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EDITORIAL

Looking Above but Not Beyond the Genome for Therapeutics in Neurology and Psychiatry: Epigenetic Proteins and RNAs Find a New Focus

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We welcome you to a special issue of *Neurotherapeutics* that highlights much of the exciting new thinking behind a burgeoning and therapeutically relevant topic—epigenetic proteins in psychiatric and neurological disease. It is now well established that expression of single genes or gene cassettes is determined by the interplay between transcription factors and epigenetic modulators. Epigenetics literally means "above the genome" and is defined by modifications of DNA, as well as chromatin that ultimately affect gene expression. Accordingly, epigenetic markers can be considered similar to punctuation marks in the English language. They define the beginning and the end of a gene; they structure the chromosomes; and they alter how the information is read, either activating or silencing transcription.

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Defining Epigenetics: You Say Tomato I Say Tomahto

The term epigenetics was first coined by Waddington in 1942. At its conception, epigenetics referred to a field that focused on how the genotype is related to the phenotype [1]. In 1996, Arthur Riggs restricted the definition to the study of mitotically hereditable changes in gene expression that occur without changes in DNA sequence [2]. Thanks to advanced technologies in genomics and gene profiling, the new millennium saw the explosion of epigenetics and revealed is relevance to diverse processes in biology. According to Adrian Bird, epigenetics is "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states" [3]. This latter definition will likely offend the purists, who, justifiably, see epigenetics in a restricted way as *heritable* changes in gene expression that cannot be explained by the codes of genes themselves [4, 5]. However, Bird's definition encompasses this traditional view of epigenetics and heritability, and is congruent with the notion that biological processes are modular, and there is selective pressure for proteins to adopt new functions that do not substitute or exclude the functions on which they were defined. Indeed, advances in technology have shown us that epigenetic changes can occur with great regularity over minutes in yeast reproducibly at distinct phases of the cell cycle. Accordingly, we now recognize that the kinetics of changes in epigenetic proteins, and, by extension, gene expression, can happen rapidly or slowly and are heritable or nonheritable, but all engage proteins or RNA that sit just above the genome, and thus qualify as part of a newer, biologically more multicultural and progressive field of epigenetics. The challenge for biologists and clinical

scientists will be to understand the regulators that differentiate this kinetics, so that therapeutic manipulations of these processes can be optimized and do not cause unexpected and durable changes through generations.

Epigenetics and Therapeutics in the Nervous System: Beyond Faddism

This issue should provide the reader with a comprehensive review of the most relevant epigenetic marks and modulators; it will present examples of dysregulated epigenetic mechanisms occurring in neuronal injury and neurodegenerative diseases; finally, this issue will describe the state of the art for small molecules to be able to target and correct these epigenetic mechanisms. The outstanding articles presented by world leaders in their respective fields offer new hope for the treatment of many acute and chronic central nervous system conditions (Fig. 1).

The issue is divided into 2 major sections, with the first section devoted to distinct families of epigenetic modifications, with some discussion of available small molecule modulators of these distinct types of modifications. The first part of the first section describes classical and emerging views of chemical modifications of DNA that affect gene expression—a process that is far more dynamic than once considered. In the review by Weng et al. (p. XX) [6], a comprehensive description of DNA methylation and demethylation, the implication of altered methylation state in neurodegenerative diseases, and the description of pharmacological and molecular approaches to correct aberrant methylation state of the DNA are described.

Chromatin is composed of DNA wrapped around histone proteins. The smallest functional unit of chromatin is called a nucleosome, where the DNA is wrapped one and three quarter times around a histone octamer. Histone proteins are rich in positively-charged amino acids, creating an electrostatic interaction with the negatively-charged DNA. Post-translational modifications of histones can alter the structure of the chromatin, creating a compact or open structure. For example, the balance between chromatin acetylation and deacetylation correlates with active and repressed transcriptional states. One way to bias histone acetylation in favor of transcription is via histone acetyltransferase (HAT) activity. In the review by Schneider et al. (p. XX) [7], a detailed description of the most promising HAT activators is reported.

The complementary strategy to HAT activation is histone deacetylase (HDAC) inhibition—a strategy that has been utilized for therapeutic success in the brain, spinal cord, and peripheral nervous system. A complete description of the state-of-the-art for selective HDAC inhibitors is reported in the review by Wagner et al. (p. XX) [8]. The description of HDAC inhibitors is focused on small molecules that target class I, II, and IV HDACs, where all the constituents share a conserved structure and present a zinc catalytic site binding. Conversely, class III HDACs are characterized by nicotinamide adenine dinucleotide^{+}-binding enzymes called Sirtuins. In the review by Langley and Sauve (p. XX) [9], the involvement of sirtuins in disease mechanisms is carefully described.

The mechanisms that determine which part of the genome are silenced or activated are evolving, and recent discoveries have highlighted the importance of noncoding RNAs in modulating or recruiting some of the factors responsible for laying down the marks or removing them. There are many classes of noncoding RNAs and 2 articles focus on 2 of the most studied classes: the microRNAs (Varela et al., p. XX [10]) and long noncoding RNAs (Quereshi and Mehler, p. XX [11]).

Interestingly, not only have epigenetic regulators been reported to be dysregulated in neurological and psychiatric conditions, there is also evidence that the use of small molecules targeting different elements of the epigenome can be a promising therapeutic approach. In the second section of this issue, we have tried to create a reference that summarizes the most interesting results reported in aging, as well as neurological and psychiatric conditions that span from monogenic diseases to multifactorial genetic and sporadic syndromes, and acute injuries. For all of these conditions, the environment is recognized to play an important role.

Zhao et al. (p. XX) [12] elaborately describe the active role of epigenetic regulation in neurobiology and emphasize the epigenetic changes that occur during normal aging. In Huntington's disease, caused by a trinucleotide expansion in the coding gene of huntingtin, transcriptional dysregulation has been thoroughly characterized. Accordingly, malfunction in all the epigenetic players like histone acetylation, methylation, DNA methylation, and noncoding RNA was reported, suggesting that a combinatorial therapy targeting several of these mechanisms could be a promising strategy (Lee et al., p. XX [13]). Conversely, in spinal muscular atrophy, another disease characterized by nucleotide repeats in a coding region of the gene, only HDAC inhibitors provided positive results in both in vitro and in vivo models of the disease, leading to the design of several clinical trials in humans, as described by Lunke et al. (p. XX) [14]. HDAC inhibitors have also been shown to rescue defects observed in Niemann-pick disease type C, which may have relevance for other disorders involving cognitive abnormalities (Helquist et al. p. XX [15]).

Multifactorial diseases, such as Parkinson's disease (Kaidery et al., p. XX [16]) and Alzheimer's disease (Sai Veerappan, p. XX [17]), are an interesting example of how the environment can modulate the genome and contribute to the outcome of neurodegenerative conditions. In amyotrophic lateral sclerosis, Martin and Wong (p. XX) [18] instead discuss the importance of DNA methylation and present potential therapeutic role of pharmacological inhibitors by targeting Dnmt3a activity. Finally, several psychiatric disorders are characterized by transcriptional impairments (Mahgoub and Monteggia, p. XX [19]). Despite the lack of evidence for therapeutics targeting the

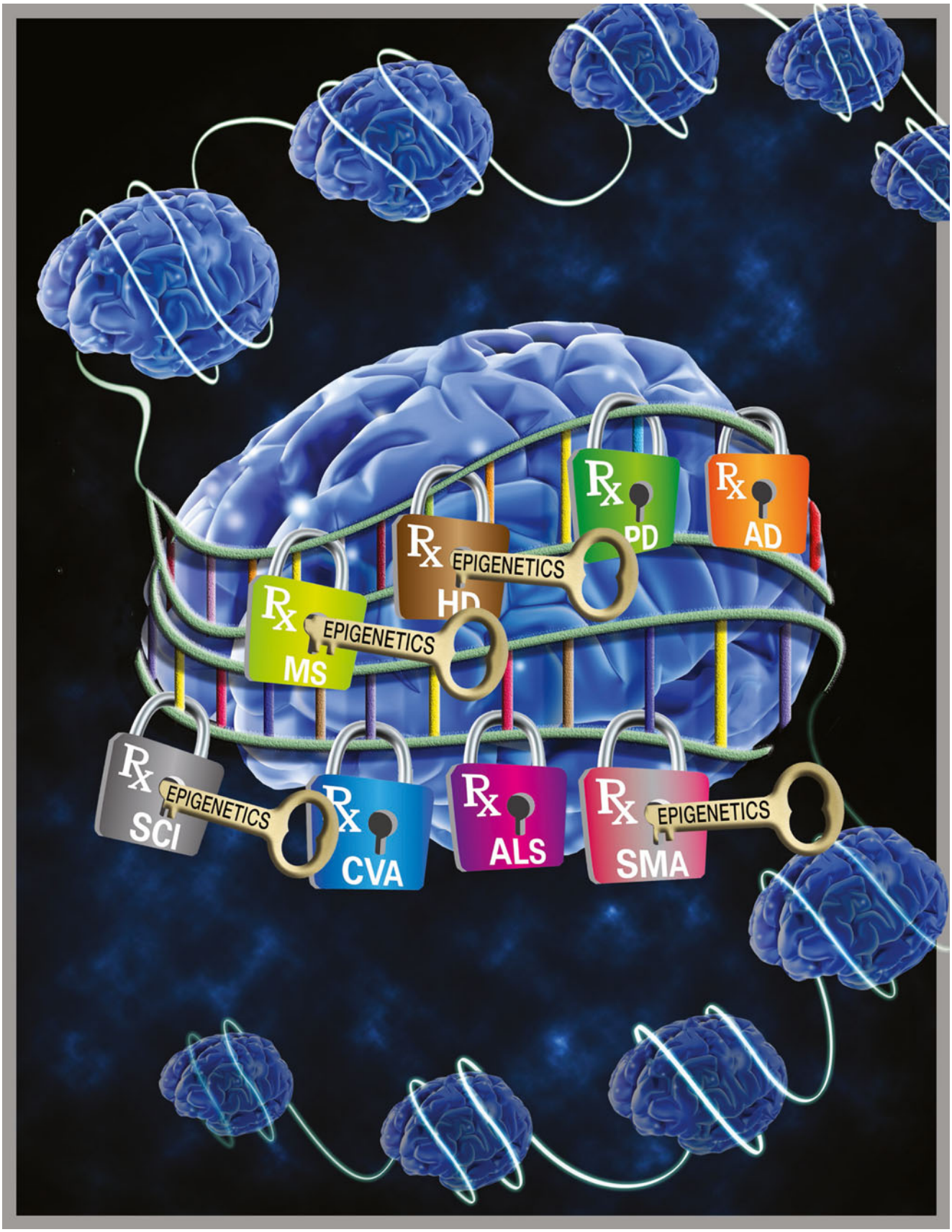

Fig. 1 A symbolic view of the role that epigenetic proteins and RNA can play in unlocking new therapeutics for challenging neurological and pyschiatric conditions

epigenome, Rangasamy et al. (p. XX) [20] extensively summarize the epigenetic alterations reported in the autism spectrum disorders (Angelman syndrome, Prader–Willi syndrome, fragile X syndrome, and Kabuki syndrome).

York et al. (p. XX) [21] describe the complexity of spinal cord injury, where several cellular populations (injured neurons, astrocytes, and oligodendrocytes) are affected and manifest epigenetic alterations. The activity of small molecule HDAC inhibitors proved to be beneficial in each of these populations by engaging the repair processes. Similarly, Linder et al. (p. XX) [22] provide a comprehensive overview of the injury-induced mechanisms that can halt neuronal regeneration, and highlight the potential of epigenetic modulators in correcting the activity of central genes like *CREB1*. To complete the overview on the role of glial cells in acute and chronic diseases, and their response to epigenetic therapeutics, Garden (p. XX) [23] reviews the most exciting outcomes in neuroinflammation. In another acute neuronal injuries, such as stroke, HDACs seem to be the major class of epigenetic regulators involved both in preconditioning (Thompson, p. XX [24]) and neuronal repair (Baltan et al., p. XX [25]). Selective isoforms responsible for the damaging effects are currently under investigation (Baltan et al., p. XX [25] and Edward Holson et al., p. XX [8]). The role of epigenetic proteins in neural plasticity and stroke rehabilitation is also reviewed, with a particular focus on polycomb proteins, adenosine triphosphate-dependent chromatin modifiers, and the role of HDACs in hippocampal-based plasticity mechanisms (Elder et al., p. XX [26]).

Finally, chromatin modifications appear to play a role in DNA repair after damage. As elegantly summarized by Brochier and Langley (p. XX) [27], DNA damage participates in the pathogenic mechanisms involved in aging, stroke, spinal cord injury, Alzheimer's disease, Huntingdon's disease, Parkinson's disease, and amyotrophic lateral sclerosis, and the broad salutary effects of HDAC inhibition in models of these conditions may be mediated via effects on DNA damage.

Emerging Areas

The role of epigenetic modulators in physiology and disease in the nervous system is moving so rapidly that even the comprehensive set of articles presented here cannot entirely capture all of the most exciting and current advances in the field. Notably, articles focused on histone methylation and other novel post-translational modifications of histones (e.g., succinylation, glycosylation, citrullination, etc.) are not included, and the reader is referred to an outstanding review in this area [28]. Moreover, burgeoning interest in cell metabolism in the context of cancer and neurodegenerative disease has stimulated much interest in how specific metabolic changes in glucose metabolism and its downstream metabolites are converted into changes in gene expression via epigenetic proteins. Many of these epigenetic proteins utilize metabolic substrates as cofactors and thus directly connect environmental metabolic changes into changes in gene expression [29]. Finally, it is now recognized that sequence variants in histone proteins provide another mechanism to generate diversity in chromatin structure and function. These studies have been led, to a good degree, by David Allis, the father of the concept of the histone code [30, 31].

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References

1. Waddington C. The epigenotype. Endeavour 1942;1:18–20.
2. Riggs A, Russo V, Martienssen R. Epigenetic mechanisms of gene regulation. Cold Spring Harbor Laboratory Press, Plainview, NY, 1996.
3. Bird A. Perceptions of epigenetics. Nature 2007;447:396–398.
4. Ptashne M. Epigenetics: core misconcept. Proc Natl Acad Sci U S A 2013;110:7101–7103.
5. Ptashne M. Faddish stuff: epigenetics and the inheritance of acquired characteristics. FASEB J 2013;27:1–2.
6. Weng Y, An R,Shin J, Song H, Ming G. DNA Modifications and Neurological Disorders. Neurotherapeutics. 2013
7. Schneider A, Chatterjee S, Bousiges O, Selvi BR, Swaminathan A, Cassel R, Blanc F, Kundu TK, Boutillier AL. Acetyltransferases (HATs) as targets for neurological therapeutics. Neurotherapeutics. 2013
8. Edward Holson E, Wagner FF, WeïWer M, Lewis MC. Small Molcule Inhibitors of Zinc-Dependent Histone Deacetylses (HDACs). Neurotherapeutics. 2013
9. Langley B, Sauve A. Sirtuin Deacetylases as Therapeutic Targets in the Nervous Systems. Neurotherapeutics. 2013
10. Varela MA, Roberts TM, Wood MJA. Epigenetics and ncRNAs in brain function and diseasse: mechanisms and prospects for therapy. Neurotherapeutics. 2013
11. Qureshi IA, Mehler MF. Long non-coding RNAs: novel targets for nervous system disease diagnosis and Therapy. Neurotherapeutics. 2013
12. Zhao Y, Jordan IK, Lunyak VV. Epigenetics Components of Aging in the Central Nervous System. Neurotherapeutics. 2013
13. Lee J, Hwang YJ, Kim KY, Kowall KW, Ryu H. Epigenetic Mechanisms of Neurodegeneration in Huntington's Disease. Neurotherapeutics. 2013
14. Lunke S, El-Osta A. Applicability of histone deacetylase inhibition for the treatment of spinal muscular atrophy. Neurotherapeutics. 2013
15. Helquist P, Maxfield F, Wiech NL, Wiest O. Treatment of Niemann-Pick Type C Disease by Histone Deacetylase Inhibitors. Neurotherapeutics. 2013
16. Kaidery NA, Tarannum S, Thomas B. Order Epigenetic landscape of Parkinson's Disease: Emerging role in disease mechanisms and therapeutic modalities. Neurotherapeutics. 2013

17. Sai Veerappan C, Sleiman SF, Coppola G. Epigenetics of Alzheimer's Diesease and Frontotemporal Dementia. Neurotherapeutics. 2013
18. Martin LJ, Wong M. Aberrant Regulation of DNA Methylation in Amyotrophic Lateral Sclerosis: A New Target of Disease Mechanisms. Neurotherapeutics. 2013
19. Mahgoub M, Monteggia L. Epigenetics and Psychiatry. Neurotherapeutics. 2013
20. Rangasamy S, D'Mello S, Narayanan V. Epigenetics, Autism Spectrum, and Neurodevelopmental Disorders. Neurotherapeutics. 2013
21. York EM, Petit A, Roskams AJI. Epigenetics of Neural Repair Following Spinal Cord Injury. Neurotherapeutics. 2013
22. Lindner R, Puttagunta R, Di Giovanni S. Epigenetic regulation of axon outgrowth and regeneration in CNS injury: the first steps forward. Neurotherapeutics. 2013
23. Garden G. Epigenetics and the Modulation of Neuroinflammation. Neurotherapeutics. 2013
24. Thompson JW, Dave KR, Young JI, Perez-Pinzon MA. Ischemic preconditioning alters the epigenetic profile of the brain from ischemic intolerance to ischemic tolerance. Neurotherapeutics. 2013
25. Baltan S, Morrison RS, Murphy SP. Novel protective effects of histone deacetylase inhibition on stroke and white matter ischemic injury. Neurotherapeutics. 2013
26. Elder J, Sleiman SF, Basso B, Edwards D, Holson E, Ratan RR. Epigenetics of stroke recovery and rehabilitation: from polycomb to HDACs. Neurotherapeutics. 2013
27. Brochier C, Langley B. Chromatin modifiations associated with DNA double strand breaks repair as potential targets for neurological disesases. Neurotherapeutics. 2013
28. Kulathu Y, Garcia FJ, Mevissen TE, Busch M, Arnaudo N, Carroll KS, et al. Regulation of A20 and other OTU deubiquitinases by reversible oxidation. Nat Commun 2013;4:1569.
29. Lu C, Thompson CB. Metabolic regulation of epigenetics. Cell Metab 2012;16:9–17.
30. Banaszynski LA, Allis CD, Lewis PW. Histone variants in metazoan development. Dev Cell 2010;19:662–674.
31. Banaszynski LA, Allis CD, Shechter D. Analysis of histones and chromatin in Xenopus laevis egg and oocyte extracts. Methods 2010;51:3–10.