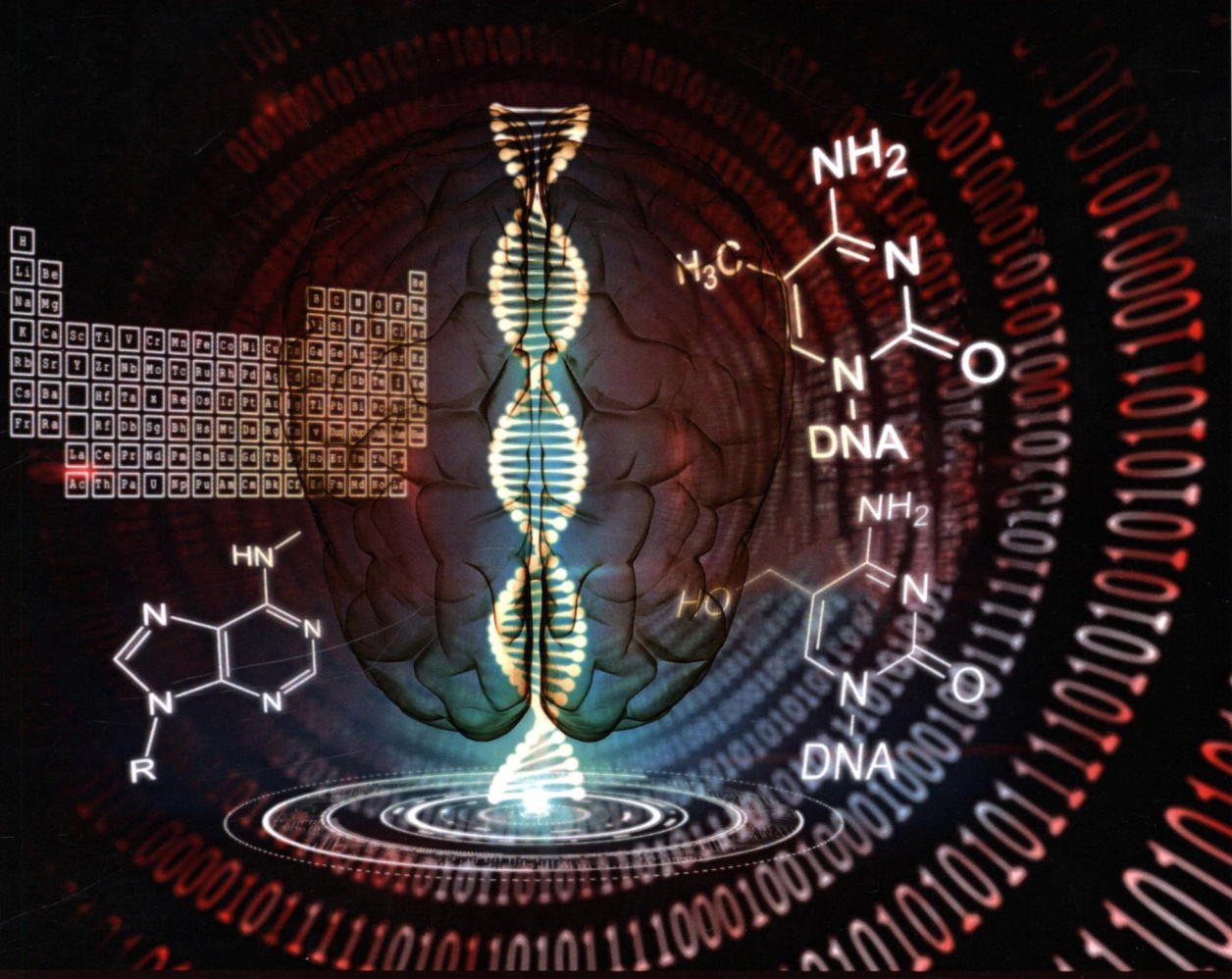
DNA Modifications in the Brain

Neuroepigenetic Regulation of Gene Expression



Edited by
Timothy W. Bredy

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The field of epigenetics is undergoing a renaissance in many fields of biology, including neuroscience. This resurgence is due to the recent observation that DNA modifications extend beyond the canonical 5-methylC. The discovery of 5-hydroxymethylC and its oxidative intermediates has catapulted DNA modification into the forefront of cutting edge research focused on understanding the means by which chemical modifications control gene expression. Despite significant progress in various areas of research, the functional role of DNA modifications and its impact on the neuroepigenetic regulation of gene expression in the brain remains to be fully elucidated. This edited volume begins with an historical overview of the early discoveries surrounding DNA methylation in the mammalian brain and then explores the evidence supporting a role for this epigenetic mechanism in controlling gene expression programs across the lifespan and in both normal and diseased states. Chapters also describe new directions and technological advances, as well as an overview of what the future holds for this exciting new field. ***DNA Modifications in the Brain: Neuroepigenetic Regulation of Gene Expression*** provides medical, graduate, and advanced undergraduate students along with researchers with a broad introduction to the dynamic nature of DNA and sheds light on evolving concepts of gene-environment interaction and their effects on adaptation and neuropsychiatric disease.

Key Features

- Provides a comprehensive overview of the many facets of DNA modifications
- Discusses the impact of this dynamic epigenetic mechanism across brain development, and the lifespan at behavioral, cognitive, molecular, and genetic levels
- Offers contributions by influential leaders in the field edited by a neuroscientist to promote synthesis between epigenetics, neuroscience, and clinical relevance

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DNA MODIFICATIONS IN THE BRAIN

Neuroepigenetic Regulation of Gene Expression

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DNA MODIFICATIONS IN THE BRAIN

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PREFACE

The field of neuroepigenetics has a long and rich history, beginning with the discovery of experience-induced DNA modifications in the brain and other landmark observations over the past 40 years by Vanyushin and Ashapkin (Chapter 1), and extended by the recent discovery of downstream oxidative derivatives of 5-methylcytosine and the elucidation of their functional roles in brain development as investigated and discussed by Li and Wei (Chapter 2), Kang et al. (Chapter 3), and Fasolino et al. (Chapter 4). This information has led to the establishment of links between DNA modification and cognition and behavior related to neuropsychiatric disease described by Mukamel and Lister (Chapter 5) and Day (Chapter 6). Therefore, it has been unequivocally demonstrated that DNA modifications are dynamic and reversible across the life span and that they play an important role in the regulation of gene expression in both the normal and the diseased brain. Together with new insights regarding the mitochondrial neuroepigenome, as introduced by Suzuki et al. (Chapter 7), and the application of recent technical advances in DNA sequencing, as discussed by Feng and Nestler (Chapter 8), these new lines of research represent the leading edge in the quest to understand gene–environment interactions and how they influence the neuroepigenetic regulation of gene expression and its impact on subsequent behavioral adaptation. It is a remarkable time for neuroscience. As discussed by Marshall and Bredy (Chapter 9), armed with new technology and freedom from the constraints of dogma, we embark on entirely new directions in the study of DNA modifications in the brain. The work described herein serves to usher in this exciting new era.

Timothy W. Bredy

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CHAPTER 1

History and Modern View on DNA Modifications in the Brain

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INTRODUCTION

Almost 70 years ago it was discovered that, along with four classical bases, so-called "minor" bases are present in DNA. 5-Methylcytosine (5mC) was found first as a minor base in various DNAs (Hotchkiss, 1948; Wyatt, 1950), and N^6-methyladenine (m6A) was soon identified in bacterial DNA (Dunn & Smith, 1955). It was later found that mammalian DNA may also contain N^2-methylguanine and 3-methylcytosine (Culp, Dore, & Brown, 1970). The mechanism underlying the accumulation of these bases in DNA was unknown for a long period. Only in 1963 were the specific DNA methyltransferases first observed in bacteria (Gold & Hurwitz, 1963) and then in eukaryotes; these enzymes transferred methyl groups from *S*-adenosyl-L-methionine selectively onto definite cytosine or adenine residues in DNA chains. It became clear that minor bases (5mC and m6A) do not incorporate into DNA during synthesis, but they accumulate as a result of enzymatic modification (methylation) of common bases (C or A, respectively) in DNA chains that are either forming or already formed. Nevertheless, the specificity and functional role of DNA methylation remained unknown for a long time. Moreover, the concept that these minor bases do not have any essential significance both in the structure of DNA itself and its functioning was quite widely disseminated. The classic model system in traditional genetics, *Drosophila*, served mistakenly very often as "irrefutable" evidence for this postulate. In fact, 5mC in the fly genome escaped detection for a very long time, leading to the conclusion that this DNA modification does not play a significant role in eukaryotic organisms. This situation did not bring very much enthusiasm to DNA methylation research in many world-renowned molecular biology laboratories, which allowed us to study this particular epigenetic mechanism without competition for many years (Table 1.1).

Actually, we have been involved in this research for more than 50 years. Similar to the great Russian physiologist (Nobel Prize Laureate) Ivan Pavlov, who erected a memorial to the dog (his beloved experimental animal), we have to erect a memorial to *Drosophila* because the preceding situation with it allowed us to peacefully

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Table 1.1 Time line of the landmark discoveries

Years	Discovery	References
1948–50	5-Methylcytosine (5mC) found as a minor base in various DNAs	Hotchkiss (1948) and Wyatt (1950)
1955	N^6-Methyladenine (m6A) identified in bacterial DNA	Dunn and Smith (1955)
1959	High content of 5mC in plant DNA found	Vanyushin and Belozersky (1959)
1962–68	CpG dinucleotides shown to be the main target of DNA methylation in eukaryotes	Doskočil and Šorm (1962) and Grippo, Iaccarino, Parisi, and Scarano (1968)
1963	DNA methyltransferases observed in bacteria	Gold and Hurwitz, (1963)
1967–73	Species, tissue, and age specificities of DNA methylation in animals discovered; role of DNA methylation in gene expression, cell differentiation, and aging proposed	Berdyshev, Korotaev, Boyarskikh, and Vanyushin (1967), Vanyushin, Tkacheva, and Belozersky (1970), Vanyushin, Mazin, Vasilyev, and Belozersky (1973), and Vanyushin, Nemirovsky, Klimenko, Vasiliev, and Belozersky (1973)
1970	First experimental evidence that methylation affects double helical structure of DNA	Vanyushin, Belyaeva, Kokurina, Stelmashchyuk, and Tikhonenko (1970)
1974–77	First evidence that neuronal DNA methylation plays a role in learning	Vanyushin, Tushmalova, and Guskova (1974), Vanyushin, Tushmalova, Guskova, Demidkina, and Nikandrova (1977), and Guskova, Burtseva, Tushmalova, and Vaniushin (1977)
1975	Conception of the maintenance DNA methylation with methyltransferases acting on hemimethylated sites proposed	Riggs (1975) and Holliday and Pugh (1975)
1978	First use of the isoschizomeric restriction endonuclease pair *Hpa*II and *Msp*I to test for the presence of 5mC in individual gene sequence	Waalwijk and Flavell (1978)
1978–80	First direct indications on reverse correlation between DNA methylation and gene activity	Waalwijk and Flavell (1978) and Sutter and Doerfler (1980)
1980	Methylation of Okazaki fragments and longer replicative intermediates found to occur immediately after replication in plants and animals	Bashkite, Kirnos, Kiryanov, Aleksandrushkina, and Vanyushin (1980) and Kiryanov, Kirnos, Demidkina, Alexandrushkina, and Vanyushin (1980)
1981	Non–CpG methylation of DNA in plants discovered	Kirnos, Aleksandrushkina, and Vanyushin (1981) and Gruenbaum, Naveh-Many, Cedar, and Razin (1981)
1981–82	Clonal inheritance of DNA methylation patterns in dividing cells experimentally demonstrated	Wigler, Levy, and Perucho (1981) and Stein, Gruenbaum, Pollack, Razin, and Cedar (1982)
1983	Selective synthesis of DNA in rat brain induced by learning discovered; mechanism of brain DNA demethylation after learning by an excision repair mechanism proposed	Ashapkin, Romanov, Tushmalova, and Vanyushin (1983)

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