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EPIGENETIC MECHANISM OF CANCER: A SHORT REVIEW

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ABSTRACT

Epigenetics can be understood as change in phenotypic characteristics without any change in genotypic structures. It is infact the study of mitotically and/or meiotically heritable changes in the function of the gene which cannot be explained by changes in sequence of DNA. In fact, all cells of a complex multicellular organism contain the same genetic information but during development, each single cell differentiates into a specific phenotype without any changes in DNA sequence. This characteristic of epigenetics implies that the accuracy of epigenetic modifications is crucial for maintaining the genome integrity and the phenotype of the cell. Cancer has been usually thought of as a genetic disease, but it is now known to be an epigenetic disease as well, caused by genetic alterations. Cancer is a disease of various types, they share many traits but each has its own working. Therefore, making it necessary to study the mechanism of action. Epigenetic attributes are reversible, meaning they can be counter-acted upon, giving a chance of curing this disease. Use of decitabine and zebularine for the treatment of blood/bone marrow cancers via epigenetic mechanisms have been FDA approved. This review summarizes the main epigenetic mechanisms of cancer.

KEYWORDS: decitabine and zebularine.

I. INTRODUCTION

In the words of C.H. Waddington, epigenetics refers to the causal interactions between genes &their products, which bring the phenotype into being.[1] Recent studies have shown that both epigenetics and genetic mutations result in cancer development.[2,3] These genetic and epigenetics mechanisms interact thoroughly during the progression of cancer. Although the genetic root has been widely accepted still the studies have shown that the epigenetics characteristics may be the key to initiate cancer.[4] And as these characteristics are reversible, it would be beneficial if we know the mechanism so that we can act upon it.

Approximately 146 bp of DNA wraps around the histone octamer protein, which includes four core proteins (H3, H4, H2A and H2B) forming the famous "beads-on-a-string" structure, the nucleosomes. These repeating units of nucleosomes form chromatin which is further condensed to form chromosomes.[5] Epigenetics basically work through by altering the working of the chromatins. These alterations can occur becauseof its change in compactness or its accessibility. These alterations are done via several different methods which are inter-related. They are:

- DNA Methylation.
- Histone modifications.
- Non- coding RNAs (miRNAs) and.
- Chromatin remodeling and gene looping.

II. DNA METHYLATION

DNA methylation is the mechanism by which methyl groups are attached to the DNA. This attachment is location specific and results in silencing of genes which leads to the regulation of gene expression. This addition of methyl group is on the cytosine residues occurring before the guanine residues of the CpG islands. CpG islands are the regions where cytosine nucleotide is followed by guanine nucleotide in the 5' to 3' direction of the DNA. The term CpG arises because of its structure, which is, 5'-cytosine-phosphate-guanine-3', meaning a phosphate group separates the two nucleotide.[6] The term island comes into existence because these CpG dinucleotides are not evenly stretched out across the DNA but are present in small concentrated CpG-rich DNA regions [7]. They are basically located at the 5' prime end of the genes and occupy 60% of human gene promoters (a site which initiates transcription).[8] Some of these CpG sites are methylated and some remain unmethylated. However, some of these sitesbecome methylated during development which leads to transcriptional silencing of the genes. When the CpG islands are hypomethylated, it results in gene activity, whereas, when they are hypermethylated, it results in transcriptional silencing of the gene. Therefore, cancer genes are hypomethylated and tumor suppressing genes are hypermethylated. Also, different types of tumors have different CpG methylation sites and express different mechanism of carcinogenesis.[9]

This DNA methylation is carried out with the help of these three enzymes –

- DNA methyltransferase 1 (DNMT 1).
- DNMT3A
- DNMT3B

DNMT1 provides parental methylation and DNMT3A and DNMT3B provide de novo methylation.[10]

III. HISTONE MODIFICATIONS

In nucleus, 1.8 linear meters of DNA is organised into a 3-D structure which is wrapped around a histone protein. This histone protein has a globular C-terminal domain and an unstructured N-terminal chain. This N-terminal chain can be widely modified which results in tightening or loosening of the DNA from the protein which further results in transcriptional changes thus altering the gene expression. These modifications can be done on specific residues and are of various types–

- Methylation: Addition of the methyl group
- Acetylation: Addition of the acetyl group
- Ubiquitylation: Addition of ubiquitin
- SUMOylation: Addition of Small Ubiquitin-like Modifier (SUMO) proteins
- Phosphorylation: Addition of the phosphorus group

All of these changes result in transcription, repair and replication. Histone modification can lead to either repression or activation, depending upon the types of residues modified and the way of modification present[11]. There are certain enzymes known which alter the histone proteins[11]. Histone Acetyltransferases (HATs) adds acetyl group to lysine residues and Histone Methyltransferases (HMTs) adds methyl group to arginine and lysine residues, whereas, Histone Deacetylases (HDACs) and Histone Demethylases (HDMs) are used to remove acetyl and methyl groups respectively. HDACs are found both naturally and synthetically and are currently used for the treatment of cancer and other psychiatric diseases. Two HDACs which are approved by FDA are – 'suberoylanilidehydroxaminc acid' and 'romidespin' which are used for the treatment of T-cell lymphoma.[12]

1. Histone Methylation

As stated above, histone methylation occurs at arginine and lysine residues present on the H3 and H4 tails of the histone proteins. Lysine methylation is catalysed by K-methyltransferases, which involves transfer of methyl group from the cofactor- S-adenosyl methionine. 'Enhancer of Zeste 2' (EZH2) is a protein, whichis used in control of stem cell differentiation and is basically a K-methyltransferase, which catalyses trimethylation of H3K27.[13] This K-methyltransferase recognises trimethylated-H3K27, which results in silencing of the gene leading to stem cell differentiation. However, there are cancer cases in which EZH2 level has been overexpressed at the transcriptional level. One example being theprostate cancer, in which an increase of EZH2 staining level was observed.[14] Moreover, overexpression of EZH2 has also been observed in breast cancer, glioblastomas and lymphomas.[15] Also, in normal cells EZH2 interacts with DNMT to control DNA methylation.[16]

2. Histone Acetylation

Histone acetylation is associated with the transcriptional activation and it occurs on the lysine residues neutralizing the positively charged histones and hence activating the transcriptional mechanism. This neutralization decreases the bonding of the histone proteins to the negatively charged DNA. HATs are also known as K-acetyltrans ferases.[12] Acetyl coenzyme is used to add acetyl groups to the lysine nucleotide which is catalysed by K-acetyltransferases. Modifications done by the usage of acetyl group, leads to a phenotypic change in the chromatin behaviour. HATS have three distinct families[17] and they all play an important role in building up of cancer.The three families are –

- Gcn5 family: plays a significant role in breast cancer.[18]
- P300/CBP family: Cyclic AMP response element-binding (CREB) protein has proved to be capable of acetylating all the four histone proteins along with non-histone proteins.[19]
- MYST family: HATs belonging to MYST family have shown importance in acute myeloid leukaemia and haematopoiesis.[20]

HATs not only help in acetylation of histone proteins but also in the acetylation of non-histone proteins. Similarly HDACs also help in deacetylation of non-histone proteins which are identified to be important in carcinogenesis. Proteins such as p53, YY1 and STAT3 are such examples.[21]

IV. miRNAs

Small non-coding, ~22nt RNAs are called miRNAs. These miRNAs are highly processed and have a role in the regulation of carcinogens as they alter the gene expression via posttranscriptional targetedgene silencing. When they are processed into mature RNAs they are responsible for targeting 3' untranslated regions of mRNA, where they directly inhibit the translation of the desired mRNA and sendit out for degradation.[22] miRNAs are responsible for controlling a variety of normal biological tasks such as apoptosis, cell differentiation and cell proliferation. miRNAs can also target DNMT3A and DNMT3B, hence modulating the epigenetic mechanism inside a cell via DNA methylation and can also cause histone modifications by targeting EZH2.[23,24]

V. EPIGENTIC CO-RELATIONS

All of these mechanisms mentioned above are interlinked. For example: miR-29 and miR-148 post transcriptionally regulate the DNA methylases.[25] HDACs inhibitor interacted with DNMTs are used in cancer therapies.[26] Moreover, DNMT-mediated promoter methylation regulates the expression of miR.[27]

VI. CHROMATIN REMODELLING

In a eukaryotic cell, genes are continuously being activated and deactivated to maintain cellular homeostasis. One of the special properties that human DNA possess is that its 2m length can be coiled and folded to fit into a small nucleus, that is to package itself into a higher order of structures. These structures are called chromatin. Chromatin can be further divided into two types: euchromatin and heterochromatin. To maintain the homeostasis as mentioned above genes residing in the euchromatin has to undergo various structural changes that result in gene activation or gene repression. To guide this remodelling, chromatin requires the presence of other proteins known as chromatin remodeling proteins or chromatin remodelers.[28] These chromatin remodelers provide guidance for cell-cycle progression therefore exerting tumor-supressing function. Mutations in such chromatin remodelers can favour the cell to escape out of the cell growth-regulatory signals.[29]

Chromatin remodelers can alter the chromatin structure and their families have been well categorized into:

- SWI/SNF: 'switching defective/sucrose non-fermenting family', was purified from *Saccharomyces cerevisiae*. This family is made up of 8-14 subunits and is ATP dependent. It is responsible for shifting and ejecting the nucleosomes. Moreover, it doesn't participate in the chromatin assembly.[28]
- ISWI: 'Imitation switch family', was extracted from drosophila embryos. The characteristic feature of this family is the presence of SANT-SLIDE domain which binds to the unmodified histone tail.[30] They control the chromatin assembly by regulating the nucleosome spacing which further changes the transcription.
- ISWI is classified into two regions – a C-terminal region which is responsible for substrate recognition. It contains 12 alpha helices which are divided into three domains and a spacer region. A HAND domain (4 helical structures represent a hand), a SANT domain (c-Myb DNA-binding like), a SLIDE domain (mostly like SANT but with extra insertions) and a spacer helix. And an N-terminal region that contains the SWI2/SNF2 ATPase domain.[31]
- INO80: purified from *S. cerevisiae*, 'inositol requiring 80', is a multi-subunit family of more than 10 subunits.[32] They perform transcriptional regulation and they also help initiate a response for DNA damage.[28]
- CHD/NuRD: Chromodomain (a protein structure, consisting of 40-50 amino acid residues) is the defining feature of this family which is present along with core-ATPase, helicase activity and DNA binding. Purified from *Xenouslaevis* it is a 5-10 multi-subunit protein complex[34]. CHD proteins promote transcription by sliding and ejecting nucleosomes.[28]

All of these chromatin remodelers' family share these basic five properties –

- Interaction with nucleosomes.
- Affinity for post-transcriptionally modified histone tails.
- ATPase activity and dependency on ATP hydrolysis for energy.
- Regulatory domains.
- Specific protein domain and motifwhich accommodates protein-protein interactions.

But still, theyhave evolved differently to perform their respective functions.[30]

VII. CONCLUSION

Study of epigenetics and its new discoveries have outgrown the traditional thinking that the cause of cancer is alteration in the genetic code itself. This field is highly progressive, as epigenetics are reversible and can be used to cure cancer. This leads to the possibility of 'epigenetic therapy'. Epigenetic therapy along with chemotherapy sessions can hold a chance of successful treatments. These treatments can also target cancer stem cells, removing problem from the root itself. But to fully exploit epigenetic therapies, we need to understand each and every mechanism thoroughly and as it is a relatively new field new literatures and discoveries are being made from time to time. Gene looping which is mentioned above is also one such mechanism on which dense studies is going on. Therefore, it can be stated that the area of cancer epigenetics is standout amongst the most logical and promising field of research to seek to cure the "incurable".[33]

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