Preface to the Volume

Biomedical research in the first decade of the twenty-first century has been marked by a rapidly growing interest in epigenetics. The reasons for this are numerous, but primarily it stems from the mounting realization that research programs focused solely on DNA sequence variation, despite their breadth and depth, are unlikely to address all fundamental aspects of human biology. Some questions are evident even to nonbiologists. How does a single zygote develop into a complex multicellular organism composed of dozens of different tissues and hundreds of cell types, all genetically identical but performing very different functions? Why do monozygotic twins, despite their stunning external similarities, often exhibit significant differences in personality and predisposition to disease? If environmental factors are solely the cause of such variation, why are similar differences also observed between genetically identical animals housed in a uniform environment? These are not necessarily new questions. More than half a century ago, Conrad H. Waddington, an insightful British developmental biologist, developed a theoretical framework to explain how identical genotypes could produce a wide collection of phenotypes over the course of development, defining epigenetics as the developmental processes "connecting" a cell's genotype to its phenotype. Even before Waddington, the term *epigenesis* was used several centuries ago to conceptualize how, starting from a uniform material, every individual acquires new forms that emerge gradually over time.

Over the last couple of decades, epigenetics has undergone a significant metamorphosis from an abstract developmental theory to a very dynamic and rapidly developing branch of molecular biology. Waddington's concept of an "epigenetic landscape" linked to phenotype has materialized into the study of complex combinations of DNA and histone modifications, together acting to coordinate various genetic functions in the cell. These modifications can be heritable, both mitotically and meiotically, but do not involve changes in the DNA sequence. Contemporary epigenetics investigates DNA methylation and hydroxymethylation, in addition to a plethora of histone modifications that together play a critical role in a variety of regulatory processes within the nucleus. Epigenetic processes primarily regulate gene expression, controlling the tissue-specific orchestration of gene activity that ultimately accounts for the development of multicellular organisms. They also have a number of other important genomic functions including the suppression of

retroelements, the instigation of X chromosome inactivation in females and a role in meiotic and mitotic recombination and chromosomal segregation.

Epigenetic studies in various species – from *Escherichia coli* and yeast to animals and humans – are now underway, highlighting how epigenetic regulation is critically important for the normal functioning of the genome. Cells can operate normally only if both DNA sequence and epigenetic components of the genome function properly. In other words, the cell needs both the DNA "hardware" and the epigenetic "software." Furthermore, epigenetic factors and the DNA sequence do not necessarily operate in isolation. Some DNA sequence variants can influence local epigenetic profiles, for example, via processes such as allele-specific DNA methylation. Likewise, epigenetic modifications can predispose certain nucleotides to be more mutagenic than others; for example, methylated cytosines are prone to spontaneous deamination and conversion to thymines.

Epigenetic information varies among cells of the same tissue, across the cells of different tissues, and also between individuals. Epigenetic changes may be rapid and short-lived (e.g., the cyclical changes observed in response to the circadian rhythm) or highly stable once established (e.g., the maintenance of tissue and cell type specificity). Despite the extremely fast growth in epigenetic research over the last decade, we are only just beginning to understand the full complexity of the epigenome. We are still mapping the epigenetic landscape of the cell, uncovering new epigenetic mechanisms, and novel roles for epigenetic processes. Recent years, for instance, have seen the recognition about the importance of noncoding RNA and RNA-mediated epigenetic gene regulation, as well as physical interactions among genes in three-dimensional space within the nucleus.

The recent advent of high-throughput genomic approaches, first via the application of microarrays and more recently via next generation sequencing, has enabled a technological quantum leap in molecular epigenetic studies; epigenome-wide mapping experiments can now be feasibly performed at unprecedented resolution. The term "epigenome" is used to describe the complex distribution of epigenetic modifications across the entire genome in a specific cell or cell population. As in genome-wide association studies, scans of epigenomes will soon become a routine procedure in experimental laboratories. Large-scale epigenomic mapping projects initiated by the NIH, European Science Foundation, and other major funding agencies have already mapped numerous layers of epigenomic information using these latest technologies. Hopefully, this effort will result in a global, integrated view of different cellular states. Unlike the human genome, mapping the epigenome is an open-end project: each cell in each individual may have a distinct epigenome that reflects its developmental state, environmental exposures, stochastic effects, among numerous other multidirectional effects that form the epigenetic uniqueness of each cell, each tissue, and each individual.

The focus of this volume is behavioral and brain epigenetics, representing a novel a frontier in neurobiological and psychiatric research. One of the primary objectives of behavioral epigenetics is to understand the molecular basis of various brain functions (e.g., memory, cognition, homeostasis, and adaptation to new environments). Of particular interest is the putative role of epigenetic dysfunction in brain pathology

and mental illness. While epigenetic factors have been intensively investigated in the malignant transformation of cells in cancer, similar processes may be highly relevant to various complex non-Mendelian diseases. Epigenetic mechanisms – often more efficiently than genetic ones – are able to integrate a number of apparently unrelated clinical, epidemiological, and molecular data into a new theoretical framework. Putative epigenetic misregulation is consistent with various epidemiological, clinical, and molecular features in complex diseases, including most psychiatric disorders. It is apparent that the dysregulation of gene activity and deviations from a normal expression pattern can be as detrimental to a cell as mutant DNA sequences resulting in dysfunctional proteins. It is important to note that epigenetic changes that are partially both inherited and acquired can be the primary disease causes, rather than just one of numerous secondary or further downstream epiphenomena.

Another pertinent question is how exposure to a wide scope of environmental factors, such as toxins, drugs of abuse, infection, nutrition, and stress can affect epigenetic regulation in the brain that ultimately translate into alterations in behavior. Epigenetic studies will provide new insights into the interface between the environment and the genome, and the mechanisms by which exposures at key points in development may mediate long-term effects on behavior. Some epigenetic changes are transient, whereas others may be relatively stable and persist much longer. Some chromatin changes are mitotically heritable and can affect somatic tissues, whereas others may even be inherited through meiosis and affect subsequent generations.

This volume represents a compilation of our current understanding about the key aspects of epigenetic processes in the brain and their role in behavior. The chapters in this book bring together some of the leading researchers in the field of behavioral epigenetics. They explore many of the epigenetic processes that operate or may be operating to mediate neurobiological functions in the brain and describe how perturbations to these systems may play a key role in mediating behavior and the origin of brain diseases. Akbarian et al. analyze the mechanisms by which epigenetic factors, such as covalent histone modifications, can contribute to dysregulation of gene expression in schizophrenia. Another chapter dedicated to schizophrenia, by Grayson and colleagues, summarizes their detailed epigenetic analysis of genes encoding reelin and glutamate decarboxylase 67. Theoretical evidence, with some preliminary experimental findings, that bipolar disorder is a promising candidate for epigenetic and epigenomic studies is summarized by Kato. The epigenetics and disease theme is further elaborated by Labonté and Turecki, who discuss the complex relationship between adverse life events and social stress, on the one hand, and major depression and suicidal behavior on the other, exploring the putative role of molecular epigenetic factors. Malaspina et al. provide epidemiological evidence that paternal age, toxin exposure, and psychological stressors may increase the risk for mental disease and suggest that these environmental hazards can be indirectly uncovered using epigenetic strategies, both in humans and animal models. The theme of epidemiological epigenetics in psychiatric diseases is elaborated by Susser et al., who discuss how prenatal famine and childhood ethnic minority status is associated with higher degree of psychopathology. Craig et al. discuss the complex epigenetic regulation of the X chromosome and its impact on human behavioral

phenotypes. Crespi, in a theoretical *tour de force*, attempts to link parent–offspring conflict, attachment theory, and genomic imprinting. The numerous roles of genomic imprinting, a classical epigenetic mechanism, in brain and behavior studies are overviewed by Isles and Wilkinson. The intriguing observations about the epigenetic effects of social experiences occurring during infancy, and its role in the establishment and maintenance of environmental programming are summarized in two chapters, one by Curley and Champagne and a second by Weaver. Finally, three chapters by Labrie, Estevez and Abel, and Reul et al. discuss evidence that epigenetic mechanisms can play a critical role in synaptic plasticity, learning, and memory.

Despite significant progress in molecular epigenetic research and its enormous potential, there are still considerable challenges to overcome before we can fully understand the role of epigenetic processes in brain function and behavior. For instance, what comprises a "normal" brain epigenome and what is the degree of tissue and cellular specificity of epigenetic landscapes in the brain? How do the multiple layers of epigenetic information interact and change over time? How common is meiotic epigenetic heritability and what role it may play in complex psychiatric disease? To what extent is the epigenome plastic and malleable in response to environmental influences? This volume demonstrates that such questions can now be explored in an experimental molecular biology laboratory. While the community is only just starting to acknowledge the importance of epigenetic processes in the brain, there is no doubt that numerous breakthrough discoveries in brain and behavioral epigenetics will be made in the decades to come.

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