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Review

Role of 5-hydroxymethylcytosine in neurodegeneration

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ABSTRACT

The recent discovery of 5-hydroxymethylcytosine (5hmC), an epigenetic modifier and oxidation product of 5-methylcytosine (5mC), has broadened the scope and understanding of neural development and neurodegenerative diseases. By virtue of their functional groups, 5mC and 5hmC exert opposite effects on gene expression; the former is generally associated with gene silencing whereas the latter is mainly involved in up-regulation of gene expression affecting the cellular processes such as differentiation, development, and aging. Although DNA methylation plays an important role in normal neural development and neuroprotection, an altered pathway due to complex interaction with environmental and genetic factors may cause severe neurodegeneration. The levels of 5hmC in brain increase progressively from birth until death, while in patients with neurodegenerative disorders, the levels are found to be highly compromised. This article discusses the recent developments in the area of hydroxymethylation, with particular emphasis on the role of 5hmC in neurodegenerative diseases including Alzheimer's disease, Parkinson's diseases and Huntington's disease. We have also included recent findings on the role of 5hmC in brain tumors (gliomas). Despite compelling evidence on the involvement of 5hmC in neurodegeneration, it is yet to be established whether this epigenetic molecule is the cause or the effect of the onset and progression of neurodegenerative diseases.

Contents

Abbreviations: AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; 5caC, 5-carboxylcytosine; CNS, central nervous system; CpG, cytosine-phosphate-guanine; DhMRs, differentially hydroxymethylated regions; DNA, deoxyribonucleic acid; DNMTs, DNA methyltransferases; 5Fc, 5-formylcytosine; HD, Huntington's disease; HDIs, histone deacetylase inhibitors; H3K4me3, histone H3 lysine 4 trimethylation; 5hmC, 5-hydroxymethylcytosine; 5mC, 5-methylcytosine; HPG, hippocampus/parahippocampal gyrus; IDH1, isocitrate dehydrogenase 1; MAPT, microtubule-associated protein tau; MFG, middle frontal gyrus; MTG, middle temporal gyrus; PD, Parkinson's disease; REST, RE1 Silencing Transcription Factor; SAM, S-adenosyl-L-methionine; TETs, ten-eleven translocation enzymes; UTRs, untranslated regions; SN, substantia nigra; SNCA, alpha-synuclein; YAC, yeast artificial chromosome.

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1. Introduction

DNA methylation is one of the important epigenetic factors that modulates the gene expression. The dynamics of DNA methylation is an essential component of epigenetic regulation in the mammalian central nervous system (Irier and Jin, 2012). 5-Hydroxymethylcytosine (5hmC), an oxidative product of 5-methylcytosine (5mC) is a newly described epigenetic modification and is a key intermediate in the DNA demethylation process (Wen et al., 2014). Genome-wide profiling reveals that 5hmC is highly enriched on specific gene regions including exons and especially the untranslated regions (UTRs), but it is depleted on introns and intergenic regions (Wang et al., 2012). The presence of high levels of 5-hmC in the brain and its lower affinity to methyl-binding proteins as compared to 5mC indicate that it might have a peculiar role in the regulation of gene expression in nervous tissue (van den Hove et al., 2012). Although 5-mC is generally associated with the repression of gene expression, 5hmC is mainly involved in up-regulation of gene expression affecting the cellular processes such as differentiation, development, and aging (Coppieters et al., 2014). The methylation status of promoter proximal cytosine-phosphate-guanine (CpG) dinucleotides is in a dynamic balance between DNA methylation and hydroxymethylation while the later process and subsequent demethylation is more complex and involves additional proteins downstream of 5hmC, including members of the base excision repair pathway (Grayson and Guidotti, 2013; Szulwach et al., 2011).

The presence of 5hmC was first reported by Penn and coworkers (1972) in mammalian DNA but renewed interest was not generated until 2009 when increased levels of 5hmC were reported in mice brain and embryonic stem cells (Kriaucionis and Heintz, 2009; Tahiliani et al., 2009). Apart from its high levels observed in the central nervous system (CNS), 5hmC continues to be detected in other mammalian tissues as well indicating its increased universal role in regulation of gene expression (Globisch et al., 2010).

In order to understand the epigenetic pathways, profiles and clinical features of neurodegenerative diseases at the global level the Human Epigenome Project has been initiated (Jones et al., 2008). Once enough epigenomic data are profiled, an integrated approach incorporating other 'omics' can help in better understanding of the pathophysiology of neurodegeneration and aging. The potential for incorporating the use of epigenetic markers in the diagnosis, evaluation and treatment of neurodegenerative disorders is promising but a clear understanding of the epigenetic and molecular pathways is important before reaching that milestone. In this review, we discussed the mechanism of DNA methylation pathway and the impact of 5hmC on neurodegeneration with particular emphasis on its involvement in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and brain tumors (gliomas).

2. DNA methylation pathway

DNA is comprised of sequential arrangement of four genetic nuclear bases namely, adenine (A), thymine (T), cytosine (C), and guanine (G). Four modified bases including 5-methylcytosine (5mC), 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) have also been discovered and classified as 5th, 6th, 7th and 8th bases of the DNA, respectively. Of these, 5mC and 5hmC are methylated and hydroxymethylated forms respectively, and play important roles in epigenetic regulation of gene expression. In the first step of DNA methylation, cytosine is converted to 5mC in the presence of DNA methyltransferases (DNMTs) that utilize S-adenosyl-L-methionine (SAM) as the methyl group donor (Fig. 1). There are five subtypes of DNMTs; the detail of their specificities is beyond the scope of this review. The ten–eleven translocation enzymes (TETs), which are a group of iron(II)/αKG-dependent dioxygenases, sequentially oxidize 5mC to 5hmC, 5fC and 5caC. Finally, 5caC is decarboxylated to the parent compound (cytosine) to complete the cycle (Fig. 1). So, only 5mC is the methylated form whereas 5hmC, 5fC and 5caC are the intermediates of the demethylation pathway. These transformations may constitute an oxygen-sensing and regulation pathway in mammalian cells (Song et al., 2011); however, fully extended pathways associated with DNA demethylation are yet to be elucidated (Franchini et al., 2012).

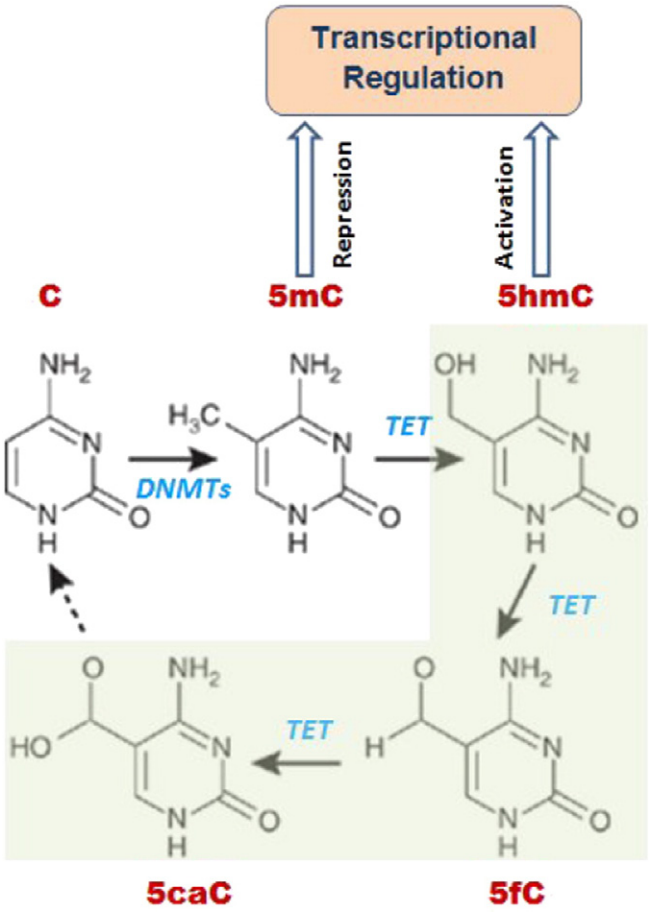

Fig. 1. Schematic representation of the DNA methylation pathway. The unshaded reaction is the methylation step. The shaded portion shows the intermediates of demethylation.

In mammals, DNA methylation ensues at the cytosine-phosphate-guanine (CpG) junctions of the CG bases in the DNA sequence. In case of humans, 80–90% of the CpG sites are methylated and not involved in transcriptional activity. The GC-rich CpG islands are the exception and harbor the promoters of more than 50% of the mammalian genes. DNA methylation, as one of the epigenetic mechanisms, is known to play an important role in genetic transcription by modifying the regulation of gene expression and occurs at the C-5 position of the cytosine moiety (Nugent et al., 2015).

3. Impact of DNA methylation on neural development

DNA methylation pathway plays an important role in neural development and maintenance. Jin et al. (2010) have reported that 5hmC undergoes significant changes in its mapping pattern from birth till death while the 5hmC modifications are dynamic with some changes occurring during early development while others taking place during the later stages of development. They reported a 2-fold increase in the levels of 5hmC in the hippocampus and a 4-fold increase in the levels of 5hmC in the cerebellum in adult mice. This study also showed a cohort of genes that showcase 5hmC modifications only at 6–8 weeks but seem to vanish as the mice continue to age (Jin et al., 2010). This same signature of genes was found to be important for neuronal cell development (Feng et al., 2010).