EPIGENETIC REGULATION IN THE NERVOUS SYSTEM

BASIC MECHANISMS AND CLINICAL IMPACT

Edited by
J. David Sweatt, Michael J. Meaney,
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NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
32 Jamestown Road, London NW1 7BY, UK
225 Wyman Street, Waltham, MA 02451, USA
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA

Front Cover: *"DNA with Methyl-Cytosine and Hydroxy-Methyl-Cytosine"*
J. David Sweatt, acrylic on wood panel (24 × 48), 2012

Back Cover: *"DNA with Methyl-Cytosine and Hydroxy-Methyl-Cytosine – Abstraction"*
J. David Sweatt, acrylic on wood panel (24 × 48), 2012

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-391494-1

For information on all Academic Press publications
visit our website at www.store.elsevier.com

Typeset by MPS Limited, Chennai, India
www.adi-mps.com

Printed and bound in China

12 13 14 15 10 9 8 7 6 5 4 3 2 1

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Preface

In a living cell, the functional definition of the human genome cannot be captured solely by its linear sequence of 3 (or 6 when diploid) billion base pairs. It is the *epigenome*, with highly regulated modifications of DNA cytosine and more than 100 site- and amino acid residue specific histone modifications, histone variants and other types of epigenetic markings which, in concert, define localized chromatin structures and functions, provide a molecular bridge between genes and "the environment", and orchestrate the expression of tens of thousands of transcriptional units, condensed chromatin clusters and many other features that distinguish between various cell types and development- or disease-states sharing the same nascent genome within the same subject.

Epigenetics in the nervous system, in particular, has made breath-taking advances over the course of the last 10–15 years. Initially, there were only a handful of studies, mainly focused on a single mark, DNA cytosine methylation, in the context of brain aging and development. Fast forward to the present, and the database grew to hundreds of studies, collectively indicating that epigenetic landscapes in brain maintain their highly dynamic and bi-directional regulation throughout the lifespan, and play a critical role in the mechanisms of learning, memory and, more generally, neuronal plasticity. Furthermore, a rapidly expanding repertoire of chromatin modifying drugs has been shown to exhibit an unexpectedly broad therapeutic potential for a wide range of degenerative and functional disorders of the nervous system and, furthermore, epigenetic dysregulation at selected loci, or even genome-wide, is thought to play a key role for the molecular pathology of major psychiatric disorders (including some cases diagnosed with autism, schizophrenia and depression) or maladaptive mechanisms associated with addiction and substance dependence and abuse.

Given these recent advances, there is clearly a need for a book that addresses molecular, cellular, behavioral and clinical roles for epigenetic mechanisms in the nervous system. It appears that the time is ripe to introduce a foundational book that will be broadly relevant to a wide variety of emerging research programs beginning to investigate the role of epigenetics in neural and CNS function and dysfunction. We hope that this book will capture and communicate to the interested reader some of the excitement that has gripped the neuroepigenetics field for the last several years, both from the basic and clinical science perspective.

Finally, the Editors would like to express their gratitude towards the various other authors and co-authors of these book chapters, without whom the compilation of these various chapters would not have been possible. We are also indebted to the most valuable support of the Elsevier editorial staff, including Kristi Anderson, and the anonymous reviewers whose valuable comments helped greatly to improve the quality of this book.

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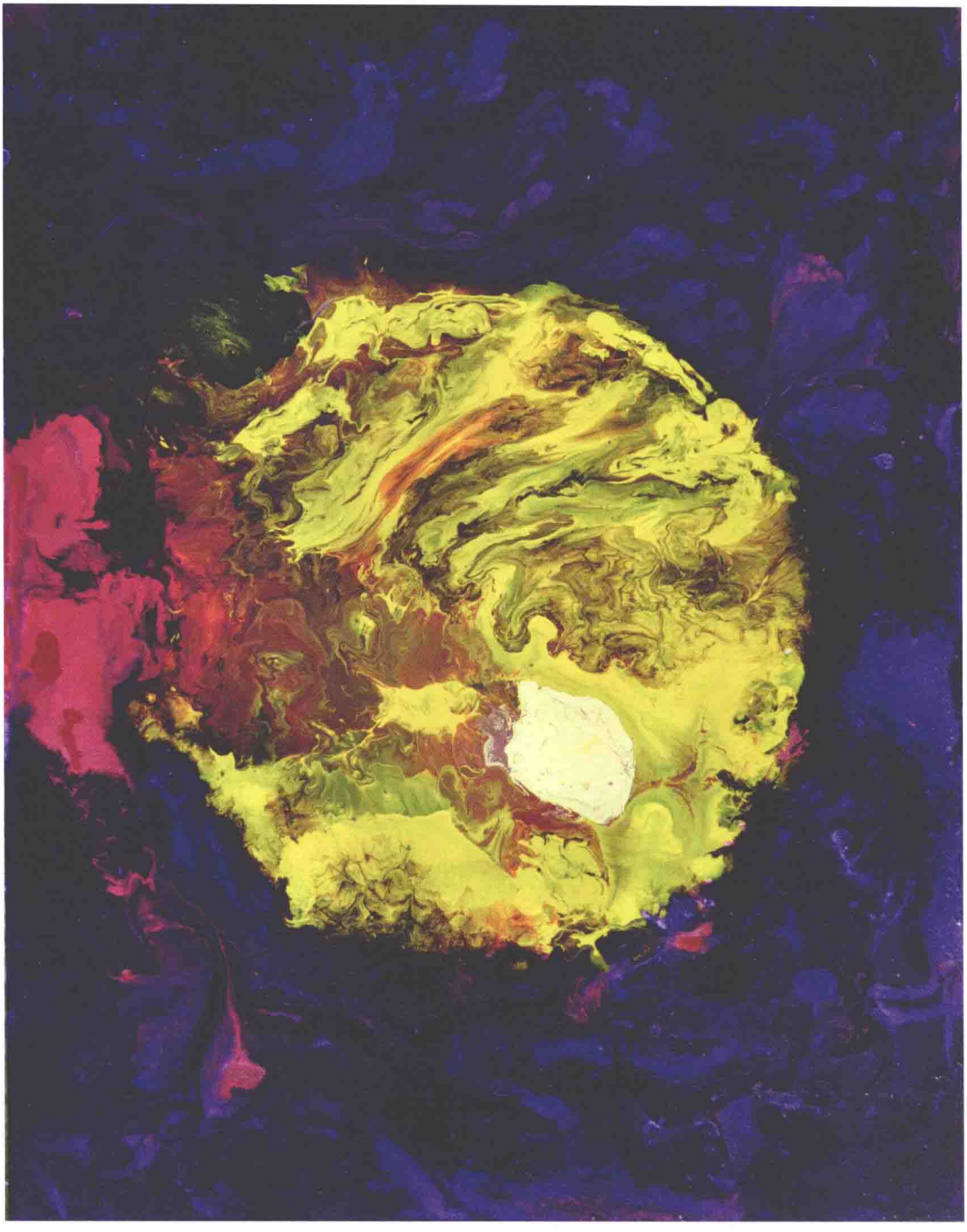

"Histone Subunit Exchange"

J. David Sweatt, acrylic on canvas (40 x 30), 2012

CHAPTER

1

An Overview of the Molecular Basis of Epigenetics

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INTRODUCTION

The role of epigenetic molecular mechanisms in regulation of CNS function is one of the most exciting areas of contemporary molecular neuroscience. This emerging field, variously referred to by neologisms such as *Behavioral Epigenetics* or *Neuroepigenetics*,[1,2] is being driven by shifts in our understanding of several of the fundamental concepts of traditional epigenetics and cognitive neurobiology. These changes in viewpoint can be categorized in a broad fashion into two domains: first, how does neuroepigenetics differ from traditionally defined developmental epigenetics; and second, what is the impact of epigenetics on the historical debate of "Nature versus Nurture"?

After a brief introduction to the basics of epigenetics at the molecular level in this chapter, this book overall will describe the current understanding of the roles of epigenetic processes at the molecular and cellular level, their impact on neural development and behavior, and the potential roles of these mechanisms in neurological and psychiatric disorders. Our goal is for the book to be the first unified synthesis of information concerning the role of epigenetic

Epigenetic Regulation in the Nervous System
DOI: http://dx.doi.org/10.1016/B978-0-12-391494-1.00001-X

mechanisms in nervous system function. This chapter is an introduction to the overall contents of the book, which spans the range of topics including molecular epigenetics, development, cellular physiology and biochemistry, synaptic and neural plasticity, and behavioral models, and also incorporates chapters on epigenetically based disorders of the CNS.

One objective of the book is to begin to embrace the complexity of epigenetic mechanisms in the context of behavioral change. This book represents a critical first step toward synthesizing the complex puzzle of the molecular basis of behavioral plasticity and neural epigenetics.

What is Epigenetics?

Epigenetics and its associated terminology have several different connotations, and specific terms need to be defined before we can discuss them in detail. We will start by defining the *genome* as DNA and the nucleotide sequence that it encodes. In contrast, the *epigenome* is the sum of both histone-associated chromatin assembly and the pattern of DNA methylation, thereby defining the moldings and three-dimensional structure of the genomic material inside the cell nucleus and providing a "molecular bridge" between genes and the environment. Despite these precise structural definitions for genome and epigenome, three definitions for the term "epigenetic" are currently in use in the literature.

The broadest definition includes the transmission and perpetuation of information that is not based on the sequence of DNA, for example, perpetuation of cellular phenotype through meiosis or mitosis. This process is not restricted to DNA-based transmission and can also be protein-based. This definition is broadly used in the yeast literature, as one example, wherein phenotypes that can be inherited by daughter cells are perpetuated past cell division using protein-based (e.g. prion-like) mechanisms.[3–5] Whether such mechanisms operate in mammalian neurons is a subject of current investigation.

Developmental biologists and cancer researchers tend to utilize a second definition for epigenetic: meiotically and mitotically heritable changes in gene expression that are not coded in the DNA sequence itself. The altered patterns of gene expression can occur through the impact on gene transcription of several mechanisms that are based on DNA, RNA, or proteins[6] (see below). The principal criterion for this definition of epigenetic is heritability. It is worth noting that the issue of heritability is fundamental to developmental biology where a major issue is the fidelity of cellular phenotype across proliferation that is critical for tissue differentiation.

A third definition posits that epigenetics is the mechanism for stable maintenance of gene expression changes that involves physically "marking" DNA or its associated proteins, which allow genotypically identical cells (such as all cells in an individual human) to be phenotypically distinct (e.g. a neuron is phenotypically distinct from a liver cell). The molecular basis for this type of change in DNA or chromatin structure in the nervous system is the focus of this chapter.[7–9] By this definition, the regulation of chromatin structure and attendant DNA chemical modification is equivalent to epigenetic regulation.

The common theme that is shared across all of the definitions is that epigenetics is a mechanism for storing and perpetuating a "memory" at the cellular level. The catalyzing phenomenon that has focused attention on these mechanisms is cell division. It is clear from