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Environmental Metals as DNA Stressor and Epigenetic Modulator

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Abstract

Exposure to some heavy metals such as cadmium (Cd), mercury (Hg), lead (Pb are known to induce a variety of toxic symptoms. Environmental metals like organic pollutants such as polychlorinated biphynyl (PCB) and other persistent organic pollutants (POPs) bio-accumulate up in the food chain because of their solubility in organic solvent. Metals are, known to trigger the formation of ROS, hence, may affect human health by regulating epigenetics signature (methylation, chromatin modulation and or RNA interference) of the genome. This mini review look at the role of environmental metals as it relate to epigenetic modification. It is known that environment plays a role in methylation, which is one hydrolytic deamination reaction away from a C to T mutation at CpG dinucleotide. Epigenetics are transient factors that play a major role in the transcriptional processes regulating gene expression. DNA methylations; histone modifications and RNA interference (RNAi) form the centerpiece of epigenetic mechanism. The human genome, are shaped by invaders, such as endogenous retroviruses and transposable elements (Alu, Ku, Single Interspersed Natural Element (SINE)), which are actively suppressed by epigenetic mechanisms. Moreover, excess environmental metal exposure do interfere with the Double Strand Break (DSB) processes, a cell repair pathways that are sub-divided into basic groups such as Homologous Recombination (HR) and Single Strand Annealing (SSA). In Nigeria, available evidence suggests women and children are readily exposed to environmental metals this should be of concern to relevant authority bearing, genetic consequences of excess environmental metal exposure are considered irreversible.

Keywords: Epigenetics; Environment; Metals; Methylation; Acetylation; Double strand break

Introduction

Information abounds on the toxic effects of environmental exposure to most metals. For instance, exposure to some heavy metals e.g. cadmium (Cd), mercury (Hg), lead (Pb) etc. are known to induce a variety of toxic symptoms in both the environment [1,2] in experimental animals and exposed human populations [3]. Most of these environmental metals like organic pollutants e.g. polychlorinated biphynyl (PCB) and other persistent organic pollutants (POPs) bio-accumulate up in the food chain, POPs have this property because of their solubility in organic solvent [4-7]. Using food chain exposure to heavy metals, we showed the effects of Cd on exposed rat plasma, and the tissue triglyceride concentration [8].

Global environmental metal levels have increased considerably since the on-set of the industrial age. Metals are now present in various environmental media and food (especially fish) all over the globe at levels that adversely affect humans and wildlife [9]. Anthropogenic sources such as mining operations, industrial processes and combustion of fossil fuels, cement production, and incineration of medical, chemical, and municipal wastes remain one of the ways humans get exposed to environmental metals particularly Hg, Pb, Cd and Cr [3]. Hg from such contributes significantly to levels in the environment, which are currently, between 3 and 6 times higher than levels estimated to have existed before industrialization [3].

According to [5-7], metals e.g, mercury is shown to produce a range of adverse health effects including damages to the central nervous system, thyroid, kidneys, lungs, immune system, eyes, gums and skin and can result in neurological and behavioral disorders. Some of the symptoms associated with environmental metal exposure includes, tumors, insomnia, memory loss, neuromuscular effects, headaches and cognitive and motor dysfunction depending on the quantity and duration of exposure. This mini-review looks at how exposure to environmental metals affect epigenetic signature, with the possible health consequences.

Discussion

Metals as epigenetic modulators

During cell division, homeostasis is required, and for human health, the genome need be copied prudently such

that a copy of each chromosome is passed on to the daughter cells. Compounds that could trigger formation of ROS, such as metals, can affect human health probably by directing epigenetics signatures of the genome, react with physiological gas (H2S) that controls a number of physiological processes at low (submicromolar) concentrations. Importantly, Cd (and possibly other metals) enhances the addition of methyl groups (-CH3) to some nucleotide particularly neighboring guanosines (CpG islands), of the genome [10]. Methylation is amongst the inherent biochemical/epigenetic machinery of cells that connect pathways allowing environmental agents to induce mutations. Facts are epigenetics are such a transient factors that play a major role in the transcriptional processes regulating gene expression [11], for, which DNA methylations, histone modifications and RNA interference (RNAi) form the centerpiece of its mechanism. Environment plays a major role in methylation, which is one hydrolytic deamination reaction away from a C to T mutation. This influences the rate of CpG dinucleotide mutations, which are thought to increase ~12 times when methylated [12,13]. It is probable that metals exert pressure on these epigenes to facilitate genomic instability via gene mutation leading to accumulation of critical mutations that promote malignancies bearing, CpG dinucleotide, are hotspots of mutations when methylated [14].

Genomic integrity is particularly important where germ cells are generated, as they provide the blueprint for the next generation. Evidence shows, when rodents are exposed to environmental toxicants (e.g. metals) inside the womb, it leads to epigenetic changes in the gametes transmitted, which can also induce genetic variability as a consequence [15,16]. Facts are mammalian genomes have been fundamentally shaped by invaders, including endogenous retroviruses and transposable elements (Alu, Ku, Single Interspersed Natural Element (SINE)), which are actively suppressed through epigenetic mechanisms, including DNA methylation [17]. By suppressing or activating these processes (binding elements within promoters), metals could or would destabilize established mechanisms such as modulation of chromatin structure that ensure stability of the genome. This increased genome instability is characterized by increased occurrences of mutations, cells with incorrect chromosome number, loss of heterochromatin and mistakes in transcription.

Current evidence support that metals being stressors exert effects on our epigenomes, which may explain the association between metal exposure early in life and toxic effects later in life, due to metal carcinogenicity [10]. An indication, exposure to environmental metal stressors/or toxicants may contribute to the concept of developmental programming phenomenon, bearing they inherently contribute to genetic modification processes, although further investigations are required proving such concept.

Damage to DNA occurs in a consistent manner by both internal mechanisms, and extracellular insults. Thus, the exposure to environmental heavy metals is one of the external source of DNA damage as it facilitate the induction of ROS, and also introduces cellular changes that influences the competitive balance between different repair mechanisms, leading to alteration in the outcome of the Double Strands Breaks (DSB) repair process. However, mutations caused by heavy metals are likely not just due to direct DNA damage, but might involve an indirect mechanism, such as seen in DNA repair inhibition [18,19]. Cd is thought to inhibit nucleotide excision repair (NER) [18,19], thereby, contributing to the accumulation of mutated DNA and a concomitant increased diseases phenotype, including cancer risk via processes that could involved the deregulation of cell proliferation through inactivation of post translational mechanisms and signaling pathways responsible for cell growth or controls, as found in tumor suppressor genes [20,21].

Several assay methods are being deployed to analyze and understand the consequences of environmental heavy metals exposure on DNA damage and repair pathways including: comet assays, quantization of chromosome aberrations and detection of sister chromatid exchange, and micronucleus tests [18]. These assays/methods provide important information but not much answers on how metals exposures affect the complex multiple actions of different pathways that occur between different repair pathways [18].

Recent experimental data [18] however, clearly indicate that heavy metal exposure significantly influences DSB/DNA repair outcomes, as they inhibit the function of critical repair proteins (e.g proteins with zinc finger motif)with ability to changing the final results of the repaired DNA [22,16].

Cells have multiple DNA repair pathways that repair DSBs. The DSB repair pathways are sub-divided into two i.e. basic groups: this repair pathways uses sequence homology (Homologous Recombination (HR) and Single Strand Annealing (SSA)), whilst the second involves repair with non-homologous end joining (NHEJ). Previous experiment [23,24], used arsenic trioxide (ArO3) to inactivate Rad51 (involved in homologous repair pathways) via the suppression of AKT activity. Further, Cd and nickel (Ni) are suggested to favor resolution of DSB through HR and SSA in addition to increasing Alu-mediated deletions (possibly through SSA). Hence Morales [17]; postulated HR/SSA repair pathways might be favored (by these group of metals) due possibly to interference with Classic-Non Homologous End Joining (C-NHEJ), by blocking binding of the Ku binding element (within the promoter) complex to the exposed DNA ends, preventing removals. Further, their experiment shows that heavy metal exposure increases sequence insertions at DSB repair sites, sign-posting enzymatic interference by metals with the processes of (alternative) alt-NHEJ repair proteins [17,18].

Specific metal compounds are thought to exhibit unique mechanisms including; disruption by trivalent chromium Cr3+), which show direct binding to DNA, and vanadate (Vn) that interacts with the phosphate binding sites of protein phosphatase

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Conclusion

It is apparent, the genetic damage emanating from exposure to metal as discussed is irreversible with deleterious consequences on genome stability. The outcome of these mutagenic events is fundamental to understanding the extent of the toxicants pathogenesis on human health. Bearing also, the subtle interference of the genomic makeup of population that are excessively exposed to environment metals could provide a new angle in understanding the emergence of pathogenesis and its adaptation, the role of adaptation and innovation in colonizing new environments, and the ecological dynamics within microbial communities. All this information may prove critical in the fight against diseases. Toxicants (metals), as discussed has potential to perturb some key signaling pathways via differential gene expression leading to alteration in protein expression, and thus, play an increasing role in the development of disease phenotype.

Environmental metal exposure has deleterious consequences hence it is worrisome as some recent field evidence gathered in Nigeria suggested women and children leaving in nearby communities where Artisanal small scale gold mining (ASGM), is practiced, are more prone to environmental metal exposure. This is further compounded as sociocultural inequalities and religious believes (especially up north of Nigeria), particularly hinder access to information for women, leaving them unaware of the risks they and their children are faced with for instance repeated Hg, Pb exposure. Bearing the effect of environmental exposure as discussed, it is important concerted efforts are put in place to mitigate unwarranted exposure, moving forward.

Conflicts of Interest

I declare that there are no conflicts of interests.

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