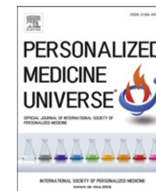
Personalized Medicine Universe 1 (2012) 7–12

Contents lists available at SciVerse ScienceDirect

Personalized Medicine Universe

journal homepage: www.elsevier.com/locate/pmu



Review

Epigenetics in cancer and inflammation

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ARTICLE INFO

Article history:
Received 22 March 2012
Accepted 27 March 2012

Keywords:
Cancer
DNA methylation
Epigenetics
Biomarker
Inflammation

ABSTRACT

Purpose: Epigenetics has a critical role in various events in both normal development and human disease. DNA methylation, a major epigenetic modification, regulates gene expression at the transcriptional level. In this review, to understand epigenetics we focus on DNA methylation in molecular biology and human disease.
Study selection: We selected 105 reports related to DNA methylation in molecular biology or human disease using PubMed (NCBI) database.
Results: In carcinogenesis, aberrant DNA methylation, such as hypomethylation of the global chromosome and hypermethylation of some tumor suppressor genes, is observed. In addition, in chronic inflammation caused by *Helicobacter pylori* infection, some genes are methylated. DNA methylation has the potential to be a biomarker for cancer diagnosis and a target for cancer therapy.
Conclusion: Elucidating DNA methylation is important for understanding molecular biology and human disease. Further studies of epigenetics will contribute to applications for diagnosis and therapy in human disease.
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1. Introduction

Epigenetics is defined as the heritable changes in the activity of gene expression without alteration of DNA sequences, which has been linked to many human diseases, including cancer [1]. DNA methylation and histone modification are well-known epigenetic changes that can lead to gene activation or inactivation [1–3]. DNA methylation is an important epigenetic factor in gene expression and the maintenance of DNA integrity and stability in many biological processes, such as genomic imprinting, normal development, and proliferation [4–6]. Patterns of DNA methylation are tissue-specific and cell-specific and are generated during development by *de novo* methylation and demethylation events.

DNA methylation, which occurs primarily at cytosine-phosphate-guanine (CpG) dinucleotides, is a tissue- and species-specific modification of mammalian DNA [4,7]. In addition, DNA methylation is often observed at transcriptional regulatory sites on the gene promoter region and the methylation effects transcriptional regulation of gene expression [2].

Cancer is caused by a combination of epigenetic and genetic abnormalities resulting in dysregulated gene expression and function. In carcinogenesis, multiple gene aberrations, such as mutations, overexpression, amplifications of tumor-associated genes, and chromosomal aberrations such as deletion and epigenetic modifications, have been observed [8,9]. In human gastric mucosae, the presence of *Helicobacter pylori* (*H. pylori*) infection, a well-known inducer of chronic inflammation and gastric cancers [10,11], is associated with high methylation levels or high incidences of methylation [12–15]. Interestingly, the widely studied epigenetic abnormality in tumorigenesis is the silencing of gene transcription associated with increases in DNA methylation in normally unmethylated gene promoter regions [16,17]. In this review, we summarize the basic mechanism of DNA methylation and the role of methylation in carcinogenesis and inflammation.

2. Basic mechanism of DNA methylation

DNA methylation is 1 type of epigenetic modification and is important for the maintenance of genomic DNA in genome imprinting, stability of the chromosome, and transcriptional silencing of repetitive genes [1–5]. DNA methylation occurs at the 5′ position of cytosine residues within the context of the sequence 5′-CG-3′, which is referred to as a CpG dinucleotide (Fig. 1). This reaction is catalyzed by DNA methyltransferase (DNMT) [18]. Because transcriptionally active regions of the genome are usually CpG rich, methylation of CpG sites is one of the critical factors that

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doi:10.1016/j.pmu.2012.05.002

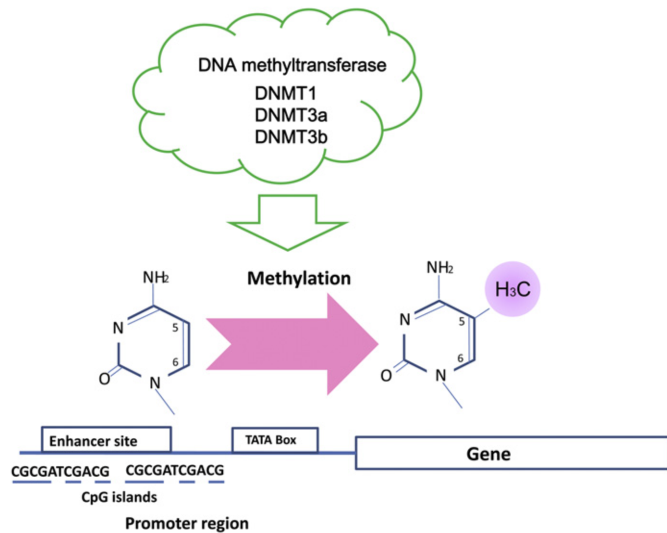

Fig. 1. *Schematic representation of DNA methylation on cytosine*. DNA methylation occurs on the carbon of the pyrimidine ring of cytosine within the CpG dinucleotide in areas such as the promoter region. This reaction is catalyzed by the DNA methyltransferase family (DNMT1, 3a and 3b).

affect gene transcription. Many regions of the genome contain large clusters of CpG dinucleotides. These regions are called CpG islands and they are present in over 70% of human promoters [19].

Target sequences for methylation are not equally distributed in the genome, but are found in long CG-rich sequences present in satellite repeat sequences, centromeric repeat sequences, and CpG islands. CpG islands are sequences longer than 200 bp with a GC content of over 50%, in contrast to the genome-wide average of about 40% [20,21]. Interestingly, CpG islands are found mainly in the 5′ regions of housekeeping genes as well as in some other tissue-specific genes; CpG islands usually extend from the promoter region into the first exon and sometimes into the intron [7,22].

Most CpG islands are unmethylated in normal cells; however, there are certain conditions where these sequences become methylated and are important for gene regulation [23]. The majority of CpG islands on the inactive X chromosome in a female cell are methylated [24], and certain CpG island-like sequences near imprinted genes are methylated in an allele-specific manner [25]. Furthermore, it has been shown that some CpG islands become methylated with age [26]. While CpG islands are usually unmethylated, other GC-rich sequences, such as the centromeric repeat sequences and satellite sequences, are highly methylated in normal cells.

DNA methylation is mediated by a family of highly related DNA methyltransferase enzymes (DNMT1, DNMT3A, and DNMT3B), which transfer a methyl group from *S*-adenosyl-L-methionine to cytosines in CpG dinucleotides [18,27]; Fig. 2). Typically, the maintenance of DNA methylation patterns in somatic cells is attributed to DNMT1, whereas *de novo* DNA methylation during embryonic development is performed by DNMT3A and DNMT3B [18,27,28]. However, DNMT1 can also contribute to *de novo* DNA methylation both *in vitro* and *in vivo* [18,27,29,30], and the maintenance of methylation in certain regions of the genome requires DNMT3A and DNMT3B [31].

The methyl-cytosines established by the DNMTs serve as binding sites for the methyl-CpG binding domain (MBD) proteins MeCP2, MBD1, MBD2, MBD3, and MBD4 [32]. Through interactions with histone deacetylases, histone methyltransferases, and ATP-dependent chromatin remodeling enzymes, the MBDs translate

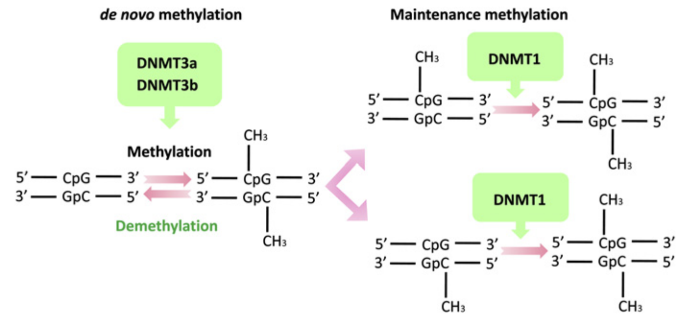

Fig. 2. *Mechanism of DNA methylation by the DNMT family. De novo* methylation is caused by DNMT3a or 3b. In the case of DNA replication during cell division, DNMT1 induces maintenance methylation.

methylated DNA into a compacted chromatin environment that is repressive for transcription [33].

3. DNA methylation and gene activation/inactivation

DNA methylation is mainly involved in regulating the repression of gene transcription, which can occur through a variety of mechanisms. The interactions of several transcription factors whose binding sites contain CpG dinucleotides have been shown to be sensitive to methylation [34,35]. However, methylated DNA can affect transcription more profoundly by interacting with methyl-CpG binding proteins and associated factors that alter chromatin structure (Fig. 3).

At first, two methyl-CpG-binding proteins (MeCP1 and MeCP2) were identified [36,37]. MeCP2 has a methyl-CpG binding domain (MBD) and a transcriptional repression domain [38]. Interestingly, mutations in MeCP2 cause Rett syndrome, which results in mental retardation and autistic behavior [39]. The MBD motif is found in four additional methyl-CpG-binding proteins (MBD1, 2, 3, and 4) [40]. MBD2 facilitates the binding of the multiprotein MeCP1 complex to methylated DNA [41].

MBD protein recruits one of two co-repressor complexes, Sin3 and Mi-2/NuRD, that in turn recruit a core histone deacetylase complex (HDAC) consisting of HDAC1, HDAC2, and two Rb-associated histone-binding proteins (RbAP46 and RbAP48) to methylated DNA [42,43]. HDACs remove acetyl groups from the lysine residues of the N-termini of histone H3 and H4 [44]; these

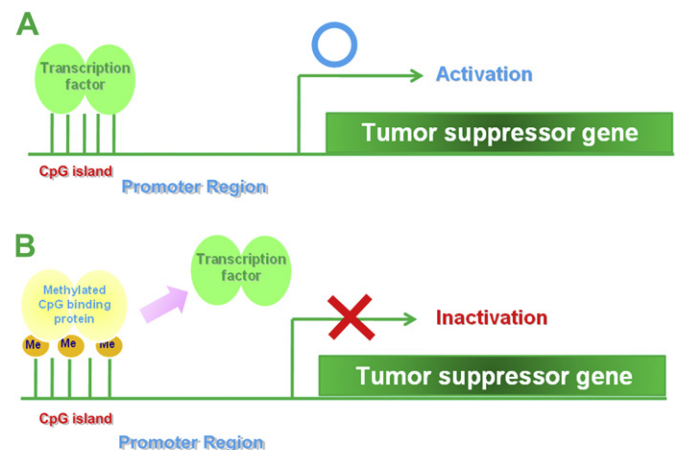

Fig. 3. *Schematic representation of gene inactivation by DNA methylation*. (A) When the CpG island in the promoter region is not methylated, the tumor suppressor gene is activated. (B) When the CpG island in the promoter region is methylated, the tumor suppressor gene is inactivated by interference of methylated CpG-binding proteins.

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