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Epigenetic mechanisms involved in toxicity induced by the environmental factors

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Abstract
A large number of toxicants and their by-products present in the environment pose a lethal and detrimental effect on the living population. Different mechanisms are involved in the neutralization of their toxic effects. The mechanism of detoxification depends on the chemical and biological composition of the compounds. They affect the gene expression level by altering the DNA and histone modification patterns by affecting the recruitment of various transcription machinery. These alterations are termed as epigenetic modifications. Compounds and toxicants reported to cause epigenetic alterations are heavy metal, Benzene, Bisphenol A, Dioxins, TCA and a number of other chemicals. Exposure to these factors may result in the predisposition of the altered epigenetic modifications from one generation to another. Dysregulation of gene expression governed by epigenetic alterations induced by exposure to toxicants results in developmental abnormalities. In this review, the common epigenetic modifications caused by toxicants and their role in development and progression of diseases is discussed. This would help better understand the toxic effects of the various factors responsible for the development of chronic diseases and their predisposition in the future generation. It also provides an insight into the therapeutic strategies to prevent adverse effects of toxicants.

Keywords: Toxicants, heavy metals, pollutants

Introduction

Living organisms are exposed to a large number of environmental factors such as light, temperature, heavy metals, harmful radiations, and a number of chemicals released by natural and anthropogenic activities. They respond to these factors through a number of mechanisms. Abnormal or deregulated responses against these factors lead to development abnormalities and progression of chronic diseases. These factors promote and modify native epigenetic patterns. The change in the epigenetic patterns affects the recruitment and formation of transcriptome, thus affecting the expression level of target proteins and subsequently cell signalling cascade. These epigenetic patterns are the most promising areas of the modern biology which fill the gap in understanding the development and progression of chronic diseases, their prevention and cure. Mutagenic and genetic effects have been studied extensively to understand disease progression in the past years, but epigenetics may play a role in better understanding of these defects.

Through experimental and epidemiological studies, it has been established that environmental factors are linked to aberrant epigenetic changes. Some of these environmental factors are heavy metals such as Cadmium, Arsenic, Lead, Mercury, and; a number of chemicals including Bisphenol-A, TCA, DES, Dioxins, and Benzene. These factors have specific mechanisms of toxicity with respect to epigenetic modifications. However, exact mechanisms of toxicity of these chemicals are yet to be elucidated (Jackson and Standart, 2007) [34]. Here, we will discuss about important epigenetic modifications involved in normal development of organisms and also to recover perturbations caused by environmental toxicants. We will also discuss some common environmental toxicants known to cause epigenetic-mediated genic alterations and disease progression.

Mechanisms of epigenetics regulation

Epigenetic mechanisms involve a number of regulating processes at different stages including DNA methylation, histone modification, and microRNAs (Allis *et al.*, 2007; Chuang and Jones, 2007) [2, 13]. DNA methylation is the modification of 5-methyl-cytosine(5MeC) which represents 2-5% of all cytosines in mammalian genomes. It is found primarily on CpG dinucleotide clustered in some regions forming CpG islands (J. Ferguson, 1988) [23]. DNA methylation is the key mechanism involved in regulating gene expression. It is also associated with chromatin structure remodelling, genomic imprinting and chromosome stability (Reik *et al.*, 2001) [52]; Grewal and Moazed, 2003 [29]. Hypermethylation in promoter region is associated with decreased expression of the gene (Orphanides and Reinberg, 2002) [47]. Epigenetic changes are flexible in nature and hence may change according to external environment and revert back in its absence (Baccarelli and Bollati, 2009) [3]. Epigenetic toxicity potentials of environmental toxicants using *in vitro* and animal model have been studied. Many toxicants including Arsenic, Cadmium, Nickel, Chromium, Mercury, BPA, DES, TCA, Dioxins etc. are found to affect epigenetic patterns specifically DNA methylation and histone acetylation (Valko *et al.*, 2005 [64]; Bleich *et al.*, 2006 [8]; Dolinoy *et al.*, 2007) [20].

DNA Methylation and Hydroxylation

DNA methylation is most important and most studied epigenetic mechanisms through which expression of cells

are controlled according to location and time. Methylation of DNA is involved in silencing of transposable element, genomic imprinting and X-chromosome inactivation (Li and Zhang, 2014) [39]. DNA methyl transferases (DNMTs) are a family of three enzymes which catalyse methylation of DNA. DNMT1, also known as maintenance methylation enzyme help in methylating new hemi-methylated DNA during replication. DNMT3A and DNMT3B are de novo methyltransferases that target unmethylated CpG sites (Bostick *et al.*, 2007) [10]; Sharif *et al.*, 2007 [56].

TET protein family contains three enzymes (TET1, TET2, and TET3) that convert 5-methyl-cytosine (5mC) into 5-hydroxymethylcytosine (5hmC) (Williams *et al.*, 2011) [68]. 5-hmC of DNA is thought to have potential for DNA demethylation. DNMTs and TET enzymes dynamically maintain the balance between methylation and hydroxylation and hence epigenetic regulation in gene expression (Tahiliani *et al.*, 2009 [58]; Ito *et al.*, 2010) [33].

In recent years, many studies have been made to understand how these processes affect cells' identity and functions. Of them hydroxylation of DNA, is one which describes demethylation mechanism of DNA through addition of oxygen group to methyl group (Tuesta and Zhang, 2014) [39, 61]. In mammalian genome CpG dinucleotides are generally methylated. (Rusiecki *et al.*, 2008) [53]. Cytosine methylation in promoter region is generally found to be associated with inhibition of transcription (Orphanides and Reinberg, 2002) [47]. S-Adenosyl-L-methionine (SAM) is the natural methyl donor in cells. Deficiency of SAM is supposed to cause reduction in methylation and hence abnormal gene expression. Environmental toxicants such as Arsenic cause a reduction in availability of SAM, hence causing a number of diseases including cancer. Dietary supplements of methyl group donors can modulate DNA methylation and associated deregulation in gene expression.

Histone modification

Histone proteins (H1, H2A, H2B, H3 and H4) are important constituents of nucleosome structure. They bind to DNA and pack it tightly thus allowing only localized opening of active elements which are involved in transcription and translation. After DNA methylation, histone protein modifications are another very important factor playing its role in epigenetic regulation. The N-terminal tails of histones protrude outwards from nucleosomes and are available for interaction with non-DNA binding proteins (Morales, V., & Richard-Foy, H. 2000). Histone modifications include acetylation, phosphorylation, methylation, ubiquitination, and sumoylation and ADP-ribosylation of N-terminal tail (Vaquero *et al.*, 2003) [66]. These modifications on the histone tail are correlated with DNA packaging and distinct biological events. Acetylation and methylation of histone at lysine residues are most commonly studied epigenetic modifications.

Tri-methylation on K4 of Histone H3 (H3K4me3) is generally associated with transcriptional activation and tri-methylation on K9 and K27 of histone H3 (H3K9me3 & H3K27me3) are associated with transcriptional repression. A number of CXXC domain family enzymes including CXXC7, CXXC9, F-box-containing, and leucine-rich proteins have been described as histone demethylases (Zhang *et al.*, 2010) [72].

RNA interference

MicroRNAs (miRNA) are non-translated (non-coding), single-stranded RNAs which play an important role in the regulation of translation of the target mRNA. These are of about 21–23 nucleotides in length and are partially complementary to one or more messenger RNA (mRNA) molecules. Binding of miRNAs down-regulate gene expression by hybridizing and degrading mRNA of a functional gene (Jackson and Standart, 2007 [34]; Wakiyama, M., Takimoto, K., Ohara, O., & Yokoyama, S., 2007).

Environmental factor affecting epigenetic regulation

Epigenetics is most responsive towards environmental factors. These responses are thought to be a protective mechanism for living system if occur in a regulated fashion. However, some toxicants we are exposed to, are known to cause persistent damage and deregulate epigenetic modifications causing abnormalities and diseases. Some important environmental factors which are known to cause their adverse effects by epigenetic modifications are discussed here.

Heavy metals

In case of heavy metal toxicity, altered DNA methylation are most studied epigenetic modification and cause of diseases caused. Heavy metals, including Nickel, Cadmium, Lead, Arsenic, Chromium, Mercury are known to cause changes in DNA methylation (Valko *et al.*, 2005) [64]. Arsenic is metalloid and a known carcinogen (Fragou *et al.*, 2011) [26]. It induces carcinogenesis in skin, lung, bladder, and kidney tissues when in the form of an inorganic compound (States, J. C. *et al.*, 2011). It binds with high affinity to thiol group (-SH group) of amino acids and reduces glutathione (GSH) (Patterson *et al.*, 2003) [49]. Exposure to arsenic occurs through drinking water containing low levels of arsenite. There is high risk of bladder cancer in people drinking water with high arsenic level (Y. Sato *et al.*, 2009) [55]. Detoxification and excretion of arsenic is carried out by methylation. Methyl group is donated by S-adenosylmethionine (SAM). Arsenic exposure also resulted in histone modification such as increased H3K9me2 and decreased H3K27me3 (Salnikow and Zhitkovich, 2008) [54]; Zhou *et al.*, 2008 [73].

Mercury is one of the major environmental pollutants known for its systemic toxicity. Methylmercury (MeHg) is the most bioavailable and toxic (Carocci *et al.*, 2014) [11]. It poses systemic toxicity particularly on CNS and kidneys (Fowler *et al.*, 1977) and can impair physiological function by endocrine disruption (Yuan, 2022). Inorganic mercury is methylated by microorganisms to form more toxic methylmercury. Production of methylmercury is found to be higher during the warmer seasons than the colder seasons (Clarkson and Strain, 2003) [14]; Dijkstra *et al.*, 2013 [17]. Prenatal exposure to low dose methylmercury caused hypomethylation in BDNF (Brain-derived neurotropic factor) promoter which causes neural abnormality.

Cadmium (Cd) is another heavy metal toxicant, classified as human carcinogen. In environment, Cadmium is added by fossil fuel combustion and industrial processes. Exposure to human occurs by food and smoking. It is known to cause lung cancer and kidney damage (EPA, 2000). However, the mechanism of toxicity of Cadmium is not yet understood. Epigenetics is thought to play major role in toxicity. DNA hypomethylation and hypermethylation have been observed in Cd exposed animal studies. 1uM Cd exposure to rat liver

cells caused inhibition of DNA methyltransferases activity and thus reduction in DNA methylation (Benbrahim-Tallaa *et al.*, 2009) [6]; Tellez-Plaza *et al.*, 2014 [59].

Different compounds of Nickel are found carcinogenic to human, particularly water-soluble Nickel sulphide (Ni_2S_2) (Govindarajan *et al.*, 2002) [28]. Exposure to Nickel (Ni) result in global change in DNA methylation and histone modification which are thought be involved in Ni-induced toxic effects (Costa *et al.*, 2001) [16]; Costa *et al.*, 2005 [15].

Bisphenol A (BPA)

BPA is a phenyl derivative compound used in manufacturing of polycarbonate plastic and epoxy resin. BPA leach out slowly from BPA containing plastics. Human exposure to BPA occurs through consumption of contaminated food and water. It is known as to cross the placental barrier and affect new born. BPA affects nervous development. Prenatal exposure to BPA results in postnatal changes in DNA methylation status and hence alteration in the expression of genes in offspring (Mileva *et al.*, 2014) [45]. In mice, exposure of Bisphenol-A (BPA) during embryonic stages resulted in abnormal hypothalamic cells due to changes in the gene expression of DNMTs (DNMT1, DNMT3a, and DNMT3b) and MECP2 isoforms. BPA-induced epigenotoxicity in Agouti viable yellow (A^{vy}) mouse caused numerous developmental, metabolic, and behavioural disorders in exposed populations. There is also increased risk of malfunction due to heritable nature of epigenetic changes caused by transgenerational inheritance of phenotypes (Bernal and Jirtle, 2010) [7].

Diethylstilbestrol (DES)

Diethylstilbestrol (DES) is a synthetic compound analogous form of the female hormone estrogen. It has been used by female for the prevention of miscarriage. Later it was found to be an endocrine-disrupting agent and potential chemical to cause cancer, birth defects, and other developmental abnormalities (Palmer *et al.*, 2006). DES exposure to mice developmental stages may cause consistent upregulation of lactoferrin and c-Fos genes (Herbst *et al.*, 1971 [30]; 1972). Studies on animal models found that DES may cause DNA changes (i.e., altered patterns of methylation) in animals which were exposed to DES during early development (Sato *et al.*, 2009) [55]. These changes can be heritable and have the potential to affect subsequent generations (Sato *et al.*, 2009) [55].

2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin (TCDD; Dioxin)

Dioxins are a group of environmental chemicals produced by forest fire, volcanic eruption, pesticide, herbicide and industrial wastes. They persist in environment for longer and accumulate in fats of organisms. Exposure to dioxins occur through diet. Prolonged exposure to dioxin causes cancer, increased risk of heart disease, diabetes and a number of reproductive, developmental and congenital defects (Eskenazi *et al.*, 2000) [21]. International Agency for Research on Cancer (IARC) has classified dioxins as group-I carcinogen. Dioxins stimulated CYP1A1 hypermethylation in human prostate cancer (Okino *et al.*, 2006) [46]. Prenatal exposure to dioxin promotes epigenetic trans-generational inheritance of adult-onset disease (Manikkam *et al.*, 2012) [43].

Radiations

We are routinely exposed to a range of radiations naturally as well as artificially. Radio therapy is used for cancer treatment and causes deregulations in gene expression in treated patients (Das *et al.*, 2015). Exposure of tissues to radiation is associated with fibrogenesis through epigenetic mechanisms (Weigel *et al.*, 2014) [67].

Discussion

Environmental factors interaction with gene is the cause of altered gene expression and development of abnormalities or diseases (Kraft and Hunter, 2005) [37]; Baccarelli and Bollati, 2009 [3]. Stem cells differentiate into functional lineages and self-renew them. Differential lineages of cell populations have same genome but differ in morphogenetic and functional characteristics. The maintenance of these cells from a generation to another follows a defined epigenetic programming. Abnormalities in these processes may play a role in tumour initiation and progression to cancer development (Bloushtain-Qimron *et al.*, 2009) [9]. Sufficient dietary levels of methyl group donor molecules are also needed to be supplemented in order to keep methylation status normal. A deficiency in DNA methyltransferases or SAM may cause abnormalities (Huang, 2002) [31].

Another study showed that methylation level of promoter CpG islands is correlated to corresponding gene expression (Fan and Zhang, 2009) [22]. Differential expression of genes in different tissues is dependent on their function irrespective of change in CpG methylation of their promoters. However, distribution of H3K9me2 and H3K27me3 are correlated with relative to CpG content between the two cell types (Li *et al.*, 2014).

Methylation of DNA is associated with formation of inactive chromatin by repressing transcription. This is brought about by recruitment of proteins such as MECP and MBD to methylation sites and hence preventing transcription machinery from accessing DNA (Lewis and Bird, 1991) [38].

In global genomic DNA hypomethylation studies it has been found that some heavy metals such as Arsenic is known to cause hypomethylation of DNA by reducing the existing methyl donor molecules (i.e. SAM) in cells (Wilson *et al.*, 1984) [69]. Genome-wide distribution of 5-hydroxymethylcytosine (5hmC) in mouse embryonic stem cells showed that 5hmc regions are clustered in actively transcribed genes indicating role of 5hmc in demethylation (Wu *et al.*, 2011).

DNA of eukaryotes is packaged with histone proteins to form nucleosome complex which are, then folded into chromatin structures. Histone proteins are responsible for loose and tight packaging of chromatin forming heterochromatin and euchromatin. Histone proteins undergo post-translational modifications of N-terminal and help in modulating chromatin structure and gene expression. Methylation and acetylation of tail are most common processes for the opening of active genes. Other histone modifications are phosphorylation, ubiquitination, sumoylation and ADP-ribosylation. In yeast (*Saccharomyces cerevisiae*), Rad6 (Ubc2), a ubiquitin-conjugating enzyme helps in methylation of histone H3 at

lysine 4 (Lys 4). According to histone code hypothesis, flexible nature of histone tail modifications is responsible for the dynamic nature of mammalian chromatin (Strahl and Allis, 2000; Turner, 2000) [57, 62].

These modifications are epigenetically regulated and responsible for the cellular response to environmental factors. A defect in normal histone protein disrupted the folding of nucleosomal fibres (Garcia-Ramirez *et al.*, 1995 [27]; Tse *et al.*, 1998) [60] and proved lethal in yeast (Ling *et al.*, 1996) [42]. Even a difference in single lysine residue may lead to changes in gene expression patterns (Dion *et al.*, 2005) [18]. More recently, a third epigenetic regulator, RNA interference (RNAi) is discussed for its role in post-transcriptional gene silencing (PTGS). Successful use of RNA interference has been applied in nematode *Caenorhabditis elegans* to manipulate gene expressions (Fire *et al.*, 1998) [24].

Future Directions

Epigenetic effects of environmental toxicants mostly methylation profiling and histone modification are discussed. A number of diseases including cancer are linked with aberrant changes in methylation pattern. These epigenetic processes are thought to be regulating mechanisms in order to adapt with environmental changes by altering gene expression and physiology. Therefore, these processes are supposed to be potential biomarker in very early stages. Thus, epigenetic understanding would help in the development of applications for finding out finer details and in finding specific effects produced by different environmental factors. Specific epigenetic changes associated with toxicant exposure would be helpful in finding suitable drugs to combat their detrimental effects.

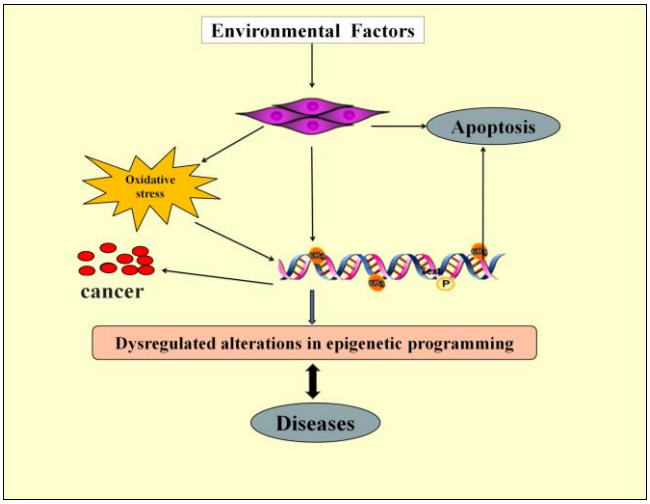

Fig 1: Epigenetic alterations induced by environmental factors and development of diseases

Table 1: Some common environmental factors known to cause epigenetic modification

Environmental factors	Epigenetic Alterations	References
Cadmium	Hypomethylation and hypermethylation	Benbrahim-Tallaa *et al.*, 2007 [5] and Huang *et al.*, 2008 [32]
Arsenic	Genome Hypomethylation, gene promoter hypomethylation and hypermethylation, and histone modification	Chanda *et al.*, 2006 [12]; Zhou *et al.*, 2008 [73]
Mercury	Global hypermethylation	Basu *et al.*, 2014 [4]
Nickle	Hypermethylation	Govindarajan *et al.*, 2002 [28]
Chromium	Hypermethylation	Konda *et al.* 2006
DES	Histone methylation	Doherty *et al.*, 2010 [19]
BPA	changes in DNA methylation pattern	van Esterik *et al.*, 2014 [65]
Radiation	changes in DNA methylation pattern	Lin *et al.*, 2014 [41]; Pernia *et al.*, 2014 [50]

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