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REVIEW

EPIGENETIC REGULATION IN NEURODEVELOPMENT AND NEURODEGENERATIVE DISEASES

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Abstract—From fertilization throughout development and until death, cellular programs in individual cells are dynamically regulated to fulfill multiple functions ranging from cell lineage specification to adaptation to internal and external stimuli. Such regulation is of major importance in brain cells, because the brain continues to develop long after birth and incorporates information from the environment across life. When compromised, these regulatory mechanisms can have detrimental consequences on neurodevelopment and lead to severe brain pathologies and neurodegenerative diseases in the adult individual. Elucidating these processes is essential to better understand their implication in disease etiology. Because they are strongly influenced by environmental factors, they have been postulated to depend on epigenetic mechanisms. This review describes recent studies that have identified epigenetic dysfunctions in the pathophysiology of several neurodevelopmental and neurodegenerative diseases. It discusses currently known pathways and molecular targets implicated in pathologies including imprinting disorders, Rett syndrome, and Alzheimer′s, Parkinson′s and Hungtinton′s disease, and their relevance to these diseases.

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Key words: epigenetics, neurodevelopment, imprinting disorders, Alzheimer's disease, Parkinson's disease, Huntington's disease.

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''*Between genotype and phenotype, and connecting them to each other, there lies a whole complex of developmental processes.*'' Waddington, 1942.

INTRODUCTION

The question of how cells in an organism develop into distinct types and fulfill different functions despite carrying the same genetic information has intrigued biologists for decades. Further, how environmental conditions can allow cellular systems to acquire specific features such as resistance to stress, and keep these features throughout life is also still poorly understood (Villeneuve et al., 2010, 2011). In an attempt to explain these phenomena, Conrad Waddington (1942) introduced the concept of epigenetics, and proposed the idea that environmental factors can modify a fixed genotype, alter developmental processes and thereby confer specific properties to cells. Epigenetics refers to changes in the functions of the genome that occur without any alteration in the DNA sequence itself (Wolffe and Matzke, 1999). Although initially restricted to heritable changes in cellular features, it also now includes non-heritable changes. The mechanisms underlying epigenetic processes have been extensively studied in the past decades. Their major functions are thought to be to dynamically regulate gene activity in

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Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; CGI, CpG islands; CBP, CREB-binding protein; DNMTs, DNA methyltransferases; ESCs, embryonic stem cells; GFAP, glial fibrillary acidic protein; HATs, histone acetyl transferases; HDACs, histone deacetylases; HDMs, histone demethylases; HMTs, histone methyl transferases; HD, Huntington's disease; NRSF, neuron-restrictive silencer factor; NSCs, neural stem cells; PD, Parkinson's disease; PTMs, posttranslational modifications; SNpc, substantia nigra pars compacta; TNF-alpha, tumor necrosis factor alpha.

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response to environmental events, and provide functional epigenomic signatures that can persist. While they operate in all cells and tissues, they are particularly important for the nervous system.

This review provides a brief synopsis of the processes of epigenetic regulation in the brain in health and disease across life. It first focuses on epigenetic mechanisms during early brain development, adult neurogenesis and aging, then discusses their implication in the pathophysiology of neurodegenerative disorders. It also discusses the possibility of novel therapeutic approaches based on the manipulation of epigenetic processes.

EPIGENETICS IN BRAIN DEVELOPMENT AND AGING

DNA methylation and histone posttranslational modifications (PTMs)

Chromatin remodeling is an essential feature of the DNA required for the regulation of gene expression. It is a complex ensemble of mechanisms mediated by epigenetic and structural processes, in particular DNA methylation and histone PTMs. DNA methylation is one of the best-known epigenetic modes of regulation by which a methyl group is added to the 5′ carbon of cytosine in dinucleotide CpG sequences. It is induced by *de novo* DNA methyltransferases (DNMTs) such as DNMT3a and b, and maintained by DNMT1 (Kinney and Pradhan, 2011). CpGs are mainly found in clusters known as CpG islands (CGI), often located in the promoter region of genes and mostly hypomethylated when compared to CGI shores (sequences spanning 2 kb up- and downstream of each CGI) and gene bodies (Davies et al., 2012). Increased methylation of CGI has a strong impact on gene transcription, and generally leads to gene silencing (Bird, 2002; Esteller, 2007). Silencing can result from negative DNA charges that create conditions preventing chromatin opening, and from the recruitment of transcriptional repressors (Tost, 2009). For instance, DNA methyl-binding domain proteins (MBD1–4) and methyl-CpG binding protein 2 (MeCP2) are recruited to methylated DNA, and engage histone deacetylases (HDACs) complexes (Jones and Takai, 2001; Klose and Bird, 2006). But DNA methylation can also be associated with transcriptional activation, through mechanisms that remain unknown (Yasui et al., 2007; Chahrour et al., 2008).

PTM of histone proteins is another epigenetic mechanism that, together with DNA methylation, alters chromatin structure. PTMs are covalent modifications of specific residues on histones N- or C-terminus tail or core and include acetylation, phosphorylation, methylation (mono, bi or tri), ubiquitylation, sumoylation or crotonylation (Talbert and Henikoff, 2010; Tweedie-Cullen et al., 2012). They are regulated by specific enzymes such as histone acetyl transferases (HATs), HDACs, protein kinases and phosphatases, histone methyl transferases (HMTs) and demethylases (HDMs), present in chromatin-modifying complexes. Histone PTMs can act in *cis* or *trans*, and strongly influence each other to form a dynamic histone code specific for each gene. By altering the net charge of nucleosomes, they modify DNA–histone interactions leading to structural changes, and transcriptional activation or silencing (Kouzarides, 2007; Zhou et al., 2011). Histone PTMs can also recruit chromatin-modifying enzymes and/or DNA-binding factors. For example, methylation of lysine at position 4 of histone 3 (H3K4) can inhibit the binding of HDACs thereby favoring acetylation, while acetylation of H3K18 facilitates the recruitment of the HAT CREB-binding protein (CBP) (Kouzarides, 2007; Zhou et al., 2011). Other epigenetic mechanisms not considered in the present review include DNA hydroxymethylation and regulation of gene expression by small RNAs (Branco et al., 2012; Kaikkonen et al., 2011) (Fig. 1).

Neurodevelopment

During development, the nervous system arises from the ectoderm, the outer layer of the embryo. This process is initiated by the formation of the neural tube followed by successive steps of cell proliferation, migration, neural patterning, cell maturation and the establishment of neuronal connectivity (Feng et al., 2007; Hirabayashi and Gotoh, 2010). Neurons and glia arise from neural progenitor cells located in highly proliferative areas including the subventricular zone. Initially, precursor cells are mainly differentiated into neurons that migrate to developing cortical areas. Then, depending on environmental signals, precursor differentiation switches to a glial fate (Brazel et al., 2003). These steps require temporally regulated waves of gene expression across key developmental stages and are, in part, regulated by epigenetic mechanisms.

During early development, two major stages of epigenetic programing control the fate of toti- and pluripotent embryonic cells. The first stage involves DNA demethylation/remethylation and reprograming of histone PTMs in somatic cells, and a second stage, the erasure and reestablishment of parental imprints (by DNA methylation) during germ cell development (van Montfoort et al., 2012). Subsequent stages of development also depend on DNA methylation.

To prevent non-neuronal cells from differentiating into neurons, proneural genes are kept in an inactive state. This is in part achieved by DNA methylation of neuron-restrictive silencer element (NRSE) in the promoter region of genes such as sodium channel type II, BDNF or calbindin (Lunyak et al., 2002; Ballas et al., 2005). Neuronal commitment then requires de-repression and (re)activation of neuronal genes such as Sox2 via decreased DNA methylation (Sikorska et al., 2008). Neuronal specification of proliferating cells during early neocortical development is also associated with the silencing of astrocytic gene loci and the suppression of astrogliogenesis by DNA methylation. This silencing is attenuated at later stages of neocortical development and results in the generation of astrocytes which correlates with the suppression of neurogenesis (Hirabayashi and Gotoh, 2010). Demethylation and expression of the genes coding for the astrocytic