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ANALYSIS AND OVERVIEW OF DNA METHYLATION AND CANCER

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Abstract - *DNA methylation is fundamental for a typical turn of events and maintenance of tissue-specific gene expression patterns in mammals. Interruption of DNA methylation cycles can lead to altered gene function and malignant cellular transformation. Generally, cancer has been seen as a genetic disorder, and it is presently turning out to be evident that cancer initiates by epigenetic variations from the norm(1). DNA methylation is a huge regulator of gene transcription, and its part in carcinogenesis has been a subject of amazing interest over the last couple of years. Deviations in DNA methylation are common in a variety of tumors. Perceiving that carcinogenesis includes both genetic and epigenetic changes has prompted a more grounded understanding of the molecular pathways that administer the occasion of malignancy and to enhancements in diagnosing and foreseeing the final product of assorted styles of cancer. Ongoing headways inside the quickly developing field of Cancer epigenetics have demonstrated broad reconstructing of every segment of the epigenetic machinery in malignant growth including DNA methylation. DNA methylation is reversible which makes it very fascinating for therapy approaches, which is now gaining ground with the ongoing FDA endorsement of three epigenetic drugs for malignant growth treatment. In this review, we examine the current comprehension of changes in DNA methylation that happen in cancer contrasted with normal cells, the function of these changes in the onset and progression of cancer, and the potential use of this data for growing more compelling treatment strategies.*

Key Words: **DNA-Deoxyribonucleic acid, DNMT - DNA Methyltransferases, TET - ten-eleven-translocation, CpG - cytosine-phosphate-guanine**

1. INTRODUCTION

Genetics is the study of genetic changes in gene activity or function resulting from direct changes in DNA sequence. These changes include point mutations, deletions, deposits and translocations. In contrast, epigenetics is the study of genetic changes in gene activity or function that are not related to changes in the DNA sequence itself. More generally, epigenetic mechanisms mediate different gene expression profiles in different cells and tissues of a multicellular organism.

Cancer cells typically have a variety of somatic genomic defects that contribute to a phenotype characterized by inappropriate proliferation, avoidance of apoptosis, tissue invasion, induction of angiogenesis, interruption of immune monitoring and metastasis. Some of the defects in the genome are genetic changes (changes in DNA sequence) such as gene mutations, deletions, amplifications, and translocations. Other genomic defects are epigenetic changes, including changes in cytosine methylation patterns and chromatin structure. This chapter presents a basic epigenetic mechanism involved in direct chemical modification of DNA called DNA methylation. Historically, DNA methylation has been discovered in mammals when DNA has been identified as genetic material (Avery et al, 1944; McCarty and Avery, 1946). In 1948, Rollin Hotchkiss first found a modified cytosine during the time spent making a calf thymus utilizing paper chromatography. Hotchkiss (1948) suggested that this fraction is 5-methylcytosine (5mC) because thymine (also known as methyluracil) is released from cytosine in the same way as uracil. This modified cytosine is thought to be found naturally in DNA as well. While many researchers suggested that DNA methylation could regulate gene expression, it was until the 1980s that several studies showed that DNA methylation was involved in gene regulation and cell differentiation.

In the pathogenesis of human cancer, somatic epigenetic changes occur earlier and more often than genetic changes. Several genes have been identified that have been silenced by episexual changes that provide novel molecular biomarkers for prostate cancer and new mechanistic clues to the pathogenesis of cancer. However, the mechanism by which epigenetic changes accumulate during the carcinogenesis process has not been established. Along with other modulators, DNA methylation is now known as a major epigenetic factor affecting gene activity. A deeper understanding of the acquisition of epigenetic changes in DNA methylation during the carcinogenesis process may provide new insights into how cancer can be better treated and/or prevented.

2. DISCUSSION

The findings in terms of DNA methylation, CpG in cancer cells, epigenetic therapy have been discussed separately.

2.1 DNA METHYLATION IN NORMAL CELLS

Despite the large differences in structure and function, all cells contain a same DNA sequence. Because other cells use or express only certain genes. DNA can be labelled with small chemicals that alter gene expression. One of these epigenetic modifications is DNA methylation. Promoter DNA methylation is involved in gene suppression and plays an important role in maintaining

cell types. For example, transcriptional activation can be inhibited by blocking the entry of transcription factors into the target binding site. In cancer, DNA methylation patterns change and are destroyed. DNA methylation is carried out by a group of enzymes called DNA Methyltransferases or compact DNMTs. There are three main category:

1. DNA Methyltransferases 1 (DNMT1)
2. DNA Methyltransferases 3a (DNMT3a)
3. DNA Methyltransferases 3b (DNMT3b)

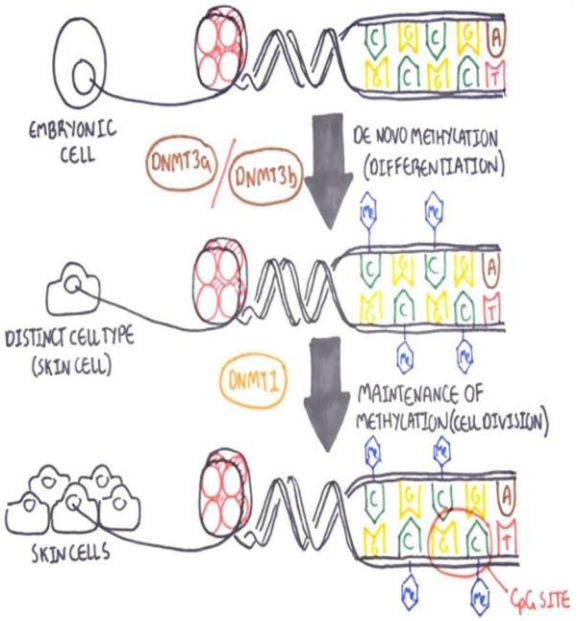

Fig -1 Early embryonic cell

In the figure 1, we are looking at an early embryonic cell and we are pulling out its DNA which is wrapped around histone octamers known as nucleosomes. After fertilization, DNMT3a and DNMT3b are responsible for de novo methylation, allowing embryonic cells to differentiate into cell types. So for example, an embryonic cell has become a distinct cell type, a skin cell. DNMT1 is responsible for maintaining DNA methylation after differentiation and is activated during subsequent cell division. The methylation patterns of each cell type are different and this reflects the gene expression pattern of the cell. Here we have one skin cell that is becoming many skin cells, this cell type has a unique methylation pattern and therefore expresses certain genes. Cytosine-phosphate-guanine sites or CpG sites are found all over our DNA. CpG islands contain many CpG sites. CpG islands are mainly located at the 5'end of the gene and make up about 60% of the human gene promoter(3). In normal adult cells, most of the CPG sites are methylated, except for the CPG promoter island, and these CPG sites are usually unmethylated(2). Promoter regions are regions in the DNA that contain regulatory elements that control the transcription of genes.

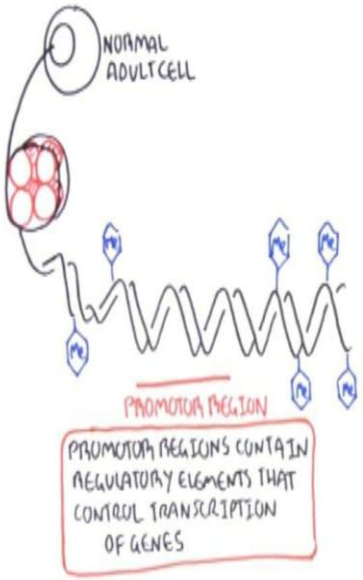

Fig -2 Promoter Begins

In Figure 2, DNA Methyltransferases 3a (DNMT3a) and DNA Methyltransferases 3b (DNMT3b) are accountable for DNA methylation in early development. This methylation usually occurs only in cytosine, which is located at 5' of guanosine in the CpG dinucleotide of higher eukaryotes.

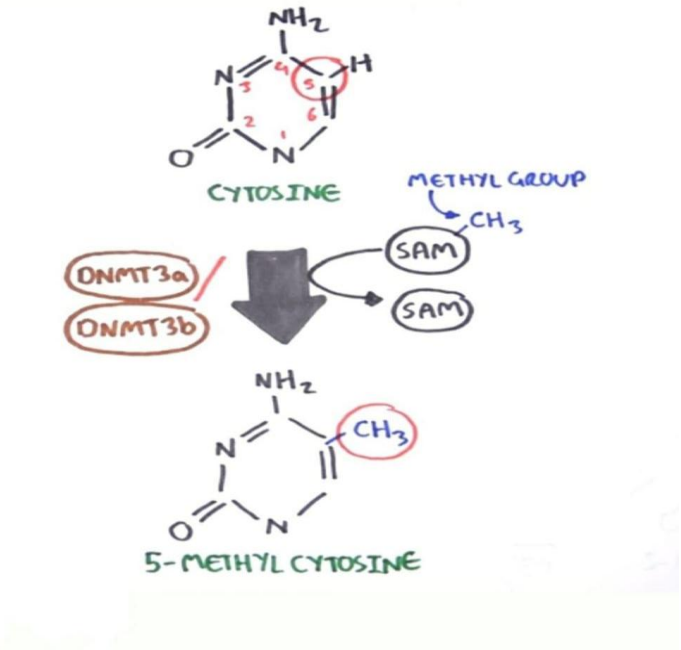

Fig -3 Structure of 5-Methylcytosine

In the Figure 3, DNMT obtains the methyl group from a molecule called Sam. The methyl group is added to cytosine forming 5-methylcytosine. It is thought that DNMT flips the cytosine base pair 180 degrees out of the strand. The DNMT enzyme takes a methyl group from Sam and transfers it to cytosine. Finally, the methylated cytosine is flipped back.

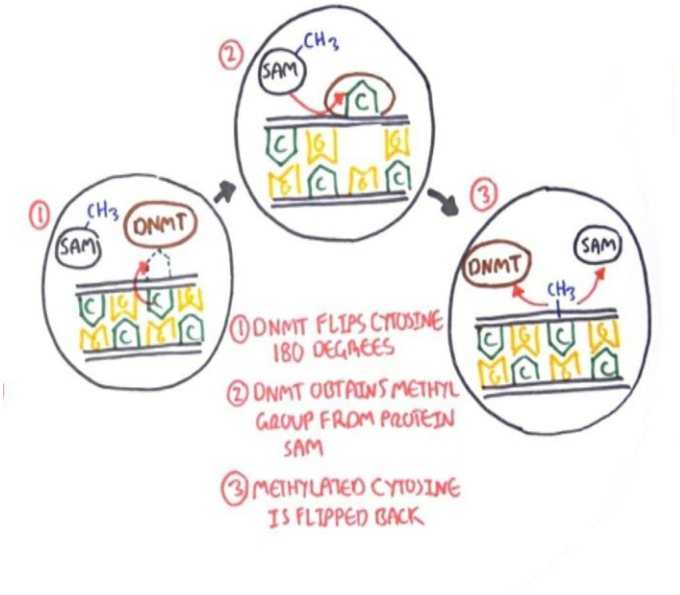

Fig -4 Transformation

In the figure 5, Human TET which stands for ten-eleven-translocation is another important enzyme that has a role in regulating DNA methylation patterns. TET is responsible for adding a hydroxyl group initially to 5-methylcytosine forming 5-hydroxymethyl cytosine. TET enzymes can also convert 5-hydroxymethylcytosine back to cytosine in several ways. Therefore, the TET enzyme is considered responsible for DNA demethylation. In a normal cell, the opposing processes of methylation and demethylation are tightly regulated in development.

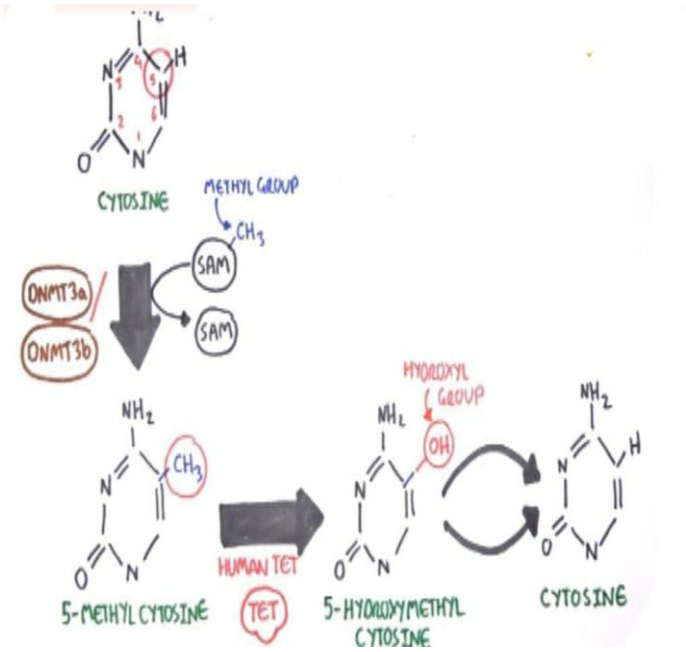

Fig -5

2.2 CHANGES IN METHYLATION OF CpG IN CANCER CELLS

The onset and progression of cancer is consistent with a significant change in DNA methylation, the first epigenetic change identified in cancer(4)(5). In cancer cells, the CpG island in front of the tumor suppressor gene promoter is often overmethylated, whereas the CpG methylation in the oncogene promoter region is often reduced. The whole genome of cancer cells contains considerably less methylcytosine than that of normal cells. The genome of cancer cells has 20 to 50% less methylation of individual CpG dinucleotides all through the genome. DNA hypomethylation plays an important role in oncogenesis and occurs in a variety of genomic sequences, including element repeats, retrotransposons, low CpG promoters, ancestors and genera. DNA hypomethylation in repeated sequences contributes to chromosomal rearrangement by increasing genomic instability. Hypomethylation of retrotransposons can lead to activation and translocation to other regions of the genome, which increases the instability of the genome. The induction of genomic instability is best evidenced by hypomethylation in patients with immunodeficiency, centrosome instability and superficial abnormalities with gonadal mutations of the DNMT3b enzyme leading to hypomethylation and subsequent chromosomal instability. This loss of DNA methylation and genomic instability has been linked to various types of human cancer. DNA hypomethylation can lead to activation of growth promoting genes such as R-Ras in gastric cancer. Thus, DNA hypomethylation leads to abnormal activation of non-coding genes and regions through a variety of mechanisms that contribute to cancer development and progression.

Unlike hypomethylation, hypermethylation of the promoter region of tumor suppressor genes can lead to inhibition of these genes. This type of epigenetic mutation causes cells to grow and multiply out of control, leading to tumor formation. When you add a methyl group to your cytosine, the DNA is tightly wrapped around the histone protein and the DNA is not transcribed. Genes generally inhibited by transcription due to promoter and methylation include cyclin dependent p16 kinase inhibitors, cell cycle inhibitors; cell cycle inhibitors; MGMT, DNA repair gene; APC, cell cycle regulator; BRCA1, DNA repair gene; And, MLH1 another DNA repair gene. Epigenetic suppression of these tumor suppressor genes can also lead to tumor initiation. In addition to directly inactivating tumor suppressor genes, DNA and methylation can also indirectly weaken the distribution of additional genes by inhibiting transcription factors and DNA repair genes. Mutations in the DNA repair gene cause cells to accumulate additional genetic damage, leading to the rapid onset of cancer.

2.3 EPIGENETIC THERAPY OF CANCER

The reversible idea of the significant epigenetic changes that happen in disease has prompted the chance of "epigenetic therapy" as a treatment choice. Epigenetic treatment aims to restore the "normal epigenetic genome" by reversing the epigenetic cause abnormalities that occur in cancer. As of late, numerous epigenetic drugs have been found that can turn around DNA methylation abortions and histone modifications that happen in cancer. DNA methylation inhibitors were one of the first epigenetic drugs proposed for the treatment of cancer. The surprising discovery that treatment with the cytotoxic agents, 5-azacytidine (5-aza-CR) and 5-aza-2'-deoxycytidine (5-aza-CdR) inhibits gene-induced DNA methylation and differentiation of cultured cells. This has enabled the potential use of these drugs in cancer treatment. These nucleoside analogs are incorporated into rapidly growing tumor cell DNA while simultaneously capturing DNA methyltransferase in the DNA, replicating and preventing DNA methylation, thereby depleting it in the cell. This drug-induced decrease in DNA methylation inhibits cancer cell growth by activating an abnormal suppressor tumor suppressor gene in cancer.

The ability of these drugs to integrate into DNA raises concerns about their potential toxic effects on normal cells. However, since these drugs only act on cell division, treatment with these drugs should primarily focus on fast tumor cells, and should have minimal effect on slow cell division. However, another approach is also used, involving the development of non nucleoside compounds that do not integrate into DNA and can effectively inhibit DNA methylation. The development of several small molecule inhibitors such as SGI-1027, RG108 and MG98 is a step in this direction. These molecules can exert inhibitory effects by blocking DNMT catalytic factor/cofactor binding sites or by acting on RNA messenger regulatory sequences. However, the weak inhibitory potential of these drugs indicates a need to develop stronger inhibitory compounds in the future.

3. FUTURE PROSPECTS AND CHALLENGES

The epigenetic revolution in biology in recent decades has challenged the long-standing view of the genetic code as an integral component of cellular gene function, and its changes are a major cause of human disease. Information about DNA methylation has led to the realization that genomic packaging can be just as important as the genome to maintain cellular identity and regulate the basic cellular processes required to initiate disease states such as cancer. A deeper understanding of the global pattern of DNA methylation modifications and the resulting changes in cancer has led to the development of improved treatment strategies. Combination approaches, along with various epigenetic treatment approaches combined with standard chemotherapy, are very promising for future success in cancer. These approaches can also help sensitize cancer cells, especially cancer stem cells that do not respond to standard chemotherapy. Along with the development of more specific epigenetic drugs, a greater understanding of cancer stem cells may be key to our ability to successfully cleanse the abnormal epigenetic genome.

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