate classes on the basis of their protein domains. Pathogenic variants in CHD7, a member of the third CHD subfamily, cause the autosomal dominant disorder CHARGE syndrome, characterized by ocular Coloboma, Heart malformations, Atresia of the choanae, Retardation of growth and development, Genital hypoplasia, and Ear abnormalities including deafness and vestibular disorders. Latcheva et al. provide evidence that loss of kismet, the *Drosophila* orthologue of mammalian CHD7, disrupts development of the neuromuscular junction. They further show that histone deacetylase (HDAC) inhibitors suppress kismet mutant phenotypes including motor deficits and abnormal neurotransmission. In addition, Koreman et al. (in this issue) summarize recent evidence that CHD7 and other histone modifying enzymes, including HDACs, regulate oligodendrocyte lineage development. Together, these articles illustrate the critical links between chromatin remodeling, human neurodevelopmental disorders, and epigenetic modifications that drive neuronal and glial fates.

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