Editorial

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Neuroepigenetics: Prospects and Illusions

Ramón Cacabelos[1,2]*

1 Institute of Medical Science and Genomic Medicine, EuroEspes Biomedical Research Center, 15166-Bergondo, Corunna, Spain
2 Chair of Genomic Medicine, Continental University Medical School, Huancayo, Peru

*Corresponding author: Ramón Cacabelos

rcacabelos@euroespes.com

Institute of Medical Science and Genomic Medicine, EuroEspes Biomedical Research Center, 15166-Bergondo, Corunna, Spain.

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Editorial

Central nervous system (CNS) disorders represent polygenic/multifactorial phenotypes with a great impact in our society due to the psychological burden, cost and disability that they may cause. Most CNS disorders are clinical entities which, in many instances, share some common features: (i) pathogenically, they are complex disorders in which a plethora of plural events (genomic defects, epigenetic aberrations, mitochondrial dysfunction, environmental factors) is potentially involved; (ii) many of them, especially those with a late onset, are characterized by intracellular and/or extracellular deposits of abnormal proteins; (iii) their diagnosis is difficult because they lack specific biomarkers (and their prediction is almost impossible); (iv) their treatment is symptomatic (not anti-pathogenic) and not cost-effective; and (v) the vast majority represent chronic ailments with progressive deterioration and bad prognosis [1,2].

The concept of epigenetics, introduced by Conrad Waddington in 1942, and its spectacular evolution, from a biotechnological perspective, has been of great help for the past 10 years in the understanding of gene regulation and expression (functional genomics), neurogenomics, and pathogenetics of CNS disorders [3-7].

Epigenetic marks contribute to natural human variation [8] and configure the emerging field of neuroepigenetics [4]. Preconceptional parental exposure to environmental stimuli may determine the offspring's phenotype via meiotically and mitotically heritable epigenetic mechanisms [3], and exposure to diverse external elements (nutrition, pollutants, drugs, toxins) may condition several categories of human diseases. Consequently, epigenetic aberrations contribute to the pathogenesis of neurodevelopmental, imprinting, neuropsychiatric, and age-related neurodegenerative disorders [2]. Some brain disorders exhibit proteoepigenomic changes resulting from primary genomic traits and/or secondary epigenetic events that induce pathogenic (structural, functional, conformational) changes in key proteins [9]. Proteomic biomarkers and epigenomic signatures may help in the prediction, early diagnosis, and prognosis of CNS disorders. Additionally, some epigenetic modifications are conceptually reversible and can potentially be targeted by pharmacological and dietary interventions [10-12]. Of paramount importance is the fact that epigenetic changes in genes involved in pharmacogenomics can also influence drug efficacy and safety and drug resistance in brain disorders and cancer [1].

Epigenetic Mendelian disorders (EMD) are a group of multiple congenital anomaly and intellectual disability syndromes resulting from mutations in genes encoding components of the epigenetic machinery [2,13]. Within this category, genetic mutations may affect writers, erasers, or readers of epigenetic marks, and chromatin remodelers, as well. Many EMD fall within the category of neurodevelopmental and imprinting disorders, and some of them may manifest in adults. EMD involving the DNA methylation machinery have been described for writers and readers of DNA methylation (Rett syndrome, 2q23.1 microdeletion/microduplication syndrome, immunodeficiency, centromeric instability, and facial anomalies syndrome, hereditary sensory and autonomic neuropathy with dementia and hearing loss, autosomal dominant cerebellar ataxia, deafness, and narcolepsy). EMD of the histone machinery have been described for writers, erasers, readers, and chromating remodelers, including Kabuki syndrome, Rubinstein-Taybi syndrome, Genitopatellar syndrome, Say-Barber-Biesecker-Young-Simpson syndrome, Widerman-Steiner syndrome, Kleefstra syndrome, Weaver syndrome, Sotos syndrome, brachydactyly-mental retardation syndrome, Cornelia de Lange syndrome 5, Wilson-Turner syndrome, Claes-Jensen syndrome, Siderius X-linked mental retardation sysndrome, Börjeson-Forssman-Lehmann syndrome, X-linked mental retardation and macrocephaly. EMD of chromatin remodelers include the following: alpha-thalassemia/mental retardation X-linked syndrome, Coffin-Siris syndrome, Rhabdoid tumor predisposition syndrome 2, Schwannomatosis, Rhabdoid tumor

predisposition syndrome 1, Nicolaides-Baraitser syndrome, Floating harbor syndrome, CHARGE syndrome and mental retardation autosomal dominant 21 [2,13].

Major CNS disorders in which epigenetics plays a pathogenic role include Alzheimer's disease, Parkinson's disease, Huntington's disease, motor neuron disorders, demyelinating disorders, schizophrenia and psychotic syndromes, depression, epilepsy, autism spectrum disorders, different forms of mental retardation and stroke, as a reduced example [2].

An important field, in which epigenetics is contributing to its expansion, is drug development. Epigenetic drugs are becoming a fashion [14-16] and some of them have been approved by the FDA in recent years for the treatment of cancer [17]. However, most epigenetic drugs are pleiotropic and are not devoid of toxicity and biodynamic complications (e.g. brain penetration) [14].

The effects of drugs (pharmacokinetics and pharmacodynamics) and their therapeutic outcome in the treatment of a given disease are the result of a network of metabolomic events (genomics-epigenomics-transcriptomics-proteomics) associated with the binomial interaction of a chemical or biological molecule with a living organism. The clusters of genes currently involved in a pharmacogenomic process include pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes [1]. In practice, the expression of these genes is potentially modifiable (transcriptionally and/or post-transcriptionally) by epigenetic mechanisms which may alter (i) pathogenic events, (ii) receptor-drug interactions, (iii) drug metabolism (phase I and II enzymatic reactions), (iv) drug transport (influx-efflux across membranes and cellular barriers), and (v) pleiotropic events leading to unexpected therapeutic outcomes. The understanding of these mechanisms is the main focus of pharmacoepigenomics in order to optimize therapeutics and advance towards a personalized medicine [2,14,18].

In the coming years, important achievements must be accomplished in different areas of neuroscience. In therapeutics, important breakthroughs will occur in some of the following areas: (i) epigenetic drug discovery for different CNS disorders and cancer; (ii) practical applications of pharmacogenomics and pharmacoepigenomics [19-22] for the optimization and personalization of current drugs and new pharmacological treatments; (iii) novel therapeutic approaches to decode and resolve potential resistance mechanisms in cancer and psychiatric disorders [23-25]; and (iv) targeting miRNAs in prevention and treatment of brain disorders [26-28].

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