5.7 Future Trends for the Management of Age-Related NDDs

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.[11] 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 (Figure 5.1).[13–16,141,153,197,198]

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 had 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.[199]

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.[144] 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 currently most-prescribed drugs for both disorders rely on a single neurotransmitter defect (enhancement of dopamine neurotransmission in Parkinson's disease, and potentiation