DNA METHYLATION AND HISTONE MODIFICATION AS A DRIVING FORCE TO CANCER

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ABSTRACT

Cancer is a major human health problem worldwide and is largely characterized by its abnormal increase in cell number and cell proliferation, decreased cell death or apoptosis, and its ability to invade surrounding tissues. A lot of factors are responsible for causing cancer one of which include epigenetic changes.

Epigenetic changes are concerned with genetic alterations to drive the cancer phenotype. Epigenetic mutations result due to DNA methylation, histone modifications, chromatin remodelling, microRNAs, and other components of chromatin [3]. Histone modifications include histone acetylation, histone methylation, histone phosphorylation and histone ubiquitination. Epigenetic changes can also be induced by exposure to various environmental factors. These stimuli include aging that was shown with increased levels of DNA methylation; physical agents such as X – rays, UV light; infectious agents such as bacteria and viruses; similarly chronic inflammation was also involved in inducing aberrant DNA methylation [1].

The sections in this chapter provide us with the controlled information about role of epigenetics in causing cancer and how it can be controlled with the help of epigenetic therapy.

KEYWORDS: Cancer, Epigenetics, Histones Modifications, DNA methylation, Acetylation, Deacetylation, tumor suppressor genes, oncogenes.

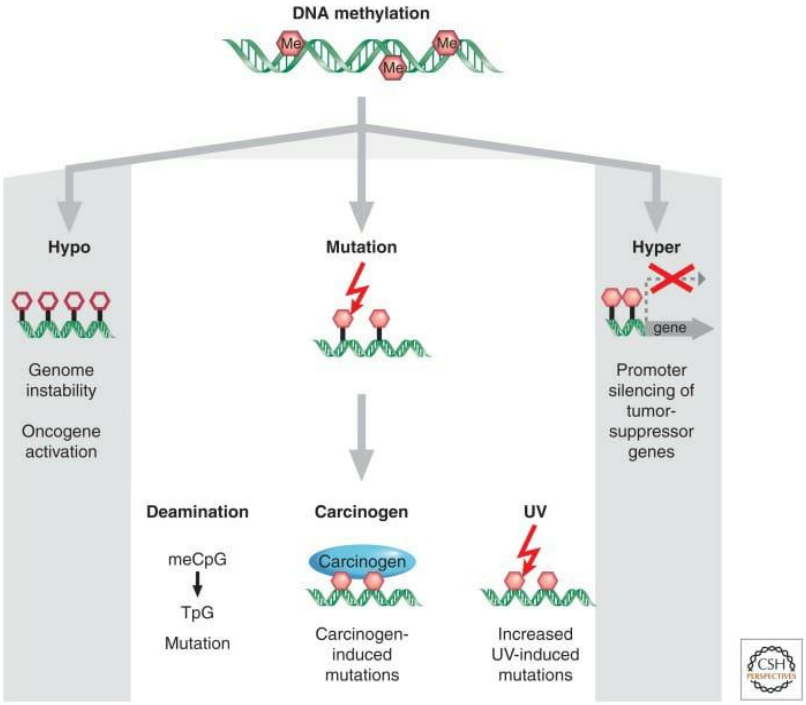
1. INTRODUCTION

In 1940 C.H. Waddington defined the term “epigenetics” which means “the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being” [4]. Accumulation of genetic mutations with epigenetic alterations together with environmental factors are the main root cause of cancer. Epigenetic alterations are reversible. These epigenetic mechanisms are regulated by four classes of epigenetic regulators in a coordinated manner. Those which add the epigenetic marks are known as

‘writers’; which remove the epigenetic marks are known as ‘erasers’; which recognize specific epigenetic marks to mediate proximate effects are known as ‘readers’; and which modify chromatin structure are known as ‘remodelers’. Mammals contain about ~ 1000 epigenetic regulators forming the largest protein group.

2. CANCER EPIGENETICS

Cancer is caused by mutations to the DNA within cells either by somatic mutations or epigenetic mutations. Mutation causing loss of function in tumor suppressor genes or gain of function in oncogenes and abnormal expression eventually leads the path to cancer. Whereas , the epigenetic pathway to cancer is determined by DNA methylation, histone modifications, nucleosome remodelling as well as miRNAs (Sharma et al., 2010). The figure below describes the various mechanisms involving DNA methylation that can led to cancer [3]. During tumor initiation and progression, the epigenome goes through multiple alterations, including loss of DNA methylation (hypomethylation), frequent increases in promoter methylation of CpG islands, changes in nucleosome occupancy, and modification profiles.



3. DNA METHYLATION

DNA methylation is a crucial epigenetic mechanism for the upkeeping of heritable changes in the process of gene transcription. This mechanism occurs by the covalent addition of a methyl group (-CH3) to the fifth carbon of the cytosine in the dinucleotide 5 ‘– CpG – 3’.

The CpG islands are present at the promoter of some regulatory genes. These possess a GC content of -60% approximately and form long stretches of DNA (1-2 KB). The human genome has 29,000 islands and all the necessary 'housekeeping' genes that are expressed constitutively have these islands. Any alteration in the pattern of DNA methylation will eventually lead to genomic instability which subsequentially is responsible for oncogenesis.

3.1 Role of DNA methyltransferases (DNA MTases) in DNA methylation

DNA methylation is catalyzed by key enzymes known as DNA methyltransferases which have an important regulatory role in preserving the integrity of the genome.

These DNA modifying enzymes are essential for mammalian development.

DNMT family comprises of the following members which include DNMT 1, DNMT 3A, DNMT 3B being present in mammals. All DNMTs have their respective roles in the process of DNA methylation.

DNMT 1 is denoted as maintenance methyltransferase in mammals with respect to its role in the maintenance of net methylation that occurs in the genome during cell division. In the course of DNA replication this maintenance methyltransferase is responsible for the restoration of the methylation pattern on the daughter strand with respect to that present on the parent strand. These enzymes show a higher attraction towards the hemimethylated DNA.

The DNMT3 family is composed of DNMT3A and DNMT3B. They are designated as de novo methyltransferases and are known for their efficient roles during embryonic development for the establishment of proper methylation patterns. This family of methyltransferases have almost equal affinity for hemimethylated and methylated DNA.

DNMT3 family also includes another critical methyltransferase namely DNMT 3L. It is characterized on the basis of its attachment with the de novo methyltransferases. Binding of DNMT 3L with DNMT3A and DNMT3B increase the catalytic activity of these enzymes to several folds.

Upregulation of any of the DNMTs family is related to serious consequences such as tumorigenesis. DNMT inhibitors play a significant role as epigenetic drugs in cancer therapeutics.

3.2 TET proteins and their regulatory role in DNA methylation

TET named as Ten-Eleven-Translocation proteins are large (-170 -240 KDa) with multiple domains and are known for their m5C oxidase activity that have active participation in both physiological and pathological processes. Domains in TET proteins include cysteine rich domain, double stranded beta helix domain along with cofactor binding sites (Fe (II) and 2-oxoglutarate (2- 0G). TET dioxygenase (TET 1, TET 2, TET 3) mediate active demethylation by oxidization of 5-methylcytosine to generate 5- hydroxymethylcytosine, 5- formylcytosine, 5-carboxylcytosine. Among all the intermediates formed two of them i.e.5-fC and 5- caC can be excised by DNA mismatch repair enzyme called Thymine- DNA glycosylase. After the excision the sites that are modified return to their non- methylated state via Base Excision Repair. Passive demethylation is progressed by loss of m5C via DNMT 1 during rounds of DNA replication and it is initiated in the absence of maintenance methylation machinery. Thus, the main function of TET proteins was to oxidate 5-methylcytosine and the intermediates formed were involved in DNA demethylation.

3.3 A typical DNA methylation and its role in carcinogenesis

Anomalistic DNA methylation pattern is closely associated with the onset of cancer as it is an initial epigenetic defect in tumor cells. The cancer epigenome shows global hypomethylation all over the genome with certain areas of localized hypermethylation being responsible for a variety of human cancers. Aberrant DNA methylation is considered a driving force in tumor development due to the overexpression of various DNMTs present in mammalian genomic sequence.

Both DNA hypomethylation and hypermethylation are inter-related to each other can give rise to malignancies.

The genome wide hypomethylation is related to increased expression of gene. It involves reduction of m5C at repeat elements which are heavily methylated such as satellite repeats and transposons for example Alu-1 and LINE-1 element repeats. Such modifications increase a higher probability of causing a number of defects such as genetic instability in cancer cells contributing to tumor progression via oncogene activation. This underlying epigenetic mechanism causes chromosomal missegregation in the course of cellular division.

Focal hypermethylation induces the transcriptional silencing of Tumor Suppressor Gene which plays key role in the progression of tumor. Hypermethylation causes dysregulation in the growth phenomenon of cells. Hypermethylation defects combine along with mutations

involved in cancer development and progression. In an experimental analysis its was seen that in spasmic breast tumor there was partial hypermethylation of BRCA1 promoter due to overexpression of DNA methyltransferases.

4. HISTONE MODIFICATION

Along with DNA Methylation, histone modification after translation does not differ the DNA nucleotide sequence enhances it efficiency for transcriptional machinery. Epigenetic machinery. It is classically represented by methylation of DNA and modification in histone. Histone modification includes acetylation, phosphorylation, ubiquitination, methylation, etc. Histone modification has role in allergic reaction that can be Manifested at two level, first regulating these cells that cause allergic inflammation, like T cells and macrophage and the participants of airway. Second, the direct connection between allergic phenotype and his modification drugs that could inhibit the History modification enzymes are potentially the anti-allergic drugs. Usually act at the end terminal of histone with amino acids like arginine/lysine furthermore threonine, serine, tyrosine etc. Histone methylation has role effective in gene expression. Methylation of histone could be either transcriptionally permeable or impermeable based on amino acid position in tail or on the number of groups added that are modified.

4.1 Histone Acetylation

Acetylation is modulated by analogously acting two enzymes histone deacetylases (HDACs) and histone acetyltransferases (HATs). The acetyl group transfer from the acetyl CoA is mediated by HAT to amino acid group like lysine residues targeted at the tail. Acetylation removes histone positivity resulting in weaker interaction between DNA and histone. Weak interaction between DNA plus histone lessens the compaction in chromatin and hence enhances its availability to the machinery of transcription. HDACs have a role in repressing gene expression by removing acetyl group from tail of the histone where lysine residue is present. Five families of HATs are known GNAT family, MYST family, p300/CBP family, steroid receptors co-activators family, and cytoplasmic HATs. GNAT family compromises KAT2A and KAT2B enzymes that regulate cell cycle, DNA repair, DNA replication along with centrosome function. MYST family comprises KAT6A/MYST3/MOZ, KAT6B/MYST4/MORF, KAT7/MYST2/HBOI, KATT8/hMOF/MYST and KAT5/Tip60 that regulate DNA repair and transcription. The MYST family enzymes have unique characteristics of autoacetylation. p300/CBP family comprises of KAT3A and KAT3B enzymes and KAT4/TBP/TAF1 and TIF

3C90/KAt12 are contributors of general transcriptional factors related to HAT family. KAT13A/SRC1, KAT13B/SRC/AIB1/ACTR, KAT13C/p600, and KAT13D/ CLOCK are members of the steroid receptor coordinators family. Cytoplasmic HATs have Kat1/HAT1 and HAT4/NAA 60 [29].

4.2 Histone Methylation

Histone methylation (HMTs) mediate histone methylation these include lysine and arginine methyltransferase along with histone demethylases (HDMs) for demethylation. Histone methylated lysine and arginine impacts the different regulatory protein binding to the chromatin indirectly. Three methyl groups can be transferred by HMTs from cofactor S-adenosyl-L-methionine (SAM) to the histone either lysine or Arginine residues. This specificity of KMTs is higher than HATs because of target-specific lysine residues. Methylation of different histone residues is mediated by different KMTs. H3K4 residue is methylated by KMT2A/MLL1, KMT2A/MLL2, KMT2F/hSETIA, KMT2G/hSET1B or KMT2H/ASH1. H3K9 is methylated by KMTIA/SUV39H1, KMT1B/SUV39H2, KMTIC/G9a or KMT1D/EuHMTase/GLP. Methylation of H3K36 is usually catalyzed by KMT3B/NSD1, KMT3C/SMYD2 OR KMT3A/SETD2. Others like H3K27 is methylated by KMT6A/EZH2 and H3K79 by KMT4/DOT1L etc. based on mechanism of catalysis and sequence homology HDMs are of two types: 1) amine oxidase type lysine-specific demethylase (lSDs or KDM-1s) 2) Jumonji C (JMJC) domain-containing HDMs. The LSDs include KDM1A/LSD1/AOF2 and KDMIB/LSD2/AOF1 that eradicate the methyl groups and demethylated H3K4. The JMJC domain incorporated HDMS acts on mono, di, and trimethylated lysine residues and catalyzes their demethylation at histone [25,44,45,46,47].

4.3 Histone Phosphorylation

Two antagonistic enzymes kinases and phosphates remove it [19,21]. phosphorylated histones are known for their three special function 1) chromatin compaction control 2) DNA damage repair 3) transcriptional activity repair. Histone phosphorylation creates a platform for the other histone modifications to interact. histone H3 phosphorylation directly affects the two amine acid residues of similar histone (H3K9ac and H3K14ac) at acetylation levels [19,21,48].

4.4 Histone Ubiquitination

Histone ubiquitination has a role in all aspect of cellular function like cell signaling pathways, especially in eukaryotes ubiquitination is regulated by a protein ubiquitin of 8.5 kD conjugated with substance protein by ubiquitin proteosome system hence managing the stability and modified target protein. Ubiquitination and DE ubiquitination are catalyzed by histone ubiquitin ligases and ubiquitin-specific peptidases ubiquitinating enzymes (DUBS) respectively the number of ubiquitin-associated results in distinct functions [51,52,53]. Mono ubiquitination regulates protein translocation transcriptional regulation and DNA damage signaling. Histone 2A Mono ubiquitination regulates gene silencing histone 2B Mono ubiquitination (H2Bub) is related with transcription activation. Activation or degradation of a certain protein is marked by polyubiquitination in cell signaling pathways. Histone ubi also provides a platform for crosstalk between other histone modifications for example: histone H3 Mono ubiquitination induces acetylation of the same histone [55].

5. EPIGENETIC THERAPY

A number of ways have been developed in treating cancer some which include chemotherapy, radiotherapy, surgery for the removal of local tumors, cytotoxic treatments etc. But due to some major drawback of these treatments like damaging or killing normal cells or limitations in their effectiveness other treatments immunotherapy and epigenetic therapy are also considered.

The bottom of epigenetic treatments relay on treating cancer cells by reversing its abnormal modifications with the help of drugs known as “epi-drugs”. Generally, the enzymes involved in epigenetic modifications are the main targets of epigenetic therapy. These enzymes a Histone deacetylase (HDACs), DNA methyltransferases (DNMTs) and histone demethylases (HDMs). Therefore, the epi-drugs being considered are inhibitors of these enzymes such as Histone deacetylase inhibitors and DNA methyltransferase inhibitors.

5.1 Histone Deacetylase (HDAC) Inhibitors

Acetylation is the process involved in histone modification and its main function is to add acetyl groups to histones. An antagonistic effect to acetylation is caused by histone deacetylation by an enzyme HDAC which eventually leads to gene silencing of tumor suppressor genes and DNA repair genes. Therefore, histone deacetylase inhibitors decrease histone deacetylase activity and indirectly increase the activity of tumor suppressors genes. Example of histone deacetylase inhibitors for clinical use includes vorinostat mefniyh{ (Zolinza®), romidepsin (Istodax®).

5.2 DNA Methyltransferase (DNMT) Inhibitors

One of the major occurrence of cancer are often result of heavy methylation and silencing of tumor suppressor genes. During DNA methylation enzymes called DNA methyltransferases add methyl groups to bases in DNA. When these epi drugs comes in contact with DNA they inhibit any DNA methyltransferase that come along and ultimately destroyed them preventing them from further methylation. Treatment of acute myeloid leukemia and myelodyplastic syndrome have been shown to be effective with the help of two epi drugs: azacytidine (Vidaza®) and decitabine (Dacogen®).

Although epi-drugs are widely used in clinical treatment, they have several disadvantages associated with it including fatigue and diarrhea. Chemical instability related with these drugs rapidly broke down and are changed into inactive compounds that can cause DNA damage and lower immune function. Also due to their lack of specificity they are also toxic to bone marrow, and can reduce blood cell counts.

CONCLUSION

In conclusion, cancer is caused when cells of the body start multiplying at a fast rate without any definite differentiation and formation of a tumour which spreads to other body organs and tissue. Cancer epigenetics is the study on how your environment and behaviour can affect the work of genes. Epigenetics changes are regulated by the genes which are turned on or turned off. These changes do not change the DNA building blocks sequences. Epigenetic changes include modifications of histone that lead to cancer, DNA hypermethylation and other environmental stimuli. The study of these epigenetic changes are useful in treating various cancers through epi drugs and the advancement in this area is much needed as well as important to meet the competitive evolving rate of cancer.

AUTHORS CONTRIBUTION

The authors confirm contribution to the paper as follows: M.P., N.S., R.M., S.S., T.C.: DATA COLLECTION AND MANUSCRIPT PREPARATION; D.D.Dean: STUDY CONCEPTION AND DESIGN, AND CRITICAL ANALYSIS. All authors reviewed the results and approved the final version of the manuscript.

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