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Review article

Exploring the role of the epigenome in multiple sclerosis: A window onto cell-specific transcriptional potential

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ABSTRACT

The field of epigenomics involves the study of chromatin, the three dimensional complex of DNA, protein and non-coding RNAs that determines the accessibility of DNA by the transcriptional machinery. The epigenome varies from cell to cell and reflects the effect of external stimuli on cell fate and cell state. Thanks to emerging platforms and analysis methods, the systematic characterization of chromatin conformation throughout the genome has begun and has yielded several reference epigenome maps for a growing number of cell types. Such maps are enabling insights into the correlation architecture of different epigenomic marks: a number of discrete chromatin states are found across different cell types. The combination of these reference maps and robust platforms for genome-wide data generation has introduced a new era in which studies of human disease are becoming feasible. Little is known about the role of the epigenome in MS, but it is likely that, as in other inflammatory disease, susceptibility factors and events along the course of the disease will alter the chromatin state of different cell types in patients with MS. Here, we review different strategies for the characterization of the epigenome and how these strategies could be used to implement new studies to explore how alterations of chromatin architecture establish a dysregulated transcriptional state in the context of MS.

Contents

1. Introduction

Conrad H. Waddington first coined the term epigenetics in 1940s, to integrate genetics with embryology (Waddington, 1939). His idea was

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to provide insight into gene–environment interactions that influence development and embryology. Since then the definition of epigenetics has evolved to include molecular mechanisms involved in this phenomenon (Zhang & Meaney, 2010; Ptashne, 2007). Here, we define epigenomics as the study of chromatin architecture, the higher order structure of DNA complexed with histones, transcription factors, non-coding RNAs and other molecules. Chromatin structure does not alter the DNA sequence but does affect the transcription of the underlying DNA sequence. Chromatin can be in an open or closed conformation, and many protein or DNA modifications have been found to correlate with the state of a DNA segment. These modifications include, among others, DNA methylation and histone modifications such as acetylation, methylation and phosphorylation. Individual cells, despite having the same genomic sequence within an individual organism, exhibit different epigenomic profiles depending on their developmental stage, tissue type, cell type and state of the cell (Bernstein et al., 2007).

In the past several years, we have seen major breakthroughs in analyzing chromatin modifications on a genome-wide scale. Thanks to rapid advances in DNA microarray and next generation sequencing technologies, epigenome-wide mapping experiments can now be performed with unprecedented resolution. Development of chromatin immunoprecipitation (ChIP) methods in combination with DNA microarrays (ChIP-chip) or sequencing (ChIP-seq) has allowed scientists to characterize epigenomic modifications on a much larger scale and in a moderate to high throughput manner (Ren et al., 2000; Robyr, 2002; Robyr & Grunstein, 2003). This has resulted in many large-scale epigenomic projects to produce a first generation of detailed reference maps of the epigenome such as the NIH Roadmap Epigenomics Program (www.roadmapepigenimcs.org) and The Encyclopaedia of DNA Elements (ENCODE) (Birney, 2007; Satterlee et al., 2010). The construction of epigenome-wide maps relevant for specific cell types or tissues in different biological states may result in new insights into the biology of human diseases that could translate into the development of specific biomarkers or contribute to the identification of targets for novel therapeutic strategies.

The role of epigenomic mechanisms in neurodegenerative and autoimmune diseases is beginning to be explored beyond targeted investigations of specific loci (Brooks et al., 2010; Sananbenesi & Fischer, 2009; Mehler, 2008a). Our disease of interest, multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system with secondary neurodegeneration that is believed to have a multifactorial origin that includes a combination of genetic, environmental and stochastic factors (Dyment et al., 1997). Genetic studies have indicated an association between MS and at least three susceptibility alleles within the major histocompatibility complex (MHC) and fifty-four susceptibility alleles within non-MHC loci (International Multiple Sclerosis Genetics Consortium et al., 2011). Previous genetic and epidemiological studies demonstrated that the gender of an affected parent might influence a child's risk of developing MS (Sadovnick, 1993a; Sadovnick, 1993b; Chao, 2009). Further, it has been suggested that maternal half-siblings are at greater risk of developing MS than paternal half-siblings implying a possible role of epigenetic mechanisms (Robertson, 1996). Finally, the predisposition of women to develop MS and many other inflammatory diseases may also have a contribution from the unique epigenomic events that involve the X chromosome: Lyonization, the random inactivation of one X chromosome in each cell of a woman's body (Brooks et al., 2010; Orton, 2006). In this review we outline recent technical advances in genome-wide approaches to dissect the epigenome and how this may inform the study of MS by opening new perspectives on the transcriptional state of cells and tissues implicated in the disease.

2. Chromatin structure and modifications

The human genome consists of approximately ~21,000 distinct protein coding genes (Neumann, 2010) which are found in over two meters of DNA which are packed into each nucleus of the human body. This genetic information is organized in the form of chromatin, a three-dimensional complex of DNA bound to histones, non-histone proteins, and non-coding RNAs in the cell nucleus. The nucleosome is the fundamental unit of chromatin and consists of 147 kb of DNA wrapped around an octamer of histone proteins H2A, H2B, H3 and H4 (Margueron & Reinberg, 2010). This results in a 'beads on a string' organization that is further compacted to form higher-order structures of chromatin such as heterochromatin and euchromatin (Kouzarides, 2007). Heterochromatin is a condensed form of chromatin where gene expression is blocked and DNA is inaccessible to the transcriptional machinery. Chromatin exists also in activated, open state called euchromatin which describes a more relaxed form associated with gene expression. External stimuli are able to alter different forms of chromatin and thus regulate gene expression (Kouzarides, 2007; Ruthenburg et al., 2007). Until recently, chromatin was thought to be largely static in cells, but recent studies have highlighted changes in the distribution of epigenomic marks over the course of minutes, such as in the brain where the activation of certain circuits leads to chromatin remodeling (Guan, 2009; Fischer et al., 2007; Haggarty & Tsai, 2011). Thus, chromatin is a very dynamic structure that is influenced by environmental exposure, and different markers capture different aspects of this architecture.

2.1. DNA methylation

DNA methylation is essential for normal development and survival of differentiated cells. Patterns of DNA methylation are established during cell development and preserved during subsequent cell division (Straussman, 2009). The level of methylation correlates with the level of transcription from a given gene, with hypermethylation of promoter regions being typically found in silenced gene (Straussman, 2009). In mammals, DNA methylation has been implicated in a wide range of pathologies; it has been studied most in the context of carcinogenesis but is also associated with rare genetic diseases that affect components of the epigenomic machinery or alter DNA methylation, generating neurodevelopmental abnormalities such as those found in Rubinstein–Taybi syndrome, Rett syndrome, and Fragile X syndrome (http://www.ncbi.nlm.nih.gov/omim) (Kacem & Feil, 2009; Reik & Lewis, 2005; Esteller & Hum Mol, 2007). DNA methylaion occurs by the covalent transfer of a methyl group from S-adenosylmethionine (SAM) to the 5′ carbon of the cytosine residues of a CpG dinucleotide (Clark et al., 1995). This process is catalyzed by DNA methyltransferases (DNMTs) that are divided into DNMTs involved in the maintenance of methylation such as DNMT1 or *de novo* methylation such as DNMT3A/B/L. These DNMTs are crucial for central nervous system (CNS) function both during development and in the mature brain (Klose & Bird, 2006; Mehler, 2008b). CpG dinucleotides cluster in regions called CpG islands, which are characterized by high content of C and G nucleotides (>50%). The majority of human promoters are associated with CpG rich regions of the human genome and are usually unmethylated in cells where the gene is expressed (Portela & Esteller, 2010). DNA methylation also occurs in regions known as CpG island shores (within 2 kb of the island's border) and shelves (2–4 kb from the island), which are characterized by lower CpG density (Portela & Esteller, 2010). Differences in methylation patterns of CpG island shores are sufficient to distinguish between different tissue types, and these methylation signatures appear to be conserved between human and mouse (Doi, 2009). The relative impact of methylation in these different regions on biological phenomena is an area of active investigation; it is currently not clear which region or combination of regions drives functional differences.

2.2. Histone modifications

Genomic programs such as transcriptional activation and gene silencing are influenced by chromatin architecture, and the correlation