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Bisphenol A (BPA) as an Endocrine Disrupting Chemical (EDC) -A Review

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Cover Letter

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Abstract

BPA stands for Bisphenol A [22 – Bis (4 - Hydroxyphenol) propane] is an organic synthetic compound, most commonly exposed chemical in everyday life. BPA is used in hard plastic bottles and as a protective lining in canned food and beverage cans. Bisphenol A (BPA) is an old synthetic chemical widely known for endocrine malfunctions and replacement of the estrogenic activity of diethylstilbestrol.[1] Various environmental pollutants are manmade chemicals like polymerised form of biphenyls and bisphenol-A have several developmental effects on endocrine and reproductive functions of living beings. Bisphenol-A causes wider effects even at low doses in both terrestrial and aquatic animals and effects major disturbances at endocrine, immune and metabolic level.[2] Since BPA is known to have 'selective estrogen receptor modulator' properties and epigenetic regulations. It affects multiple reproductive organs such as testis, ovariesetc.as it causes reproductive biohazard and endocrine disruption.[3] This review summarizes the highlights of BPA as an Endocrine disrupting chemical (EDC) and how it effects multiple organs in the body.

Key Words: Bisphenol A, Endocrine Disruptor, Estrogen

Introduction

Bisphenol A (BPA) is an estrogenic chemical which has been used widely in the production of polycarbonate plastics and epoxy resins.[4]It was **first synthesized in 1891 by Aleksandr** (Russia) and first mention of BPA in scientific paperwas made in 1905 by Thomas Zincke (Germany). Many household electronic appliances, several medical devices, safety equipment used in sports, plumbing equipment are few objects that contain BPA. BPA is also used as a supplement in the production of brominated flame retardants and brake fluid, Bisphenol Aglycidyl methacrylate and bisphenol A-dimethacrylate are BPA derivatives used as a component in the production of dental fillings and sealants in the dental industry.[1] With BPA being used so widely, it has drawn immense attention due to its various effects on human health[5].

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BPA detected in canned and brewage food cause health problems especially for developing foetus, infants and children. The estimated exposure levels of BPA are from **0.01 µg/kg/day in Children** and **4.2µg/kg/day in adults.**BPA consumption causes male infertility, heart diseases, depression, Type 2 Diabetes, loss of memory, asthma and carcinoma of brain. BPA being a potent reproductive and genotoxic agent has severe effects on the normal physiological functions[4]. BPA has a weak estrogenic activity and can interfere with the endocrine system, and can increase the possibility of testis and breast cancer[6].

The major adverse effects of Endocrine Disrupting Chemicals (EDC) are observed in hormone system malfunction. It alters the essential physiological functions by distorting endocrine regulation. There are potent EDCs in the environment such as natural and man-made steroid estrogens which includes 17β-estradiol (E2), estrone (E1), and 17 α-ethinylestradiol (EE2). Bisphenol A (BPA) and nonylphenol (NP) are other common industrial chemicals involved in interfering the function of endocrine system in animals[7].

Endocrine Disrupting Chemical (EDC)

EDCs are exogenous agents that interferes with the function of hormones like secretion, release, transport, binding, action and metabolism that are responsible for the maintenance of self-equilibrium and the regulation of developmental processes [7]. Natural and synthetic chemicals interfere with the body's hormones (endocrine system). EDCs have effects on the normal organ development, reproductive system, brain function, immune system as the Endocrine disruptors are found in several routine products such as food containers, plastic water bottles, hot and cold metal soft drink cans, detergents, baby toys, wider range of cosmetics and pesticides [8].

Source of EDC

There are multiple routes of entry for EDCs into the environment from diverse sources. It can be from the air, soil or water. EDC sediments have been traced in both in biota and fish that enter the aquatic ecosystem through wastewater, agricultural run-off and groundwater discharge. Significant contributors of EDCs to surface waters are discharges from municipal wastewater treatment plants (WWTPs)[7].

Discharges to water treatment facilities include hormones, pharmaceutical estrogens excreted by humans flushed down from home toilets, PPCPs excreted or washed from the

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body, plant material, waste products from fire retardants, regular household cleaning products, insecticides and pesticides are the main sources. WWTPs might also receive waste products from industrial processes that use plastics containing BPAs and storm water run-off that contain EDCs.[7]

Endocrine-disrupting chemicals usually takes time to break-down in the environment. Thus, makes them potentially hazardous over time. Endocrine disrupting chemicals also causes adverse effects in animals. Human beings are also exposed to EDC, however to assess its effects on health is an enormous task. Moreover, traces of endocrine-disrupting chemicals may be unsafe. Normal endocrine functioning in the body involves very minimal changes in hormone levels. However, these small fluctuations are sufficient to bring out significant developmental and biological changes. Some of the studies also shows that even a minimal exposure to EDC alters the normal functioning of the body leading to major health related issues [8].

BPA as EDC

Action of BPA is at the hormonal level. When there is a distortion of hormonal balance, estrogenic related receptors are stimulated and brings about an abnormal estrogenic effect. Thus, giving rise to several hormone related abnormalities that has been previously reported in some studies (Fig:1) [9]. Similarly, BPA also acts on the endocrine system through several receptor mediated mechanisms. BPA acts like Xenoestrogen which binds and activates the estrogen receptor. Even though BPA has a lower affinity for genomic ER than estradiol, the circulating concentrations of BPA are biologically active and has higher affinity than estradiol. In addition, BPA is as bioactive as estradiol, particularly in those mediated by nongenomic signaling [10].

Mechanism of BPA over some of the endocrine functions are as follows:

- BPA being an antiandrogen binds to androgen receptor and interferes the normal action of androgens.
- BPA alters the synthesis and circulation of steroid hormone concentrations
- Alters the thyroid activator receptor and
- Disrupts the glucocorticoid signaling [11].

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BPA acts on Estrogen Receptor (ER)

BPA can behaveas a weak inducer of estrogen activity or also have a anti estrogen effect. It can bind with ERα and ERβ (estrogenic receptors). BPA blocks estrogenic response by competing with endogenous E2 [1].

BPA as an Antiandrogen

Androgenacts through ligand activated steroid hormone receptor called Androgen Receptor (AR). BPA acts by antagonising the AR signalling to inhibits the proliferation of Sertoli cells and male reproductive toxicology [14].

BPA alters steroid synthesis

BPA is an endocrine disruptor. Adult female exposure to BPA can cause potential effects on fertility, leads to decrease in oocyte fertilization rate for women in invitro fertilization. BPA affects granulosa cells both in vivo and female fertility. Higher dose of BPA shows granulosa steroidogenesis, ovarian disruption and maximal reproductive potential. The effect of BPA on Follicle Stimulating Hormone stimulating the process of relatively high concentrations with human luteinized granulosa cells shows more sensitive than KGN cell line [13].

BPA disrupts the Thyroid Hormone (TH) signalling

BPA acts on Thyroid Hormone in a negative feedback mechanism by inhibiting β-TR (Thyroid Receptor) action and involved in T4 elevation by the action of unopposed α- TR in the hippocampus. During Maternal exposure, BPA increases serum T4 and also shows higher level of expression of RC3/Neurogranin. Eventual exposure of BPA may influence signalling of Thyroid Hormone (TH) in the developing fetal brain [15].

Developmental and parental exposure to BPA alters the cell morphology and embryological developmental of adult health and disease. It is associated with decrease in young adult's anogenital distance which acts as an androgen sensitive endpoint. BPA doesn't cause DNA mutation directly but induces epigenetic embryological changes ends in adult-onset disease [11].

BPA as an Epigenetic Regulators

Epigenetic regulators play an important role in controlling gene expression by chromatin modification. Some of the epigenetic regulators are histone acetyltransferases,

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chromatin remodelling enzymes, methyltransferases etc., BPA induces epigenetic modifications in both human and animal cells. BPA not only modifying the methylation pattern of gene coding protein but also directly induces the gene responsible for DNA methylation (Fig: 2). BPA induces epigenetic modifications such as:

a) DNA Methylation
b) Histone Modification
c) Non – Coding RNAs[7]

DNA Methylation

DNA methylation is a regular biological process of the epigenetic regulator. It is defined as methyl groups (CH_3) are added to the DNA molecule. DNA methylation process alters the DNA segment activity without changing the sequence (Fig:3). Transcription of Gene repression acts by DNA methylation [16]. DNA methylation either regulates the gene expression by recruiting the protein or inhibiting the transcription factors binding with DNA [17,24].

DNA methylation is essential for general development in human beings. It consists of following processes including

- Genomic Imprinting
- Inactivation of X-chromosomes
- Repression of transposable elements
- Ageing and
- Carcinogenesis

There are four bases in DNA. Only two bases of DNA can be methylated i.e., Cytosine and Adenine. DNA base with addition of methyl group to cytosine is commonly seen in all organisms [6]. In plants and other environmental organisms, DNA methylation is found in three different sequences:

- CG
- CHG or
- CHH

In mammals, DNA methylation is usually found in CG dinucleotides with the cytosines on both strands methylated [26]. Non – methylated CG found in embryonic stem cells,neural tube development and hematopoietic progenitor cells [17].

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DNA methylation disrupts the gene transcription in two ways.

1. Binding of transcriptional proteins to gene are prevented or delayed
2. Methyl CpG – binding domain proteins (MBDs) – Protein bound methylated DNA[17].

MBD protein includes additional proteins to the gene locus like histone deacetylases and other remodelling chromatin proteins that can modify histones and forming compact, inactive form of chromatin called as heterochromatin[16].

DNA methylation is a heritable epigenetic alternator which causes carcinoma, atherosclerosis, genomic imprinting disorders and cardiovascular diseases [18].

There are three major methods to identify and quantify DNA methylation.

1. Conversion and sequencing of Sodium bisulfite
2. Differential enzymatic DNA cleavage and
3. Affinity captures of methylated DNA.

Restriction enzyme based differential cleavage of methylated DNA is locus-specific.[16]

Histone modification

A histone is a protein that helps to form chromatin structure (DNA-wrapped protein octamers). Histone methylation is one of the post-translational epigenetic modification. It is defined as transfer of methyl groups to histone proteins with the help of histone methyltransferases (HMTs) [19]. Histone modifications include covalent modifications such as addition or removal of chemical groups such as acetyl groups, methyl groups, phosphates, and ubiquitin to the positively charged histone protein. These modifications change the chromatin structure by alteration of gene expression [20].

Addition of acetyl groups to any of the DNA base (Lysine) in histone neutralizes the cations and loosening the DNA nucleosome's grip. Histone modifications proceeds the transcriptional process to detect DNA and genes are active [21].

Three types of histone modification involved in chromatin remodelling. It primarily occurs at N- terminal histone tails. These enzymatic modifications are

- Acetylation
- Methylation
- Phosphorylation and

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- Ubiquitination.

Non-Coding RNA (ncRNA)

A non-coding RNA are group of RNAs, originally does not encode functional proteins and regulates the expression of genes at post transcriptional and transcriptional level.

The involvement of Non-Coding RNA in Epigenetic modifications can regulate gene expression and controlling the cell differentiation in chromosomal level. The ncRNAs which are involved in epigenetic process are classified into two major groups:

1. Small or Short non-coding RNA and
2. Long non-coding RNA [22].

Small or Short ncRNA

Small or Short ncRNAs plays major role in eukaryotes. Different Short ncRNAs are essential for developmental process. Different types of small coding ncRNAs are:

- MicroRNAs (miRNAs)
- Short Interfering RNAs (siRNAs)
- Piwi-interacting RNAs (PiRNAs) [23,25].

MicroRNAs (miRNAs)

MicroRNAs (miRNA) is an endogenous single stranded RNAs highly prone to structural changes. It is the expression product of biological gene. MicroRNAs can regulate hundreds of different gene at same time. It binds with specific mRNA to induce cleavage and degradation[22].

Short interfering RNAs (siRNAs)

Short interfering RNAs (siRNA) is exogenous long double stranded RNAs. Its origins from viral infection either by gene transfer or gene target. Short interfering RNAs have similar action mechanism like miRNAs by mediating gene silencing and degradation[22].

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Piwi-interacting RNAs (piRNAs).

Piwi-interacting RNAs (piRNA) are named due to their specific reflection facts with the piwi protein family. It comes from single chain precursor and arising from long single stranded molecule. PiRNAs serve as a primary transcript. It has the ability to induce euchromatin histone modifications. PiRNA/Piwiprotein acts as a specific determinants of DNA methylation in germ cells and mediates the methylation of transposons[22].

Long ncRNAs

lncRNAs combine with modified chromatin proteins and recruit their catalytic activity to specific binding sites in the genome by chromatin modifications and induces gene expression. The majority of non-coding RNA transcription belong to the group lncRNAs. Long ncRNAs plays an essential role in process of dosage compensation, genomic imprinting, developmental differentiation and patterning and stress response. It can either upregulate or downregulate gene expression in all human beings [22].

Conclusion

Endocrine system plays an important role in balancing hormone in our body. Reproductive glands and thyroid gland secreting hormones function together to maintain homeostasis [14]. Many recent studies proved that indicating Endocrine Disrupting Chemical (EDC) causes developmental disorders, metabolic syndrome, obesity, cancer and infertility.Bisphenol A acts as an EDC causing developmental anomalies due to its Endocrine disrupting properties. Bisphenol A interferes with tissue and organ development, alters the mechanism of different diseases. Many researchers are effectively working to understand more about Endocrine Disrupting Chemicals and its impact on human health and environment.

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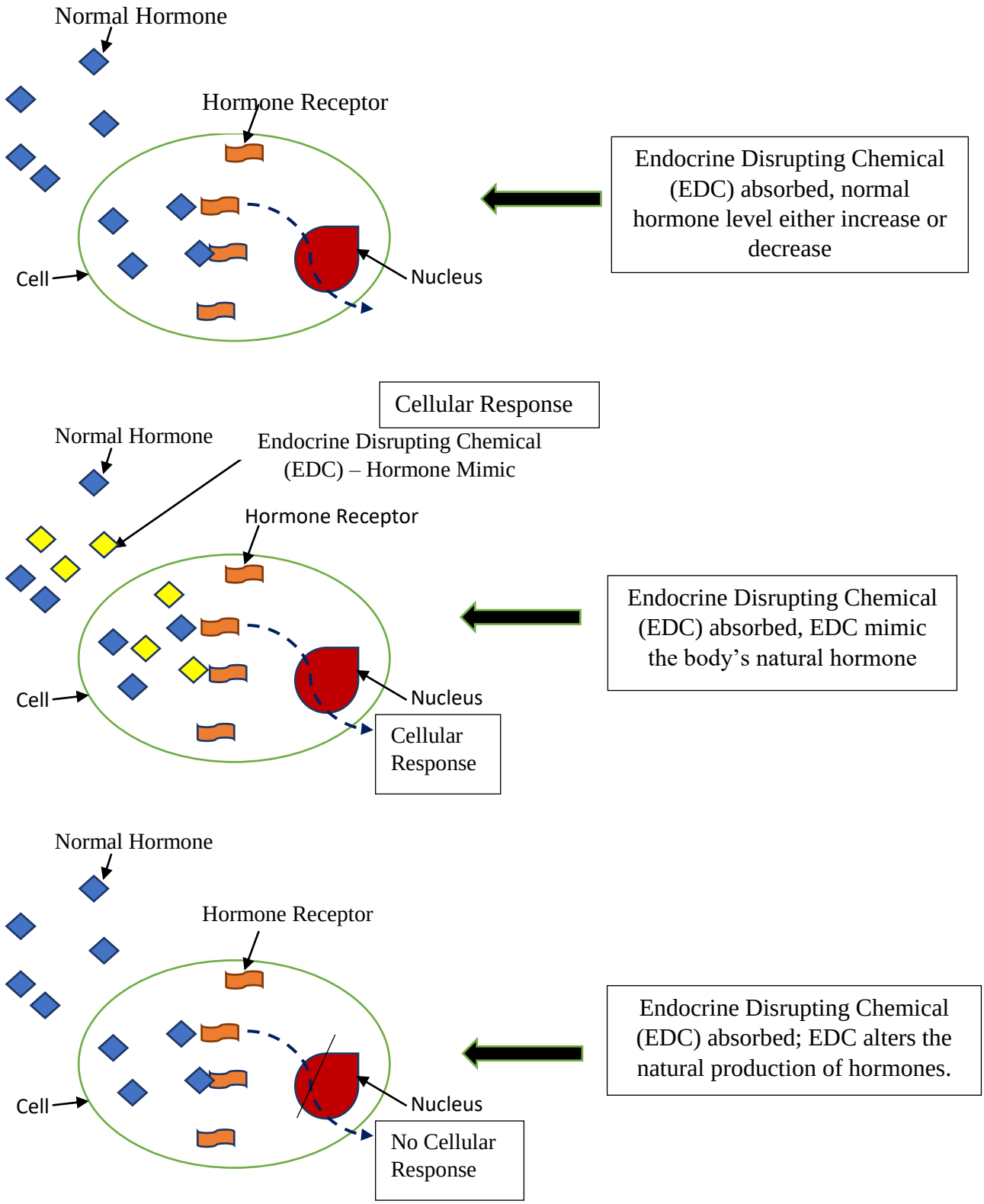

Figure 1: Endocrine Disruptors

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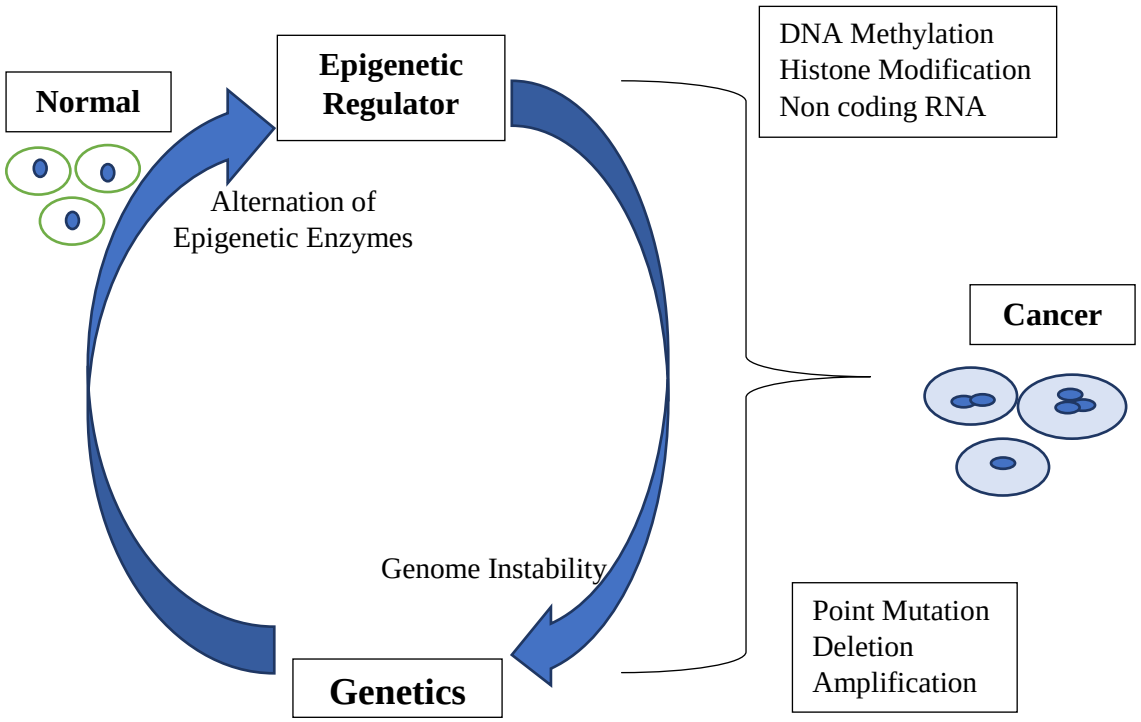

Figure 2: BPA as an Epigenetic Regulator

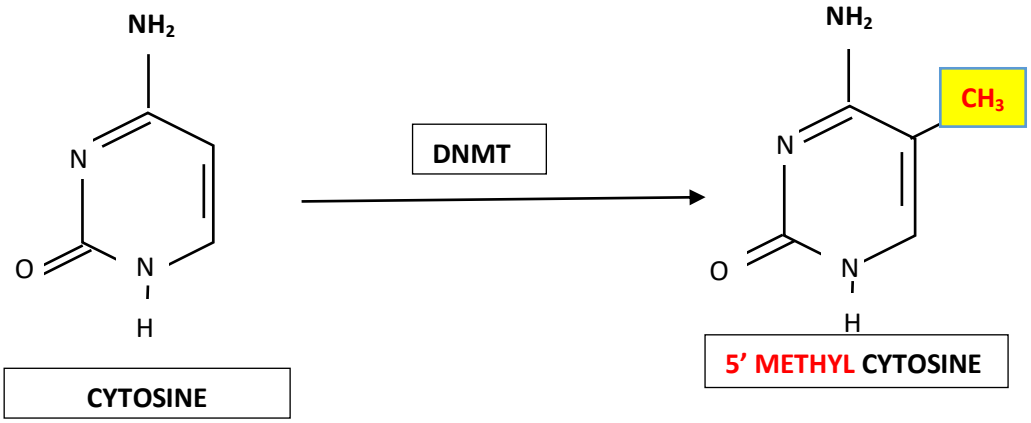

Figure 3: DNA Methylation