

## Proteoepigenomic Biomarkers of Brain Disorders

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Most central nervous system (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]. 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 [2-4].

Gene expression and protein function experience profound modifications throughout the life span. It is likely that the frontier between health and disease is not only associated with specific SNP variability and epigenetic aberrations (in conjunction with environmental risks) but also with a salutary/pathogenic threshold of transformed protein accumulation in critical cells (especially in neurons). Over the past decade, progress in epigenetics and proteomics has helped to understand many aspects of pathogenic phenomena which remained obscure or unaffordable to our technical capabilities for the assessment of genomic dysfunction, epigenetic dysregulation, and abnormal protein expression. Transcription errors represent a molecular mechanism by which cells can acquire disease phenotypes. The error rate of transcription increases as cells age, suggesting that transcription errors affect proteostasis particularly in aging cells. Accordingly, transcription errors accelerate the aggregation of peptides and shorten the lifespan of cells [5].

Novel methodologies have allowed us to configure new pathogenic hypotheses for a better understanding of brain disorders. In this endeavor, epigenetics and proteomics have been of great benefit. Epigenetic studies have revealed the important role that epigenetic modifications have on brain development and maturation, synaptic plasticity, brain sex differences, neurodevelopment and imprinting disorders, mental disorders, neurodegeneration, and the new field of epigenetic Mendelian disorders [6]. Structural genomic defects cannot explain in full the pathogenesis of CNS disorders. Many old concepts related to the pathogenesis of CNS disorders should be eliminated. Parkinson's disease is not the result of a single deficiency in dopamine; Alzheimer's disease is not the consequence of a cholinergic deficit; however, the basic principles for the development of the most currently prescribed drugs for both disorders rely on a single neurotransmitter defect (enhancement of dopamine neurotransmission in Parkinson's disease, and potentiation of cholinergic transmission with acetylcholinesterase inhibitors in Alzheimer's disease). These old-fashioned pathogenic concepts are completely out-of-date, and the new conceptions on neurodegenerative disorders are based on the pathogenic cascade represented by genomic-epigenomic-transcriptomic-proteomic-metabolomic disturbances leading to a

specific phenotype which in the future will require a personalized therapeutic intervention (pharmacogenomics, pharmacoeugenomics) for phenotype disease modification [1]. The same must happen with most mental disorders whose psychopharmacological treatments rely on a reductionistic view based on the regulation of 6 neurotransmitters (dopamine, noradrenaline, serotonin, acetylcholine, histamine, GABA), assuming for the past 50 years that major psychiatric disorders (schizophrenia, depression, anxiety, bipolar disorder, autism, attention deficit hyperactivity disorder) are merely neurotransmitter disorders. However, as pointed out by Riley et al. [7], systems analysis is believed to help deconvolute complex biological responses involving hundreds or thousands of genes assayed by OMICs methods. Although systems-style approaches have been applied to CNS tissues, most studies have used simple functional overview approaches resulting in the identification of differentially expressed genes, or pathways. While these approaches expanded our understanding of disease-related changes, they are not able to elucidate the complex interconnectivity of biological and pathological processes present within diseased tissue. These approaches are "low resolution" descriptive methods with limited projection in terms of clarifying molecular pathogenesis, experimental follow-up, and clinical application.

Global protein profiling by mass spectrometry-based proteomics has evolved as a new hypothesis-free avenue to optimally unravel new candidate protein biomarkers involved in different CNS disorders. Technological developments and improvement of sensitivity, specificity and speed of different proteomic approaches have facilitated the discovery of an enormous number of biomarker candidates; however, most biomarkers have not yet been validated, which limit their application in clinical practice. The correct interpretation of thousands of data derived from proteomic and epigenomic analysis is an additional problem for the practical implementation of biomarkers in the clinical setting [8]. Novel neuroproteomic tools and powerful bioinformatic resources are needed to accelerate the incorporation of proteomic and epigenomic analysis to the diagnostic process [9-11].

Another important field, in which epigenetics and proteomics are contributing to its expansion, is drug development. Epigenetic drugs are becoming a fashion [12-14] and some of them have been approved by the FDA in recent years for the treatment of cancer [15]. However, most epigenetic drugs are pleiotropic and are not devoid of toxicity and biodynamic complications (e.g. brain penetration) [12,13].

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Received December 03, 2015; Accepted December 08, 2015; Published December 10, 2015

Citation: Cacabelos R (2015) Proteoepigenomic Biomarkers of Brain Disorders. *Metabolomics* 6: e143. doi:10.4172/2153-0769.1000e143

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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 [12,16,17].

In the coming years, important achievements must be accomplished in different areas of neuroscience: (i) brain development and maturation, (ii) toxicogenomics, (iii) functional epigenomics, (iv) proteoepigenomics, (v) pathoepigenomics, (vi) predictive proteomics, (vii) diagnostic proteomics, (viii) prognostic proteomics, (ix) pharmacoepigenomics, and (x) epitherapeutics. It is likely that systems biology will dominate the -omics signatures [18]. Relevant information obtained from the ENCODE Project will be incorporated into a more versatile map of clinical neuroscience and practical medicine [19]. Development is a dynamic process that involves interplay between genes and the environment. Postnatal environment is shaped by parent-offspring interactions that promote growth and survival and can lead to divergent developmental trajectories with implications for later-life neurobiological and behavioral characteristics. The impact that nutrition, emotions, drugs and environmental toxicants during prenatal development may have on brain maturation and late CNS disorders requires urgent clarification [20]. Important advances related to the role of epigenetics in the pathogenesis of brain disorders will occur in the near future with reliable applications. Predictive, diagnostic, and prognostic proteomics, as well as the use of biomarkers to monitor the effects of drugs will experience a profound change from the present immature stage of the field to a more specific and validated area with various applications in CNS disorders.

In therapeutics, important breakthroughs will occur in some of the following areas: (i) epigenetic drug discovery for different CNS disorders and cancer [12,13,21]; (ii) practical applications of pharmacogenomics [1,17] and pharmacoepigenomics [22-25] 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 [22]; and (iv) targeting miRNAs in prevention and treatment of brain disorders [26].

Based on recent knowledge, several conclusions can be delineated: (i) Epigenomic regulation is a common phenomenon of gene expression control during development, maturation and aging in physiological and pathological conditions. (ii) Classical epigenetic mechanisms (DNA methylation, chromatin remodeling/histone modifications, and miRNA regulation), are among the major regulatory elements that control metabolic pathways. (iii) Preconceptional parental exposure to environmental stimuli may determine the offspring's phenotype via heritable epigenetic mechanisms, and exposure to diverse external elements may condition several categories of human diseases and CNS disorders. (iv) Mutations in the genes encoding elements of the

epigenetic machinery can lead to epigenetic Mendelian disorders. (v) Epigenomic dysregulation contributes to the pathogenesis of neurodevelopmental, imprinting, mental, neurological, and neurodegenerative disorders. (vi) Some epigenetic aberrations are conceptually reversible and can potentially be targeted by pharmacological and dietary interventions. (vii) Proteomic biomarkers can be useful for both early and accurate diagnosis and prediction of CNS disease progression. (viii) The correct interpretation of thousands of data derived from proteomic and epigenomic analysis is still a problem for the practical implementation of biomarkers in the clinical setting. Novel neuroproteomic tools and powerful bioinformatic resources are needed to accelerate the incorporation of proteomic and epigenomic analysis to the diagnostic process. (ix) Epigenetic changes in genes involved in pharmacogenomics (pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes) can also influence drug efficacy and safety and drug resistance in brain disorders and cancer. (x) Proteomic biomarkers, novel therapeutic approaches to decode and resolve potential drug resistance mechanisms, and targeting miRNAs in prevention and treatment of brain disorders are promising developments in the field of proteoepigenomics.

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