DNA METHYLATION AND HISTONE MODIFICATION AS A DRIVING FORCE OF 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 changes 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 stimuli. 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 triggered by various factors 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.

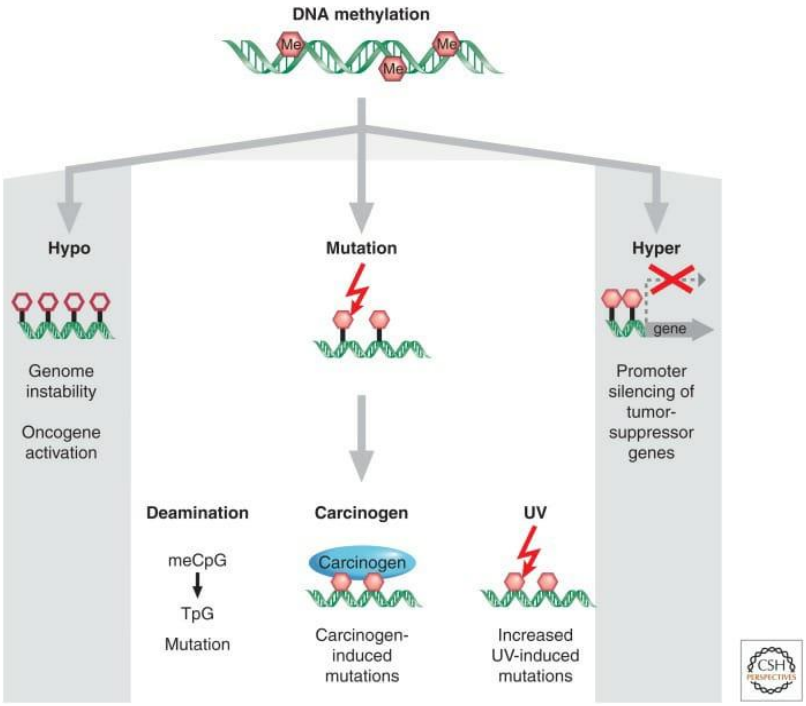
1. INTRODUCTION

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 changes 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

Gene expression is controlled in eukaryotes, but methylation of DNA is a common epigenetic signalling tool that cells use to lock genes in the "off" position. DNA methylation is an important regulator of gene transcription, and its role in carcinogenesis has been a topic of

considerable interest in the last few years. Alterations in DNA methylation are common in a variety of tumors as well as in development. Of all epigenetic modifications, hypermethylation, which represses transcription of the promoter regions of tumor suppressor genes leading to gene silencing, has been most extensively studied. However, global hypomethylation has also been recognized as a cause of oncogenesis. New information concerning the mechanism of methylation and its control has led to the discovery of many regulatory proteins and enzymes. The contribution of dietary folate and methylene tetrahydrofolate reductase polymorphisms to methylation patterns in normal and cancer tissues is under intense investigation.

As methylation occurs early and can be detected in body fluids, it may be of potential use in early detection of tumors and for determining the prognosis. Because DNA methylation is reversible, drugs like 5′-azacytidine, decitabine, and histone deacetylase inhibitors are being used to treat a variety of tumors. Novel demethylating agents such as antisense DNA methyl transferase and small interference RNA are being developed, making the field of DNA methylation wider and more exciting.

3.1 Hypermethylation and Silencing in driving tumorigenesis

In tumor suppressor genes hypermethylation of promoter region is commonly observed in cancers, a phenomenon that has been implicated with driving tumorigenesis (Baylin and Jones, 2011). Cell cycle and DNA repair genes, such as *RB*, *BRCA1/2*, and *PTEN*, have all been shown to be hypermethylated or mutated/deleted in cancer (Hatziapostolou and Iliopoulos, 2011). Epigenetic silencing also induces cancers by abnormal activation of signalling pathway, further promoting the expression of several genes whose products are responsible for cell proliferation. As a result of survival and proliferation, these cells accumulate genetic mutations in other components of the several signalling pathway. Such as in normal cells secreted frizzled- related proteins (SFRPs) antagonize WNT signalling, silencing of these SFRPs accumulate in WNT signalling pathway [5].

3.2 DNA Methyltransferase Family and Establishment of DNA Methylation Profiles

The first identified DNA methyltransferase DNMT1 is known as a maintenance DNMT. It is responsible for the exact copying of the DNA methylation pattern on the neo-synthesized strand during DNA replication. Therefore, it principally localizes to the DNA replication fork. Due to its importance in DNA replication, DNMT1 expression is tightly regulated during the cell cycle by several mechanisms and maximal expression occurs during S phase.

Since its role is to ensure the inheritance of the DNA methylation pattern through cell division, DNMT1 expression is maintained after development. From a transcriptional point of view, two transcript variants of DNMT1 mRNA were identified: a full-length form of 1,616 amino acids, and an oocyte-specific variant that lacks the N-terminal 118 amino acids of the full-length form (DNMT1o) but both are enzymatically active.

DNMT1 is capable of *de novo* methylation but its affinity for unmethylated DNA is far lower than for hemi-methylated DNA. As an illustration of the crucial role of DNMT1, the genetic loss of *DNMT1* gene in the mouse model is embryonic lethal. The *de novo* DNA methyltransferases DNMT3a and DNMT3b are responsible for the establishment of DNA methylation patterns during development. They are highly expressed during embryogenesis. Similarly, to DNMT1, DNMT3a and 3b expression is increased in S phase but they do not localize at the DNA replication fork. Immuno-fluorescence studies show that both *de novo* DNMTs localize to heterochromatin 6, and further experiments demonstrate that DNMT3a and DNMT3b are strongly associated to nucleosomes containing methylated DNA, and promote propagation of DNA methylation through stabilization of those enzymes.

3.3 DNA Methylation Alterations in Cancers

Alteration of DNA methylation patterns is a hallmark of cancer. Numerous studies describe repression of tumor suppressor genes (TSG) involved in various cellular pathways (cell cycle, apoptosis or genome maintenance) during carcinogenesis by DNA hypermethylation of their promoters. Paradoxically, cancer cells exhibit a global genome hypomethylation that leads to genomic instability and re-expression of silenced genes.

Mechanisms underlying this paradox are still not clearly explained. Wild and Flanagan depict current knowledge on genome wide DNA hypomethylation associated with cancer. Briefly, two competing theories of “passive” *vs.* “active” demethylation processes could explain this phenomenon. The former implies a disruption of the link between histone modifications and DNA methylation establishment, an aberrant localization of DNMT1 to DNA damage sites or a metabolic imbalance favoring a decrease in the methyl group donor, *S*-adenosyl-methionine.

Conversely, the latter theory relies on a class of enzymes harboring a demethylase activity. The TET protein family (Ten Eleven Translocation proteins) is described to actively demethylate methyl-cytosines by their oxidization and elimination through different mechanisms in physiological conditions. Briefly, the TET enzyme family facilitates passive

DNA demethylation by oxidizing methyl-cytosines to 5-hydroxyl-methylcytosines (5 hmC) leading to a considerable reductions in UHRF1 binding (ubiquitin-like containing PHD and RING finger domains) and in DNMT1 methyltransferase activity at the replication fork.

A second mechanism involves the DNA repair pathway. Hydroxy-methyl cytosines are converted either by further oxidization or by deamination that leads to a nucleotide mismatch, which will be excised and replaced by a cytosine. Last, DNMT3a demonstrates methyltransferase activity in reducing conditions and conversely, dihydroxy methylation in oxidizing conditions that converts 5 hmC in cytosines.

Recent studies report that the induction of TET suppresses breast tumor growth, invasion and metastasis in mouse xenografts. Moreover, TET down-regulation in hepatocellular carcinoma correlates with a decreased level of 5 hmC and is associated with tumor size and poor overall survival. Taken together, these observations are controversial, with a pro-oncogenic effect of TET mediated-DNA demethylation.

4. HISTONE MODIFICATION

Along with DNA Methylation, histone modification after translation does not alter the nucleotide sequence of the DNA enhances it efficiency for transcriptional machinery. Epigenetic machinery is classically represented by DNA methylation and histone modification. Histone modification includes acetylation phosphorylation, ubiquitination, methylation, etc. Stone 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 histone modification drugs that could inhibit the histone modification enzymes. They usually act at the end terminal of histone with amino acids such as arginine or lysine as well as threonine, serine tyrosine etc. Histone methylation has effective role in gene expression. Methylation of histone could be either transcriptionally permeable or impermeable based on the position of the amino acid in tail or number of the group added that are modified.

4.1 Histone Acetylation

Acetylation of histone is modulated by two analogously acting enzymes histone deacetylases (HDACs) and histone acetyltransferases (HATs). The acetyl group transfer from acetyl CoA is mediated by HAT to the amino acid group of lysine residues targeted at the tail. Acetylation

removes histone positivity resulting in weaker interaction between DNA and histone. Weak interaction between DNA and histone lessens the compaction of chromatin and hence enhances its availability to the machinery of transcription. HDACs have a role in repressing gene expression by removing the acetyl group from the tail of 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, and replication and are also important for centrosome function. The 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 factor related 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 methylation of lysine or Arginine influences the binding of different regulatory proteins to the chromatin indirectly. Three methyl groups can be transferred by HMTs from cofactor S-adenosyl-L-methionine SAM to the histone lysine or Arginine residues. The specificity of KMTs is higher than HATs because of the 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 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 which remove the methyl groups and demethylated H3K4. The JMJC domain containing 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 the same histone (H3K9ac and H3K14ac) at acetylation levels [19,21,48].

4.4 Histone Ubiquitination

Histone ubiquitination has a role in every aspect of cellular function in 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 regulating the stability and turnover of target protein. Ubiquitination and DE ubiquitination are catalyzed by histone ubiquitin ligases and ubiquitin-specific peptidases ubiquitinating enzymes (DUBS) respectively [51,52,53]. the number of ubiquitin-associated results in distinct functions. Mono ubiquitination regulates protein translocation transcriptional regulation and DNA damage signaling. Histone 2A Mono ubiquitination deals with gene silencing. Histone 2B Mono ubiquitination (H2Bub) is associated 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 HDAC inhibitors and DNMT 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, HDAC inhibitors decrease Histone deacetylase activity and indirectly increase the activity of tumor suppressors genes. Example of HDAC 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 DNMTs 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 in less than an hour 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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