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Epigenetics and Environmental Regulations of Genotypes

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Abstract

Genotoxicity is one of the major issues in the present world related to effect of environmental chemicals around us on human health concerning with changes in lifestyle. Irreversible changes in the DNA sequences, including deletions and chromosomal and gene mutations are the part of genetic mechanisms. Epigenetics is an important branch of gene toxicity which covers the study of alterations in gene expression due to variations in DNA methylation and some histone modifications, without altering the original DNA sequence. Environmental factors are responsible for change in epigenetic pattern as well as miRNA expression; this has been established by many in vivo and in vitro studies. Among the related studies a lot of focus is on influence of environment on genetics and its long-lasting effect. Apart from the environmental exposure drug safety evaluation, there is an increasing evidence that drug processing genes (DPGs) and nuclear receptors are regulated by epigenetic mechanisms, namely DNA methylation, histone modifications, and microRNAs. This article will give an overall view on epigenetic and changes observed in genes after exposure against environmental chemicals and pollutants and would provide novel insights towards drug safety evaluation for human consumption with increased drug efficacy.

Keywords: Epigenetics; DNA; Histone; Environmental regulations

Introduction

Epigenetics is related to the study of genetic alterations in gene expression that occur without the changes in genome sequence within the cells. It deviates from the core stream of genetics, which largely focuses on the transfer of genetic information based on differences in DNA sequence [1]. With modern lifestyle changes the extent of exposure to chemical toxicants has increased. The magnitude of pharmaceuticals in our day to day life has also increased with hike in health problems. Addiction habits of tobacco, alcohol, other substance of abuse has also given an exponential increase in toxicants we are surrounded with our day to day activity. Industrial waste products around us pose high risk of exposure to such chemicals around us. These chemicals might end up showing mutagenesis or physical damage to DNA sometimes it may lead to the level of epigenetic changes. Differences in the epigenetic profile of an individual leads to variation in gene expression patterns. The nucleosomes which is present in the nucleus, i.e., covalent modifications of chromatin comes under epigenetic studies. DNA methylation is a process in which DNA goes through direct covalent modification, in which three encoded enzymes that are called as DNA MethylTransferases (DNMTs) catalyzes the addition of a CH3 group to cytosine of pyrimidine ring at the 5-position. At developmental stage epigeneticregulates expression or repression of genes and plays an important role in plants and animals [1,2].

DNA Methylation

The pharmacology of xenobiotics including absorption, metabolism, distribution, and excretion are controlled by enzymes that are encoded by DPGs, namely uptake transporters, phase I and phase II enzymes, and efflux transporters [3].

Changes in chromatin structure and changes in gene expression is catalyzed by the family of enzymes called DNA Methyl-Transferases (i.e., DNMT1, DNMT3A, DNMT3B, and DNMT3L), in the DNA methylation [4] Several studies have established an association between DNA methylation and environmental metals, including nickel, cadmium, lead, and particularly arsenic. Environmental chemicals may modify multiple biological processes that affect epigenetic mechanisms, which includes DNA methylation, histone codes, and miRNA expression. Metalsare observed to increase production of Reactive Oxygen Species (ROS) in a catalytic way. Interaction between methyltransferases and DNA is reduced by Oxidative DNA, thus a generalized altered methylation of cytosine residues at CpG sites is formed [5,8]. In Bangladesh a

global dose-dependent hypermethylation of blood DNA was observed among adults suffering from chronic arsenic exposure [9]. The more is the methylation the greater is the decrease in the gene expression. Among mammalian cells, methylation is the key regulator in inhibition of transcription and formation of heterochromatin [10]. The p16LUC- reporter allele has shown a lower effect of arsenic exposure on the rate of p16INK4a accumulation with aging according to certain studies [11]. This effect might be due to indirect or direct effects on DNA damage repair [12]. Exposure of carcinogens is seen under a new light after specific understanding of DNA adducts. Like, finding acrylamide-globin adducts connected with formation of acrylamide due to cooking of certain food items, and similarly linkage of aflatoxin DNA adducts found in urine with human liver cancer [13]. Cytophosphane, a chemotherapeutic drug which forms DNA adducts as a result of its toxic effect [14].

A study reports DNA hypomethylation due to acute exposure of cadmium for a week on TRL 1215 rat liver cells although longer exposure for 10 week resulted in DNA hypermethylation. These results were confirmed by one more study which reported that a 10-week exposure to cadmium induced malignant transformation associated with DNA hypermethylation at the global level, overexpression of DNMT3b DNA methyltransferase and increased DNMT activity, promoter hypermethylation and reduced expression of the RASSF1A and p16 tumor suppressorgenes [15-17].

In an interesting findings prenatal exposure of PAH Poly-Aromatic Hydrocarbon exposure was observed to be linked with hypomethylation among Umbilical Cord White Blood Cell (UCWBC) DNA. About 0.42 ng/100mg total DNA was decreased among the newborns resulting upon maximum PAH exposure as compared to those exposed to minimum level ($p < 0.01$).of PAH in the group [18].

Histone Modifications

Histone modifications play a central role in epigenetic regulation along with DNA methylation. Loss of function in an active gene or gain of function in a silent gene can be due to the result ofhistone modifications [19]. Around 146 base pairs of DNA are wrapped around a protein core, which consists of two subunits of each of the different histones H2A, H2B, H3, and H4. The N- terminal tails of the core histone proteins go through a variety of different posttranslational modifications viz. methylation, acetylation and phosphorylation [20,21]. While histone acetylation, mainly at multiple residues in the N-terminal tails of histones H3 and H4; is often found in open chromatin conformations (active chromatin, euchromatin), histone methylation - depending on the modified residues is able to confer both a closed chromatin state (inactive chromatin, heterochromatin) and an open configuration [22]. The most investigated histone-modifying enzymes are HISTONE ACETYLTRANSFERASES (HATs), which acetylate histone H3 at the K9 residue as well as other residues and H4 tails at a number of residues, and Histone Deacetylases(HDACs), which deacetylate histone tails [23]. Histone acetylation is believed to be a predominant signal for an active chromatin configuration [24].

Chromium exposure results in forming DNA adducts by inhibiting Cyp1A1 expression. Which indicates it may also be linked to histone modifications and carcinogenic. Chromate exposure is reported to increase protein and mRNA levels of G9a, specifically methylates H3K9 [25,26].

Non-coding RNAs (ncRNAs)

Now a day's researchers are focused on dissecting the regulatory functions of ncRNAs. These are functional molecules that are unable to get translated to final protein products. The widely studied ncRNAs are a distinct group of ncRNAs, the microRNAs (miRNAs), which regulate the protein-coding genes expression. Matured miRNAs contain around 22 nucleotides, and could be base paired with complementary sequences located in the 3′ Untranslated Region (UTR) of the targeted mRNA molecules in a sequnece. The expressions of many genes are regulated by these ncRNAs and could occur in either trans or in cis positions in a subset. Several studies have outlined the involvement and importanfce of miRNAsin cellular memory and epigenetic regulations and could add a new dimension in a drug discovery research [27].

Nanotechnology and Epigenetics

Recent advancement in medical technology has provided a niche to nanotechnologies which can provide us with novel methods of understanding and detecting epigenetic changes. Various studies have been conducted using molecular biology techniques for studying epigenetic reprogramming. Scientists are carrying out a lot of potential work which involves nano-carriers creating a landmark in epigenetics [28]. Conventional techniques used for the studies of epigenetics which sometimes may include conformational modifications observed in chromosomes have itsown limitations which can be overcome by innovative methods which are based on micro- and nanoscale molecules. Studies have explored the use of nanoscale and microscale devices in the study of DNA modifications, chromatin modifications and higher-order chromatin structures which is a better approach for negating the problems faced by researchers in this area. One such study demonstrates the basic building blocks for epigenetic analysis of DNA. There are reported studies where the mapping of methylated regions in DNA with heterogeneous 5-methyl cytosine modification using a specific fluorescent marker has been carried out. The study also shows that an intact histone structure can be stretched similarly like a DNA. Histone tails can be detected using fluorescent antibodies using nano-technologies advancements [29,30]. Althoughnano-technology is mostly used for understanding the phenomena of epigenetics it can also pay a path to curing genetic aberrations encountered in diseases. Nano-medicine can used for target drug deliveries in

cancer patients based on epigenetic biomarkers. The drug interaction at the site with the epigenetic molecules can be studied for the development of effective and rapidtreatment methods [31].

Epigenetics for Drug Safety Evaluation

It has been clearly seen that these epigenetic mechanisms control expression of many genes including drug metabolism in different conditions such as aberrant DNA methylation is a well-studied endpoint/marker of cancer onset [32]. Along with DNA methylation apoptosis is also studied widely to identify cancer markers viz apoptosis induced by Declofenac and Tolbutamide [33,34]. The best studied epigenetic process is the DNA methylation which accounts more than 90% of drug metabolizing genes. We must be entirely cautious when a drug is administered to see its epigenetic effects in terms of drug disposition, safety and metabolism especially when it has been intended for long term usages.

Conclusion

Gene expression is not tenacious only by DNA base sequence; it additionally depends upon epigenetic phenomena, as gene-regulating activities that do not involve an alteration to the base sequence (i.e., base-pairing is not altered) and can persist through generations [35]. Subsequent to epigenetic changes the mutagenicity and/or altered genome stability resulting from expression and movement of transposable elements, in particular, LINEs and SINEs, may occur [36]. Changes due to xenobiotic exposure should be documented for further studies and understanding genome expression [37].

Epigenetic changes can be acquired over a period of time during the life of an individual and then inherited to the offspring. Thus, despite the achievement of principles of Darwinism, epigeneticshas syncs with Lamarckian aspect of biology [38]. The difficulties are just not in characterizing genetic effects of limited amplitude but also limitations in basic research approaches, which by and large still aims almost exclusively at detection of polymorphisms related to diseases, ignoring environmental influences [39]. The development and application of methods for locating sites of altered DNA methylation is the need of the hour for epigenetic regulations in drug metabolism, safety and effectiveness [40].

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