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DNA Methylation and Its Effect on Various Cancers: An Overview

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Abstract

DNA methylation is a normal phenomenon which helps in gene expression, cell differentiation and is an inheritable process. Altered DNA methylation patterns in coding strands lead to epigenetic modification. These epigenetic changes enhances DNA adduct formation, somatic mutations and oncogene activation. During silencing of tumor suppressor genes, various genes/proteins involved in signaling pathways gets disturbed. These changes are reversible but if mutations occur they become irreversible. Hence early detection of these genes/proteins involved in epigenetic alterations may help in decreasing the associated changes in the body.

Keywords: DNA methylation; Epigenetic modifications; Oncogene activation; Altered methylated pattern

Introduction

The process of covalent addition of methyl group to cytosine residue of DNA molecule is called DNA methylation. The methyl group adds to the 5' carbon of cytosine ring forming 5-methyl cytosine as shown in Figure 1.

These methyl groups project into major groove of DNA, which in turn inhibit transcription [1]. Thus, methylation of DNA occurs mostly at CG sites as shown in Figure 2.

The stretch of DNA where there is frequent appearance of methyl cytosine is called CPG islands. These islands are mostly seen near promoter region of transcription (initiation site) thereby inhibiting the process of transcription [2]. DNA methylation of non-coding region of DNA helps to maintain transcriptional silencing whereas in coding region of DNA it leads to an epigenetic modification. Epigenetics is a heritable change in gene expression without a change in nucleotide sequence. These epigenetic modifications include spontaneous deamination, enhanced binding of DNA to carcinogens and increased ultraviolet absorption by DNA.

This in turn enhances the rate of mutations and DNA adducts formation and gene inactivation [3,4]. Methylation of DNA is catalysed by DNA methyl transferase in which methyl donor is S-adenosyl methionine (SAM). This methylation of DNA not only causes change in transcriptional activity but also leads to change in chromatin structure in promoter region of the gene [5]. This paper attempts to review genetic changes attributed to abnormalities in DNA methylation which in turn activate tumoriogenic potential of cells further leading to cancer.

Changes in chromatin structure on DNA methylation

DNA methylation alters histones of chromatin structure by activating histone deacetylase (HDA). HAD enzyme removes acetyl group from histone which allows stronger interaction between DNA backbone and histones. This induces a tight chromatin structure which becomes inaccessible to transcriptional machinery. Thus, DNA methylation alters chromatin configuration from open to closed form, silencing gene expression [6].

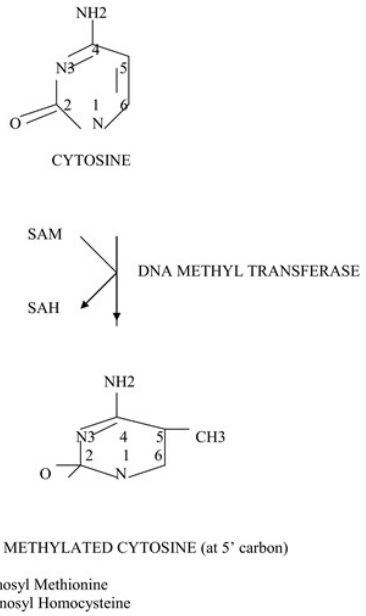

Figure 1: The reaction showing methylation of cytosine residues.

The amino terminal tails of histone protrude from nucleosome which can undergo post-translational modifications (like acetylation, ubiquitination, phosphorylation etc.). This in turn, affects the repressive/permissive behavior of transcription of gene [7]. The open chain histone confirmation shows permissive nature whereas closed confirmation represses the process of transcription [8]. Thus, DNA methylation influences histone modifications as shown in Figure 3.

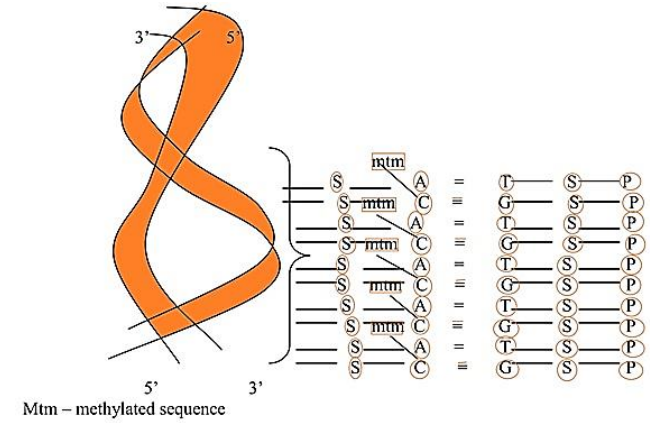

Figure 2: Diagrammatic representation showing DNA strand with methylated cytosine residues.

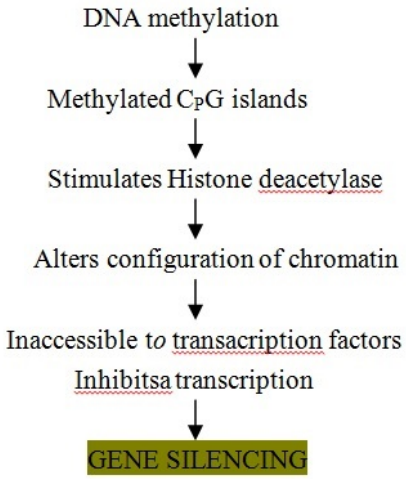

Figure 3: Flow chart showing sequence events of DNA methylation on chromatin structure.

Role of DNA methylation in cancer-a generalized view

In a normal healthy individual DNA methylation ensures proper gene expression, differentiation during embryonic stage, and to transmit the methylated patterns from parent to offspring in one of the allele of the gene representing germ line transmission. The process of transmission of methylated patterns from one generation to next is called imprinting. Loss of this imprinting leads to Prader-Willi syndrome, Angelman's syndrome etc. The altered DNA methylation pattern in somatic tissue leads to cancer. The mismatched DNA methylated patterns are majorly seen in promoter region of the gene [9-12]. DNA methylation and its role in generation of cancer are shown in Figure 4.

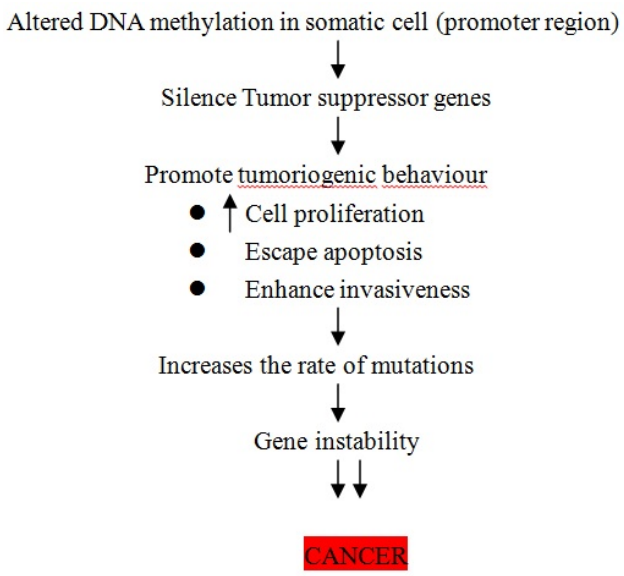

Figure 4: Flow chart of DNA methylation changes leading to cancer.

Thus, hypermethylation on DNA, causes silencing of retroviral endogenous elements leading to enhanced somatic mutations and oncogene activation/inactivation of tumor suppressor genes.

Epigenetic alteration induced mutation

DNA methylation silencing of tumor suppresor genes leads to change in nucleosome positioning at the transcriptional start site as well as loss of histone acetylation (HA). The normal histone acetylation can be restored by the use of HA inhibitors which leads to anti-tumorigenic effects revealing the fact that HA inhibitors may reactivate the silenced tumor suppresor genes. Reactivation of these genes by DNA methyl transferase inhibitors as well as HA inhibitors contribute to loss of nucleosome from promoter site of transcription [13,14].

Ovarian Cancer

Ovarian cancer is the most lethal cancer of female genital tract. Its detection gets delayed as it shows few symptoms during its course [15]. A large number of genes get hypermethylated and silenced in ovarian cancer [16]. The most altered genes include CDKN2A, which is a cell cycle control gene silenced by promoter methylation and is a predictive marker for ovarian cancer [17,18]. Previous research studies have indicated that CDH13, a gene coding for cell adherence protein (H-Cadherin) is another one which frequently causes hypermethylation and can be responsible for ovarian cancer [19,20]. Previous studies have also noted that RASSF1, a tumor suppressor gene does transcriptional silencing by incomplete promoter methylation [21,22].

Breast Cancer

Breast cancer is a heterogeneous disease, both biologically and clinically. These cancers are subdivided into basal-like, ERBB2+, luminal B and luminal A [23,24]. These subtypes showed different methylation patterns. Basal-like tumors showed least methylation and luminal B displayed highest methylation pattern [25]. It was observed

that expression five biomarkers varied between basal-like and other subtypes. In basal-like tumors NPY, FGF2, HS3ST2, RASSF1 and Let-7a showed lack of methylation [26].

Endometrial Cancer

It is seventh most commonly occurring cancers in women worldwide. The underlying reason for development of endometrial cancer is not clear but epigenetic modification like DNA hypermethylation provides complete explanation for development of endometrial cancer. This hypermethylated DNA in turn causes breakdown of DNA, mismatch repair mechanism causing a change in expression of genes like human Mut L homolog 1 (hMLH1) and human Mut S homolog 2(hMLH2) [27]. DNA hypermethylation in turn down regulates expression of genes like APC, E cadherin, CHFR, CASP8 [28-30]. Research has observed that APC (Adenopolyposis coli) hypermethylation which is not found in normal endometrial hyperplasia was seen in endometrial cancer [31]. CHFR (Checkpoint with FHA and RING) hypermethylation also was noted to cause endometrial cancer [32]. Sprouty 2 (SPRY 2) promotes growth of glandular structures, acts as antagonist to regulator of MAPK receptor tyrosine kinase and its action is in accordance to menstrual cycle. Extreme low expression of these genes was noted in invasive and endometrial cancer [33-35]. RASSF1A gene regulates cell proliferation and apoptosis by regulatory MAPK pathway and its low expression indicates advanced stages of endometrial cancer [36]. GPR 54 is a suppressor gene for cancer metastasis and its reduced expression leads to endometrial cancer [37]. Low expression of CDH1 gene could be linked to generation of endometrial cancer [38]. X-linked Ribosomal S6 kinase (RPS6KA6)/(RSK 4) was noted to inhibit transcriptional activity of tyrosine kinase receptor. This is associated with activation of FGFR2/RAS/ERK signal pathway and acts as a tumor suppressor. Reduced activity of CDH1 gene is therefore seen in endometrial cancer [39]. EPCAM (Epithelial cell adhesion molecule), is an intercellular adhesion molecule that prevents metastasis. Mutation of gene coding for this molecule was observed to cause endometrial cancer [40,41].

Lung Cancer

It is one of the most prevalent cancers and leading cause of cancer deaths in the world. Several tumor suppressor genes get methylated and become inactive and could be responsible for genesis of lung cancer. RAR Beta (Retinoic acid receptor beta -2) gene involved in mediating growth control responses was observed to become defective in both primary and non-small cell lung cancers (NSCLCS) and heavy smokers [42-44]. Previous research has noted that RASSF1A gene activity was lost in lung cancer [45]. Other recent studies have indicated that abnormality in FHIT (Fragile Histidine triad) gene could be linked to lung cancer [46,47]. Research studies in the past have noted that Cadherins are a family of cell surface glycoproteins responsible for cell recognition and adhesion and that defect in CDH 13 could be responsible for lung carcinoma [48,49]. A previous study has noted that APC (Ademato us polyposis coli) is a gene which gets methylated frequently in lung cancer [50]. Another study has found that P16 gets methylated and binds to cyclin dependent protein kinase and inhibits binding to cyclin D1 which may be linked to lung cancer [51].

Stomach Cancer

Gastric cancer remains a common cancer type in humans. Various factors like smoking, diet and Helicobacter pylori infection could contribute to gastric cancer. Research has noted that hypermethylation and silencing of E (epithelial) cadherin, a tumor suppressor gene is frequently observed in gastric carcinomas [52]. Silenced E cadherin gene in turn was associated with development of Epstein-Barr virus (EBV) associated gastric carcinoma [53]. Thus, DNA methylation at promoter region of tumor suppressor gene alters cell cycle, growth and motility, as well as adhesion molecules by silencing expressions of p16, p15, DAPK, RUNX3, MLH. Loss of oncogene promoter region leads to over expression genes such as S100A4, VEGF-C, PAR2, SNCG and MAGE-A1-3 in gastric cancer [54,55].

Liver Cancer

Hepatocellular carcinoma/Liver cancer is one of the most common cancer worldwide due to its poor prognosis. Hypermethylation of genes like RASSF1A, CDKN2A, CCNA1, P16 were identified in cancer tissue of liver compared to healthy tissue [56]. Similarly, KLK10 and OXGR 1 genes were also noted to induce hypermethylation. KLK10 hypermethylation was found to be associated with Hepatitis C virus (HCV) infection and liver cirrhosis [57]. Hypomethylation of AKR1B10, CENDH, MMP9, MMp12, PAGE 4, S100A5, MMp2 and NUPR1 was also noted in liver cancer [58]. The etiological factors like hepatitis B viral infection (HBV), alcohol consumption can alter DNA methylation patterns leading to epigenetic changes and tumorogenesis.

Colon Cancer

Colon cancer is the third most diagnosed cancer in both men and women. The genes MGMT, hMLH1, P16, MINT1, MINT31, COX2, cyclin A1, CDX1, RAR-b, MYOD1, P15, CDH13, CXX1, P73 and WT1 showed altered methylation pattern and could be associated with colon cancer [59]. Previous studies have also observed that CDH5 gene inactivation can lead to changes in chromatin structure and that genetic disruption of APC, RAS and P53 pathways could initiate colon cancer [60,61]. DNA methylation pattern and epigenetic modification can be reverted but if there is mutation of genes in this process it becomes an irreversible change.

Brain Tumor

Gliomas or brain tumors are the tumors of central nervous system (CNS) with wide spectrum of different tumor types. The genes CDKN2B, MYOD1, CDH1, TIMP3, THBS1, PTGS2, CALCA showed methylation changes and these genes had a role in cell cycle, growth regulation, cell differentiation, angiogenesis and tumor metastasis [62-64].

Skin Cancer

Globally, skin cancer is the most frequent form of cancer responsible for more than 40% of cases. In skin cancer, methylation of E cadherin prevents cell adhesiveness. Studies in the past have observed changes in HaCa4 cells in later stages of cancer. It was also noted that hypermethylation of E cadherin demethylates snial protein, recruits histone deacetylase activity and inhibits methyl transferase enzyme [65-67]. The target genes involved in gene silencing and primary skin cancer includes IGFBP3, CMKAR4, PRDX1, CSRP2

[68-70]. Thus, tumor suppressor gene inactivation leads to activation of cascade of events to skin cancer.

Challenges and Future Perspective

Further studies concentrating on altered DNA methylation pattern may be crucial in early detection of tumerogenic activity and also could help in designing drugs for treating human diseases attributed to altered DNA methylation. DNA methylation biomarkers should be considered as a corner stone in the diagnosis of cancers. Studies in the future should concentrate on the development and validation of potential DNA methylation biomarkers. DNA methylation abnormalities could also be linked to other diseases that include and not limited to developmental disorders leading to neurological defects, cardiovascular diseases, endocrinal disorders, nutrition and exposure to environmental toxins and stress conditions. Markers of epigenetic changes although are currently available, they require extensive and large scale validation studies before being used either for the diagnosis or prevention.

Conclusion

The process of DNA methylation is a natural phenomenon to ensure proper growth, cell adhesion, and genetic transmission. Abnormal or altered DNA methylation leads to silencing of tumor suppressor genes, thus promotes enhanced multiplication of cells, extensive invasive nature to the cell and in turn cells are transformed to cancerous cells. During its transformation to malignant cells a large number of proteins involved in different signaling pathways are altered or sometimes become mutated (irreversible). Hence early estimation of these protein levels in blood may help to know the altered DNA methylation pattern and thus we can minimize the risk of cancer due to this abnormal pattern of DNA methylation.

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