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Review

Epigenetic modulation by small molecule compounds for neurodegenerative disorders

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RG108 (PubChem CID:702558)
SAHA (PubChem CID:5311)
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ABSTRACT

The accumulation of somatic and genetic mutations which altered the structure and coding information of the DNA are the major cause of neurological disorders. However, our recent understanding of molecular mechanisms of 'epigenetic' phenomenon reveals that the modifications of chromatin play a significant role in the development and severity of neurological disorders. These epigenetic processes are dynamic and reversible as compared to genetic ablations which are stable and irreversible. Therefore, targeting these epigenetic processes through small molecule modulators are of great therapeutic potential. To date, large number of small molecule modulators have been discovered which are capable of altering the brain pathology by targeting epigenetic enzymes. In this review, we shall put forward the key studies supporting the role of altered epigenetic processes in neurological disorders with especial emphasis on neurodegenerative disorders. A few small molecule modulators which have been shown to possess promising results in the animal model system of neurological disorders will also be discussed with future perspectives.

1. Introduction

The human genome encodes over 20,000 genes and these genes are composed of DNA sequences that carry information essential for the normal growth, development and survival of an organism. In order to facilitate the packaging of 2-m-long DNA strand in the compact nucleus of eukaryotic cells roughly around 10 μm diameter, the DNA present in the nucleus of these cells associate with histones, non-histone proteins and RNA to form a highly organized and complex structure termed as Chromatin. The fundamental and functional unit of Chromatin is the nucleosome, which is formed by wrapping of 146 base pairs of DNA around octamer of four core histone proteins (H2A, H2B, H3 and H4). These structures are further arranged through a series of successively higher order structures to eventually form a Chromosome which adds up both level of compactness and an extra layer of regulatory control that ensures fidelity of gene expression [1]. During the process of all DNA templated phenomenon: repair, replication, recombination and transcription, dynamic opening and closing of chromatin structure in a precise manner is essential for the cellular and organismal homeostasis. Highly regulated epigenetic enzymes through signal dependent cross talks establishe the epigenetic language for the functional genome fluidity [2]. In mammalian cells, three major epigenetic mechanisms operate in conjunction to fine tune the gene expression. These include reversible covalent modifications of DNA and DNA associated proteins along with non-coding RNA (Fig. 1). These epigenetic modifications direct the development and differentiation of cells with identical genome into various cell-types by turning on or off the gene expression in a stimulus specific manner.

There are around 170 billion cells (approximately 86 billion neurons and almost similar amount of non-neuronal cells) with specific functions in the human brain, making it a highly complex and specialized organ [3]. Interestingly, all cell types are originated from a

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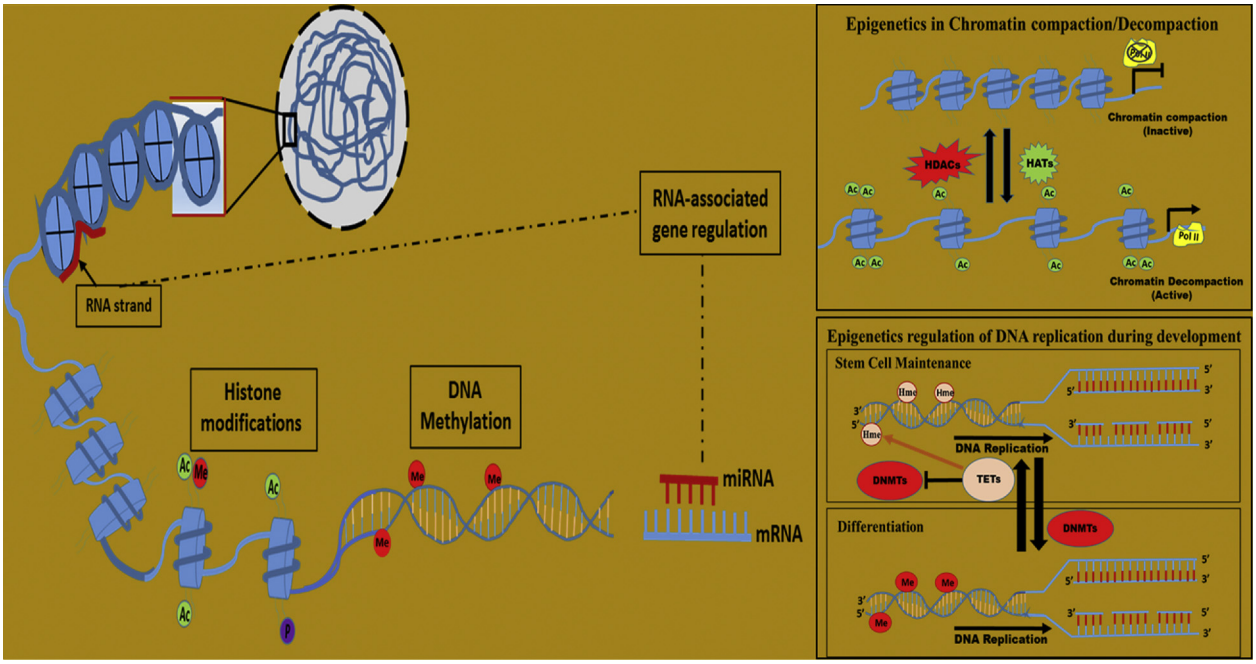

Fig. 1. Fundamental of epigenetics. Three major epigenetic mechanisms that operate in conjunction to fine-tune the gene expression are DNA methylation, covalent modification of histones, and non-coding RNAs. These epigenetic machineries play crucial role in several cellular and molecular functions such as chromatin compaction/decompaction during gene expression and regulation of DNA replication during development.

common neural-lineage restricted stem cells (NLRSCs) which possess the same genetic content [4]. Thus, it is quite evident that epigenetic modifications play a key role during neural development by precisely controlling gene expression in temporal, spatial and cell-type specific manner. Several epigenetic marks have now been well established and characterized with various neuronal functions such as learning, cognition, plasticity and behavior. Additionally, the global alteration in the epigenetic patterns during the aging process is quite well-established and is termed as epigenetic drift which results in progressive decline in cells, tissues and organisms' functions, thereby increasing the risk of several cerebrovascular and neurodegenerative diseases. For a long time neurological disorders had been thought to be caused majorly through accumulation of somatic and genetic mutations that alters the structure and coding information of the DNA. Dysregulation of epigenetic processes have been found to be crucial for several neurological disorders such as Alzheimer's, Parkinson's, Huntington diseases and many more [5–7]. Thus, these modifications are considered to be potential targets for therapeutics. In this review, we will be discussing the key studies supporting the role of altered epigenetic processes in neurological disorders with especial emphasis on neurodegenerative disorders, and how modulating these epigenetic processes through small molecule modulators is emerging as a therapeutic options in the field of neurodegenerative and neurological disorders treatment. Finally, we discuss about the current status and future perspective of these small molecule epigenetic modulators as a specific therapeutic option for neurological disorders.

2. Epigenetics and neurological disorders

The emerging cases of neurodevelopmental and neurodegenerative disorders possess a great treat to human health. The genetic basis of some of these disorders have been characterized. Based on these information, specific diagnostics are yet to be developed. However, at present, these diseases are diagnosed largely through disease symptoms and neuronal imaging at very advanced stage. Neurodegenerative diseases are characterized by damage of neurons in specific region of brain due to accumulation of specific intracellular proteins. However, it is still unexplained whether these aggregations are the primary cause of neurodegeneration or some combination of dysregulated cellular mechanisms such as replication, transcription, translation, protein homeostasis or mitochondrial dysfunction. Besides the genetic factors (both somatic and hereditary) epigenetic modifications in the brain cells seems to be critical for the development and progress of several neural disorders. Here, we will discuss the role of epigenetic factors: DNA methylation, Histone modifications, and non-coding RNAs in neurological functions and disorders.

2.1. DNA methylation in neurological disorders

2.1.1. DNA methylation

DNA methylation is the covalent modification of DNA catalyzed by a group of enzymes called DNA methyltransferases (DNMTs) which adds a methyl group on 5th position of cytosine in CpG dinucleotide sequence [8,9]. It correlates with transcriptional repression and was reported to decrease in level during the aging process leading to decreased cellular, molecular and organismal functions [10]. For a long time, this modification of DNA was thought to be irreversible/stable epigenetic mark, but, very recently, an enzyme Ten Eleven Translocation protein1 (TET1) that catalyzes the conversion of 5-methyl cytosine (5mc) to 5-hydroxymethyl cytosine (5hmc) has been identified [11]. Other proteins such as GADD45a and GADD45b were also suggested to catalyze DNA demethylation during electroconvulsive treatments (ECTs)-induced adult neurogenesis [12]. These studies suggest that this epigenetic mark is not stable and can be modified in stimulus specific condition. Emerging evidence show that the DNA methylation play crucial role during neural development and aging process. It also brings about phenotypic and structural changes in synapses in a stimulus specific manner that accounts for synaptic plasticity during experience dependent learning and memory. For instance, work from Miller and group show that there is hypermethylation of *calcineurin* gene in prefrontal cortex of rats after contextual fear conditioning training and this hypermethylation persists even 1 month after the training [13]. Similarly, JD Sweatt and his colleagues had shown there is transcriptional silencing of a memory suppressor gene *Pp1* through increased