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Review

Hydroxymethylation and its potential implication in DNA repair system: A review and future perspectives

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ABSTRACT

The 5-hydroxymethylcytosine (5-hmC) is known to exist as a predictive indicator for a variety of cancers, neurological abnormalities and other perilous diseases. The precursor of 5-hmC i.e. 5-methylcytosine (5mC) has already gained attention as an important epigenetic regulator whereas 5-hmC remains less explored. The two modified DNA bases (5mC and 5-hmC) have absolute diverse distribution, i.e. 5-hmC is mostly restrained to the 5′ end of DNA with levels directing the gene transcription whereas 5mC is mainly located at the intra- or intergenic regions of DNA repeats and within certain gene bodies. It has been reported that levels of 5-hmC in different tissues provide a useful tool for detecting numerous associated diseases and their progression. Therefore, to unravel the role of hydroxymethylation in various resulting diseases in humans, comprehensive information on this crucial process has been explored and compiled for its implication in DNA repair system. The role of miRNAs in cancer through hypo- and hypermethylation has also been explored and discussed. In this review, a broad and exclusive insight into hydroxymethylation and its association with repair mechanisms is extensively presented and it is estimated that the accessible information will be of utmost use to the biological community working in the relevant research area.

Contents

Abbreviations: C, Cytosine; DNMT, DNA methyl transferase; BER, Base Excision Repair; NER, Nucleotide Excision Repair; TET, Ten Eleven Translocation protein; 5mC, 5methylcytosine; 5hmC, 5-hydroxymethylcytosine; 5fC, 5-formylcytosine; 5caC, 5-carboxylcytosine; ESC, Embryonic Stem Cells; NHEJ, Non-homologous End Joining; HRR, Homologous recombination repair; PGC, Primordial germ cells; AID, Activation-induced DNA-cytosine deaminase; APOBEC, Apolipoprotein BmRNA-editing catalytic polypeptides; MLL, Myeloid/Lymphoid or mixed lineage lymphoma; PRC2, Polycomb repressive complex 2; SIN3A, Swi-independent 3A; TDG, Thymine DNA glycosylase; AD, Alzheimer's disease; SZ, Schizophrenia; GAD67, Glutamic Acid Decarboxylase 67; RELN, Reelin; DRD2, Dopamine D2 Receptor; PD, Parkinson's disease; SNP, Single Nucleotide Polymorphism; EGFR, Epidermal GrowthFactorReceptor; IR, Ischemia/Reperfusion; miRNA, MicroRNA; MBD, Methyl-CpG-Binding Domain; UHRF, Ubiquitin-like with PHD and Ring Finger Domains.

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1. Introduction

Over the recent years, DNA hydroxymethylation has been examined as a crucial process in different laboratories but its biological role is not yet evidently understood. The process is being explored for its critical role in epigenetic regulation as well as its participation in other processes such as cancer development, progression, neurological abnormalities and renewal of stem cells. The process of hydroxymethylation is observed after methylation of DNA at C5 position of cytosine (C) residue via DNA methyltransferases (DNMTs) i.e. DNMT 1, 3a & 3b which are then oxidized by ten eleven translocation (TET) enzymes. The abnormal cytosine hydroxymethylation has been linked to several disorders and a variety of cancers. It has been reported that the paternal genome experiences genome-wide DNA demethylation via an active mechanism before DNA replication (Wossidlo et al., 2011).

Studies have also suggested that the search for enzymes responsible for this demethylation has produced numerous candidates and reaction mechanisms (Gehring et al., 2009) that mainly lie within three main categories: the mechanism involving direct reversal of the methyl group from the 5C position of cytosine; DNA repair, involving either base excision repair (BER) or nucleotide excision repair (NER); and iterative enzymatic oxidation which leads to conversion of 5methylcytosine (5mC) to 5-hydroxymethylcytosine (5-hmC) by using cofactors Fe^{2+} and α-ketoglutarate (α-KG) (Klose et al., 2007) and further to 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) (He et al., 2011; Pfaffeneder et al., 2011). This conversion is mediated by TET proteins of the DNA dioxygenase family (Gu et al., 2011). The entire process and possible conversions are very well described by Schomacher (2013) as represented in Fig. 1. It has been identified recently that the conversion by these TET proteins is another imperative epigenetic modifications in DNA along with the histone modifications (Tahiliani et al., 2009a). This cytosine hydroxymethylation has critical role in regulating the gene expression (Munzel et al., 2011) since hydroxymethylation levels are found to be associated with the pluripotency of stem cells (Wu and Zhang, 2011a). In general, the 5mC generated from DNA methylation downregulates the gene expression or leads to gene silencing whereas 5-hmC, with molecular formula $C_5H_7N_3O_2$, produced from DNA hydroxymethylation is known to perform alternative functions.

The two modifications, namely methylation and hydroxymethylation are quite dissimilar as 5-hmC recruits different transcriptional regulators, repair proteins and chromatin regulators as utilized by 5mC and these modifications heavily rely on the transcriptional activity (Wu and Zhang, 2011b). It has been reported that 5-hmC is not only important for embryonic development but also regulates cellular differentiation (Straussman et al., 2009). DNA hydroxymethylation is also drawn in diverse processes associated with neurological abnormalities and immune processes by mainly utilizing the TET enzyme family. The chemical composition of mC and hmC vary both in their polarity and sizes. mC is hydrophobic while hmC can form hydrogen bonds and is bulkier than the methyl group and therefore needs a larger binding pocket to be accommodated. Due to chemical differences between the various oxidized forms of mC derivatives, there is a requirement of distinct binding patterns and thus biochemical and structural studies are required to decipher the molecular mechanisms and functions.

In addition to DNA repair associated proteins (helicases and glycosylases) and mechanisms, there are other accessory components such as transcription factors and chromatin modifying enzymes which interact specifically with mC derivatives. Till date, it was observed from various studies that most of the 'classic' methyl-CpG-binding domain (MBD) proteins have substandard affinity for hmC as compared to mC. However, methyl CpG binding protein 2 (MeCP2) was reported to specifically bind hmC, even though with slightly lower affinity compared to mC (Sprujit and Vermeulen, 2014). Another mammalian protein MBD3, which does not bind mC with a high affinity, was also reported to interact with hmC (Sprujit and Vermeulen, 2014). There

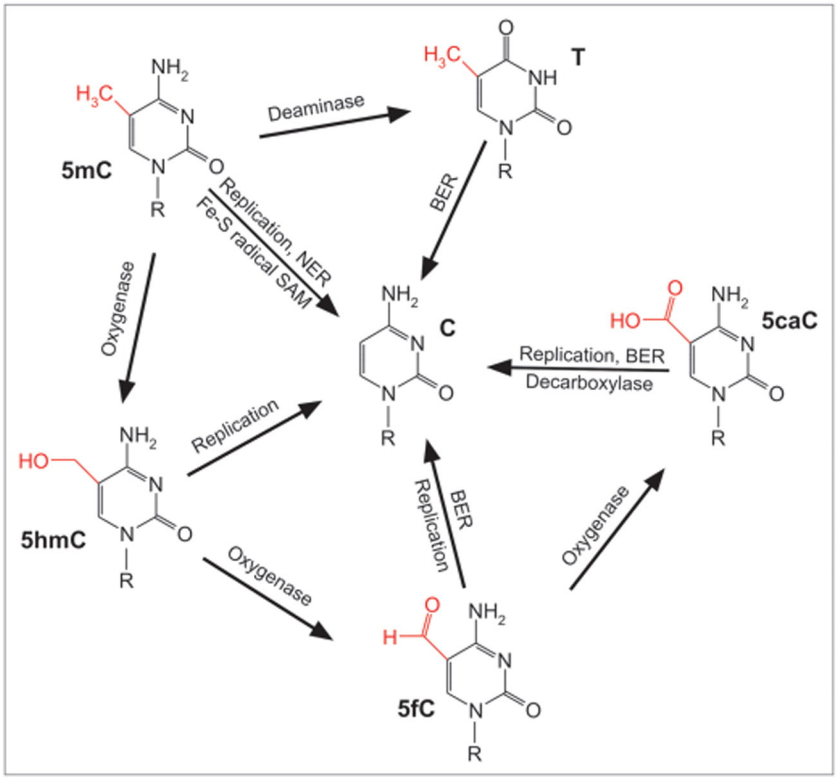

Fig. 1. Transformations in mammalian DNA demethylation process. Different enzymes associated in 5mC demethylation. The exocyclic group at C-5 of each cytosine derivative is highlighted in red. Abbreviations: C, cytosine; T, thymine; 5-hmC, 5-hydroxymethylcytosine; 5fC, 5-formylcytosine; 5caC, 5-carboxylcytosine; BER: base excision repair; NER, nucleotide excision repair. Reused with permission from the author. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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