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Review

Rising environmental cadmium levels in developing countries: Threat to genome stability and health

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This paper is the full presentation of an invited plenary at the 34th Annual Meeting of the Environmental Mutagen Society of India (EMSI), and international symposium on 'Genomics and Molecular Basis of Human Diseases', 17-19th March, 2009 held at the Magadh University, Bodhgaya, India

Summary: Cadmium (Cd) is a ubiquitous environmental pollutant of increasing worldwide concern. It is thought to be of greater concern to rapidly industrializing developing countries because of the increasing pace of industrial activities in these countries with increasing consumption and release into the environment. Traditionally, health concerns in exposed human populations have revolved around the association of Cd with bone disease, emphysema and possibly hypertension. Accumulating evidence suggest that Cd is involved in the disruption of many genomic processes, the mechanisms of which are being gradually understood. Changes in DNA Methylation may be induced by cadmium leading to epigenetic alterations. Additionally, though Cd is not thought to induce reactive oxygen species (ROS) directly because it is not capable of accepting or donating electrons under physiological conditions, 8-hydroxy deoxyguanosine (8-OHdG) (a marker of oxidative stress to DNA and a risk factor for cancer among others) has been shown to be elevated in the DNA of testes from rats treated with cadmium chloride, at least in part because Cd inhibits DNA repair mechanisms. Cadmium is also a metabolic antagonist to Zinc (Zn), an important micronutrient involved in numerous molecular activities. This antagonism alters the physiological stoichiometric relationship between Cd and Zn leading to high Cd/Zn ratio, one consequence of which is high error rate and lack of efficient DNA repair systems leading to high mutation and genome instability culminating in many carcinogenic states, particularly prostate carcinogenesis. Cadmium has also been shown to replace Zn in the tumor suppressor protein, p53 thereby impairing p53's DNA binding activity and associated repair processes. The expression of the p53 protein is significantly depressed by cadmium. Although the rising level of Cd in the environment is widely acknowledged, the occult threat it poses to genome stability largely through inhibition of normal DNA damage repair, oxidative stress and apoptosis and health is poorly recognized. This paper examines the involvement of Cd in the molecular pathways of human disease, providing insight for the prevention of genome instability and associated disease susceptibility particularly cancer across populations through micronutrient intervention, aiding upregulation of the antioxidant defense and DNA repair systems.

Keywords*:* Cadmium, DNA repair inhibition, Environmental pollutants, Genome instability, Micronutrient intervention, Industrial activities, Oxidative stress

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INTRODUCTION

Cadmium (Cd) is a non essential heavy metal belonging to group IIB of the periodic table of elements (IARC, 1993) which is a wide spread environmental pollutant that has recently gained greater public prominence due to its increased use in industrial processes particularly due to world-wide increase in discard of electronic –waste such as cell phones and computers containing this toxic metal (Rydh and Svärd;2003; Järup, 2003; Wong et al., 2007). Unlike essential trace elements such as copper, iron, selenium, zinc and others, Cd largely has no known biological function.

Previously human exposure mainly occurred through ingestion of contaminated food or water or smoking. The increasing presence of cadmium from increasing industrial activities may now make these secondary and accentuate them and increase the potential for cadmium to be present in biological systems. The potential for cadmium to cause toxicity has been demonstrated by the results of numerous experimental and epidemiological studies. The persistent nature of Cd in the environment and in biological tissues has great potential health effects, especially, with respect to the role of cadmium as a human carcinogen (IARC, 1993; Joseph, 2009).

A toxic peculiarity of cadmium is that exposure of cells to low, micromolar concentrations of Cd results in significant toxicity (Othumpangat etal., 2005; Badisa et al.,2008). Cadmium exposure produces a variety of adverse effects in humans and animals. Normally the concentration of Cd is relatively low in the natural environment, but its wide distribution and long half life makes it cumulative in living cultures (Tsurgita and Tsuchiya, 1995). Chronic inhalation of Cd from a contaminated environment leads to various pathological manifestations, such as inflammation and fibrosis and eventually causes organ dysfunction and injury. Furthermore, Cd is considered a carcinogen and exposure to it has already been linked to cancer of the prostate, liver and lung. The outbreak of Itai-Itai (Ouch-Ouch) disease in the Fuchu- Toyama prefecture in Japan first brought public awareness to the health risk of exposure to Cd with reports of women residing in a cadmium polluted region suffering from advanced renal disease and bone disease (Tsuchiya, 1978). There is also growing evidence that diseases that have genome instability as their precursors (cancer, developmental disorders etc) are on the increase (Tomatis and Huff, 2001). There appear to be an unrecognized association between the prevalence of these diseases and the rising level of cadmium in the environment. Recent data (Jarup, 2003;Joseph, 2009) indicate that adverse health effects of cadmium exposure may occur at lower exposure levels than previously anticipated. Additionally, several recent studies have revealed the mechanisms, by which cadmium may be involved in perturbation of genome stability (Waalkes, 2000). Bertin and Averbeck (2006) have shown that cadmium has a number of cellular effects; modification of biomolecules, modulation of DNA repair and genotoxic consequences. Specifically Cd is known to impair DNA repair mechanisms and apoptosis. Cadmium is also a metabolic antagonist of zinc well recognized for its role in DNA repair mechanisms (Joseph, 2009; Nordberg, 2009) This heavy metal has also been implicated in oxidative stress, a phenomenon widely recognized for its role in DNA damage (Joseph, 2009). Cadmium has also been reported to impair the protein p53, a protein involved in tumour suppression through a number of mechanisms including apoptosis (Ho, 2004). Very recently cadmium has been incriminated in alteration in the emerging science of epigenetics (Takiguchi, 1997). This is a recently recognized mechanism of gene expression that does not involve DNA sequence alteration. The involvement of Cd in these fundamental molecular processes and its implication for genome stability and health and approaches to counter or ameliorate the phenomenon has received very little attention. This contribution attempts to draw attention to this occult but real event and suggests ways to avert or at least ameliorate it by the use genome protective micronutrients.

Industrial Uses of Cadmium and Risk of Genome Instability

Cadmium is utilized in many industrial processes (table 1).

Table 1: Industrial uses of cadmium

Electroplating and galvanizing
Mining and processing of many metals
Pigment in many paints and plastics
Component of batteries
Component in electronic circuitry in computers and cell phones.
Welding and Ni-Cd batteries
Printer's ink

Cabrera et al (1998) have observed that this largely contributes to the contamination of vegetable crops, farmlands and irrigation water. As some of these countries export crops and vegetables grown on contaminated farmlands it means that a much larger population will be affected globally. Cadmium is selectively taken up by certain edible food items, thus food is often reported as a source of human exposure to cadmium. Even in unexposed areas of industrializing countries Cd is now known to be an insidious component of the food chain (WHO, 1992). It is also known that workers in the occupations indicated in table 1 above are exposed to cadmium at significantly higher levels than the general public. Thus the risk of associated genome instability may be higher in these workers. Similarly, residents of areas contaminated with cadmium are exposed to higher quantities of Cd.

Cadmium in Ores and Non-recognition of Genome Instability

Cadmium is a by-product of zinc (Zn) production and commonly occurs with zinc ores (WHO, 1992). In the past cadmium pollution arose principally from mining pollution, use of non-ferrous metals and disposal of material containing or contaminated with Cd. The worldwide production of Cd in 2005 was

estimated to be 20,000 metric tons (Joseph, 2009). This is in addition to cadmium generated from wastes including e-wastes. Though the scientific community had been concerned about the toxic effects of cadmium for decades its possible effects on the genome have not been explored. Cadmium is classified as a category 1 carcinogen, but is not directly genotoxic or mutagenic in bacteria. It is known to affect genome stability via inhibition of DNA repair and generation of free radical-induced damage. At the cellular level, cadmium induces oxidative stress by depletion of endogenous antioxidants such as glutathione (GSH) and is associated with mitochondrial damage, induction of apoptosis and disruption of intracellular calcium signaling.

Cadmium in the environment of Fast Developing Countries

Progressive industrialization in the developing countries is currently evident and desirable to improve standard of live and income in these countries. This has culminated in the greater use of chemicals and other materials estimated to be over eighty thousand (80,000) chemicals currently in use (Pimental et al., 1995). Nriagu (1996) has pointed out the increasing global metal pollution and increasing production and consumption of heavy metals including, Cd since the industrial revolution. This is probably more true of the fast developing countries currently. Human exposure to Cd is currently a serious concern in the fast developing countries, particularly China and India (Sun et al., 2006; Govil et al., 2007; Yan et al., 2007). This also applies to other developing countries that consume these products. Satarug et al. (2003) had indeed predicted that given the current rate of release of cadmium in to the environment, Cd content in the human body is likely to increase in the future. This is consonant with the prediction of Carson (2002) many decades earlier about chemicals generally which has been confirmed by many subsequent investigators. The stability of the genome appears to be an ignored target of this increasing chemical burden. It is a threat to be viewed seriously and efforts at mitigating it considered a priority.

Itai –Itai Disease: A Disease of Industrialization

In the first half of the 20th century an endemic disease was observed in a certain population in the Fuchu-Toyama prefecture of Japan; Itai- Itai (Ouch-Ouch) disease that its pathogenesis involved disordered bone metabolism and kidney impairment [9]. This disease was first observed after World War II. In this disease, elevated levels of Cd in urine were found (Ishizak, 1969). In 1968 the disease was declared by the Japanese government to be a disease related to environmental pollution. Cadmium released from a mine in the mountains was carried by the Jinzu River into the plain where the contaminated water was used to irrigate rice fields (primitive industrialization at the time). The rice plants took up Cd from the soil and consumption of contaminated rice was the main pathway of exposure of the general population. This contamination is thus originating from industrial activities which have been heightened in the rapidly industrializing developing countries currently.Itai itai disease can therefore be plausibly regarded as a disease of industrialization.

Cadmium and the Human Genome

Environmental exposures to toxic chemicals modify the genome leading to diseases including cancer. This is why cadmium is very important among others. Cadmium has thus been aptly described as a genotoxic prime environmental pollutant of great public health significance (Bertin and Averbeck). Cadmium consequently leads to higher incidence of a number of diseases. Genotoxicity is occult, of long latency but more deleterious on the long run. This is why it is considered a great omission or under estimation of the potential threat Cd poses to the human genome thus public health regionally and globally. Several years ago The Pacific Basin Consortium (a regional assembly of rapidly industrializing and industrialized countries), ostensibly a response to the expanding industrial activities in the Pacific Basin Rim and the associated threat to human health, oblivious of genome impact had a conference. This consortium is home to a third of the world's population including the wealthiest and the poorest countries. In this large sub- global gathering not enough prominence was given to Cd in its 2005 11th scientific conference inspite of emerging evidence implicating it in genome instability (Achanzar et al., 2002; Arnold et al., 2005).

Cadmium is absorbed from both the gut and respiratory tract (lungs) but poorly excreted. Even though absorption takes place in the gastrointestinal tract (GIT) that through the respiratory tract is of greater magnitude (10% versus 50%) (NTP, 2004). A near peculiarity of cadmium is that it is a cumulative toxicant. Once absorbed it is principally deposited in the liver and kidney both accounting for over 50% of the total body burden (WHO, 2004). Though accumulated body burden may damage the kidney, hitherto considered critical target of cadmium toxicity, emerging evidence now suggest that this may be overtaken by genotoxicity (Bertin and Averbeck, 2006; Joseph, 2009). This development though considered occult is real.

This is probably why Cd is now considered a human carcinogen and has been implicated in many types of cancer, prostate, lung and kidney (IARC, 1993; Joseph, 2009; Nordberg, 2009).

Cadmium: A Human Carcinogen

Strong evidence, based on experimental studies, exists to support the carcinogenic potential of Cd. Cell transformation, a procedure routinely employed diagnostic in vitro test for the carcinogenic potential of chemicals, has been utilized in a number of studies to demonstrate the carcinogenic potential of cadmium and gain insight regarding the potential mechanisms underlying cadmium carcinogenesis (Abshire et al., 1996; Achanzar et al., 2001; Joseph et al., 2004a; Joseph et al., 2002b; Joseph et al., 2004c). The major mechanisms attributed to Cd carcinogenesis may broadly be classified into four major categories as follows:

- Aberrant gene expression
- Inhibition of DNA damage repair
- Inhibition of apoptosis
- Induction of oxidative stress

These have significant overlap among themselves. Additionally, the ability of cadmium to cause aberrant DNA Methylation cannot be ignored (Huang et al., 2006; Benbrahim- Tallaa et al. 2007a) though of minor significance compared to the above mechanisms. Other mechanisms of relative minor importance with regard to the carcinogenic potential of Cd are endocrine disruption (Benbrahim et al., 2007b) and cell proliferation (Benbrahim- Tallaa et al., 2007a).

DNA damage induced in human peripheral blood lymphocytes by industrial solid waste and municipal sludge leachates have been reported in some developing countries and it is interesting that cadmium was reported to be a major constituent in this (Bakare et al., 2007). This may be considered evidence in support of threat to the genome of the populations in these countries. A further insult to that already is existing from micronutrient deficiency disorders. The micronutrients particularly zinc plays vital roles in genome integrity (Ho et al., 2009).

Cadmium in the Inhibition of DNA Repair

Maintenance of genome stability of genome stability is crucial for avoiding carcinogenesis. Many human cancers display an array of chromosomal aberrations, a characteristic referred to as genome instability. The relationship between cancer and genome instability is well recognized, nevertheless the cause of genome instability in the development of cancer, particularly the possible contribution of Cd is poorly understood. The DNA damage response element safeguards the integrity of the genome by uncovering abnormalities (alterations), halting cell cycle progression, and repairing DNA damage. Cadmium interferes with a number of these processes (Potts et al., 2001). Cells with defective DNA damage responses are characterized by genomic instability.

Cadmium's ability to inhibit DNA repair has been demonstrated repeatedly (Potts et al., 2001; Giaginis et al., 2006). Cadmium like most chemicals in general, induces cancer by genotoxic or non-genotoxic mechanisms. Exposure to cadmium results in chromosomal aberrations, sister chromatid exchange, DNA strand breaks, and DNA-protein crosslinks in a variety of cell lines (Ohchi and Ohsawa, 1985; Misra et al., 1998; Fatur et al., 2002). DNA-strand breaks are among the most lethal forms of DNA damage; incorrectly repaired breaks can lead to gross chromosomal rearrangements, aneuploidy and ultimately carcinogenesis. DNA repair plays a very important part in maintaining genomic integrity and deficiencies in repair enzyme systems are known to promote cancer development. The potential for cadmium to cause mutation in CD59 locus, a human-hamster hybrid (AL) cell model, that is known to be highly efficient in detecting mutations involving large deletions, has been reported (Filipic and Hei, 2004). Palus et al. (2003) have established a good correlation between Cd level and genotoxicity in peripheral blood mononuclear cells obtained subjects occupationally exposed to Cd. Despite these reports, it should however be noted that Cd has not been found to exert genotoxic effect in the traditionally used bacterial test systems (Ames test) instead only weak mutagenic effect was demonstrable in mammalian cell systems (Rossman and Roy, 1992). Other studies reported that very high concentrations of cadmium, about the concentration of 1 mM were required to elicit the genotoxicity of Cd in some cases. Consequently, the general consensus that cadmium is at best a weak genotoxic agent, may not apply in the developing countries where protective micronutrients involved in repair processes are inadequate (Underwood and Smitasiri, 1999). This implies that at such concentration Cd may still pose a significant threat in these countries.

A number of reports provide evidence that the genotoxicity of induced by cadmium is not a direct effect of the genotoxicant, but arising largely from the generation of reactive oxygen species and the attendant oxidative stress. Single strand break induced by cadmium in cultured V-79 cell was demonstrated only under aerobic conditions (Ochi and Ohsawa, 1985; Filipic and Hei, 2004). Studies indicate that exposure of cells to Cd resulted in the generation of 8-OHdG; a well known and reliable index of oxidative DNA damage (Mikhailova et al., 1997; Filipic and Hei, 2004). Pre-treatment with human-hamster hybrid AL cells with buthionine sulfoxime (BOS) resulted in the depletion of cellular glutathione (GSH) and a concomitant accentuation of the genotoxicity of Cd (Filipic and Hei,2004) corroborating a role for ROS in cadmium-induced genotoxicity.

As earlier indicated, despite Cd being a weak genotoxic chemical, it exhibits remarkable potential to inhibit DNA damage repair, and this has been identified as a major mechanism underlying the carcinogenic potential of cadmium (Waalkes, 2000; Waalkes, 2003 Giaginis et al., 2006). Again this may be of greater significance in the rapidly industrializing developing countries that are resource poor and suffer from malnutrition Nweke and Sanders, 2009).

Endogenous and exogenous factors contribute to DNA damage in cells which if not properly and timely repaired may result in genotoxic and ultimately carcinogenic consequences. The potential for cadmium to inhibit DNA damage repair has been demonstrated consistently by several investigators (Williams et al., 2000; Joseph et al., 2004a; Joseph et al., 2004c). Exposure to alveolar epithelial cells to Cd significantly reduced the activity of formamidopyrimidine DNA glycosylase, an enzyme involved in the recognition and removal of oxidative DNA damage such as 8-hyroxylguanine and 8-hydrohyadenine (Potts et al., 2001). Alveolar epithelial cells adaptation to Cd has been observed to be associated with a significant loss in the ability to repair oxidative DNA damage (Potts et al.2001). Lewinska et al. (2007) have reported that the repair of 8-oxoG in lymphocytes of cadmium exposed workers was inversely correlated with the dose and level of DNA strand breaks. Cellular GSH content has been demonstrated to be a determining factor influencing the effect of cadmium on the DNA damage repair process. Depletion of glutathione induced by cadmium in rat testes was associated with increased 8-oxoG formation as well as decreased rates 8-oxoG repair suggesting that in the absence of efficient detoxification process ROS accumulate in the cells resulting in the inhibition of DNA repair (Hirano et al., 1997).

Inability to repair DNA damage can result in the accumulation of damaged DNA which contributes to mutation and carcinogenesis. Inhibition of DNA damage repair by cadmium is also significant as regards the incidences of spontaneous cancers and those induced by other genotoxic chemicals. This is of particular import for developing countries where the Cd levels are rising and indeed may be linked with the rising incidence of cancers particularly occupational cancers in these countries (Tomatis and Huff, 2001) . In situations of Cd-induced inhibition of DNA repair, spontaneously appearing DNA damage in cells may remain unrepaired leading to genome instability and may result ultimately in mutations and spontaneous cancers.

The role of cadmium has been investigated in part as an inhibitor of DNA damage repair in smokers who have a greater risk of developing cancer particularly prostate cancer (Schrauzer, 1987; Drasch et al., 2005; Anetor et al., 2008a). This is because cigarette smoke contains a significant amount of cadmium and a large number of potentially genotoxic chemicals. Evidence exist that that Cd-induced inhibition of DNA damage repair in experimental models that are exposed to cigarette smoke may facilitate the accumulation of DNA damage brought about or caused by genotoxic chemicals present in cigarette smoke, culminating in mutations that may ultimately lead to cancer. By extension, Cd co-exposure may enhance the carcinogenic potential of other genotoxic chemicals commonly found in the environment and occupational locations, or yet enable the genotoxic chemicals to cause cancer at concentrations less than those required to induce cancer following their individual exposure (potentiation).

Cadmium is a metabolic antagonist of zinc, a very important micronutrient involved in DNA repair and genome stability, but unfortunately commonly deficient in populations in developing countries (WHO, 2002; Anetor et al., 2008b). Cadmium-induced inhibition of DNA repair is believed to be due to its effects on the enzymes which play key roles in the repair process. A number of these enzymes are Zn-dependent (members of the zinc finger family of proteins). Cadmium, because of this well known metabolic antagonism can substitute for zinc in these enzymes and proteins with substituted Cd do not perform their functions as efficiently as DNA damage repair enzymes (O'Connor et al, 1993; Ho et al., 2003).

Cadmium and Zinc Antagonism

In addition to the observations above on inhibition of DNA inhibition by cadmium, zinc is a cofactor in proteins involved in oxidant defenses, DNA repair and p53 protein expression. Ho et al [39] have examined the effect of Zn deficiency on oxidative stress, DNA damage and DNA repair in primary human lung fibroblast. Zinc deficiency did not only cause oxidative stress and DNA damage, but also compromised repair of the damage. Toxicity of Cd has been so dependent on disturbances of Zn metabolism that Cd has been described as an antimetabolite of Zn (Vigliani, 1969). Anetor et al. (2008a) in their study of cigarette smoking and the greater risk to cancer of the prostate in these subjects reported high Cd/Zn ratio which leads to high error rates and lack of efficient DNA repair system leading to high mutation rates in prostate cancer.

Cadmium, p53 Protein and Apoptosis

The p53, tumor suppressor protein is a critical mediator of cell cycle arrest and apoptosis in response to genotoxic stress. Abrogation of p53's function is a key factor in tumor development and may result in altered DNA damage response.

Cadmium replaces Zn in p53 and by impairing the binding of p53 to DNA causing genome instability. This impairment decreases the ability of cells to respond to DNA damage (Meplan et al., 1999).

Apoptosis is a genetically highly regulated and conserved form of cell death which plays a key role in the development and maintenance of tissue homeostasis in multicellular organisms. Apoptosis plays an essential role in the elimination of mutated or transformed cells from the host. Consequently, for survival, cancer cells and their precursors must develop highly efficient mechanisms to avoid apoptosis. Indeed the avoidance of apoptosis is considered a hallmark of cancer cells. This may inadvertently be promoted in developing countries as a result of the rising cadmium levels given the negative effect of Cd on this fundamental molecular process.

Cadmium and Selenium

Selenium (Se) like Zn is a micronutrient modulating a variety of cellular function (Arthur et al., 1993). Selenium compounds are effective antioxidants and inhibitors of tumorigenesis. Elemental and organoselenium compounds at comparatively low concentrations inhibit mutagenesis, chromosome break and cell proliferation from chemical carcinogens. Rodent studies indicate a protective effect of selenium on viral or chemical –induced mammary carcinomas (Mo, 1987).Uptake, transport, metabolism and physiological activity of selenium is influenced by interaction with Cd and other heavy metals. Selenium deficiency like that of Zn will be permissive of genomic instability and associated disorders. A physiological role of selenium in genome stability maintenance has been suggested (Cheng, 2009). Cadmium is one of the elements exhibiting high affinity for Se and exerts significant interaction at levels close to no-effect threshold levels (Schrauzer, 1987). Schrauzer (1987) has observed that exposure to low levels of Se antagonists like cadmium leads to genome instability, abolishing the cancer protecting effects of selenium. Drasch et al. (2005) have demonstrated that high Cd /Se ratio in human prostate is indicative of risk of prostate cancer and that the risk is greater in smokers than in non-smokers. They also observed that the aggressiveness and lethality of the disease is greater in smokers than in non smokers. This is not surprising in that the substantially raised Cd burden will upturn the DNA repair capability as well as inhibit or overwhelm the antioxidant capacity of selenium. Additionally, the inhibitory effect of Cd on apoptosis may also come to play. Cadmium also alters fidelity of DNA replication (Williams et al., 2000).

The rising Cd level in the emerging economies or rapidly industrializing developing countries may be an indication to increase micronutrient levels or a different RDA for Se and other genome protective micronutrients in the populations in these countries.

Cadmium, Cobalt and the Genome

Understanding of the mechanisms of toxicity of cadmium remains incomplete and appears to embrace a whole spectrum biochemical, cellular and molecular events. All mechanisms are however interrelated and advances in the study of this pervasive toxicant keep revealing more mechanisms. Cadmium has the capacity to replace cobalt, a micronutrient with close affinity to iron absorption mechanism (Hamilton and Valberg, 1974; Flanagan, 1993). This may not be surprising owing to the well known inverse relationship between iron and cadmium toxicity (Flanagan, 1993). The replacement of cobalt by cadmium however has a number of biochemical and molecular importance and on genome stability. Cobalt is an important component of Cyanocobalamin, vitamin B_{12}, which plays a vital role in purine metabolism and genome stability (Fenech, 2002). Thus, the replacement of Co by Cd is another potential mechanism of the disturbance of genome stability by cadmium exposure.

Cadmium, Epigenetics and Disease

In addition to genetic factors, the rising number of epidemiological and experimental studies provides evidence for a role for environmental toxicants in human cancer development. To understand the mechanistic basis for environment associated cancers, it is crucial to understand how environmental factors interact with genes that are involved in human malignancies. Recent reports strongly suggest that epigenetic changes of DNA methylation and histone modifications (methylation and acetylation) play crucial role in the development of human cancers.

Epigenetics encompasses heritable alteration in gene expression and chromatin without accompanying changes in DNA sequence (independent of DNA sequence changes). Epigenetic changes arise from interplay of DNA Methylation, post-translational histone protein modification, RNA mediated gene silencing and other currently unknown mechanisms. Epigenetics is essential for normal development and differentiation.

Deregulation of epigenetic information has been associated with a variety of human diseases, notably cancer. The recent revelation (Feinberg and Tycko, 2004) that environmental factors can deregulate epigenetic information and alter gene expression pattern in a heritable manner leading to malignant transformation is instructive. Cadmium not surprisingly has been linked with this epigenetic perturbation (Takiguchi et al., 2003). Waalkes et al. (2000) have reported that exposure to cadmium is linked with several tumor types including cancer of the lungs, liver, prostate, kidney and stomach.

Accumulating evidence indicates that aberrant DNA methylation and histone modification patterns may be induced by excessive exposure to cadmium in the environment. Cadmium is an enzyme inhibitor showed to efficiently inhibit DNA methtyltransferase; leading to hypomethylation (Takiguchi et al., 2003). Prolonged exposure to Cd can also lead to hypermethylation, suggesting, that Cd may have triggered global hypomethylation and promoter specific hypermethylation both of which are implicated in carcinogenesis. Available current evidence suggests that there is currently excessive exposure to Cd in the environment (Bakshi et al., 2008; Joseph, 2009). Cadmium is currently accepted as an unequivocal carcinogen (IARC, 1993, Joseph, 2009). It is also in light of emerging evidence considered an epimutagen that can deregulate epigenetic information, alter gene expression patterns in a heritable manner leading to malignant transformation which is always preceded by genome instability (Feinberg and Tycko, 2004). Thus from both the genetic and epigenetic perspectives Cd leads to genome instability that is a factor in carcinogenesis.

Cadmium and Prostate Carcinogenesis: A Probable Clinical Evidence of Genome Instability

Genome stability is essential for normal tissue replication and health of many organs including the prostate. Genome instability is one of the defining features of cancer cells, and is associated with both tumorigenesis and tumor progression. The prostate is one organ that accumulates Cd and it is probable that this may be associated with genome instability a precursor of tumorigenesis.

Prostate cancer is currently considered the most common cancer in men accounting for 29% of fresh cases of cancer (Jemal et al., 2007). The environmental contribution from the rising level of Cd is poorly recognized. Cursory appraisals suggest possible positive correlation. Experimental and epidemiological evidence exist for a potential association between Cd exposure and the prostate in humans and rodents (Waalkes et al., 1989; Goyer et al., 2004; Vinceti et al., 2007). Cadmium accumulates in men as they age owing to slow excretion rate (Baecklund et al., 1999; Satarug et al, 2004). The prostate is considered one of the organs of the body with high bioaccumulation of cadmium (Linegaard et al., 1990; Achanzar et al., 2001). Patients with prostate cancer appear to have higher circulating and organ level of Cd probably by displacing Zn (Brys et al., 1997; Anetor et al., 2008a).

Cadmium and Prostate Epithelial Cells Transformation

Cadmium exposure has been reported to cause neoplastic transformation of human epithelial cells dose dependently (Achanzar et al., 2001; Nakamura et al., 2002). The potential involvement of apoptosis as mechanism for cadmium carcinogenesis has been demonstrated by a series of studies conducted by Waalkes group (Achanzar et al., 2000; Yuan, 2000; Achanzar et al., 2002). These investigators exposed normal human prostate epithelial cells to 10 µM $CdCl_2$ resulted in their malignant transformation (Achanzar, 2001).These Cd- transformed cells exhibited loss of contact inhibition and changed into highly invasive and occasionally malignant adenocarcinomas when injected subcutaneously in immune compromised mice. In a second study by the same investigators it was observed that exposure of RWPE-1 cells to $CdCl_2$ resulted in activation of genes, such as c-jun and c-myc, genes that are involved in cell proliferation (Achanzar et al., 2000). In this study the expression of p53 tumor suppressor gene was significantly reduced in the Cd-treated cells compared to the control at intervals beyond 48-hour post exposure to cadmium chloride. A disproportionate number (>65%) of the Cd exposed cells died following exposure to cadmium and this was attributed to induction of apoptosis. About 35% of the experimental cells survived and these were found to be normal and resistant to Cd-induced apoptosis. Additionally, the Cd-resistant population of cells demonstrated 2.5-fold more metallothionein content compared to normal, untreated RWPE-1 cells. Thus it appears that its ability to induce apoptosis and cell death notwithstanding, Cd may enhance the selective enrichment of genetically damaged and apotosis resistant cells with enhanced proliferative capacity culminating in malignant transformation.

Goyer et al (2004) have also reported that longer exposure to the same dose of cadmium caused emergence of malignant phenotype resistant to apoptosis, increasing cell proliferation rate, disruption in DNA repair mechanisms, broad based changes in gene expression and epigenetic expression patterns. Cadmium exposure has also been observed to accelerate transit through the cell cycle of prostate epithelial cells, aborting sub-G1 peak and inhibition of apoptosis (Bakshi et al., 2008). Taken together, these data suggest major changes in transcriptome expression and probably partly the molecular mechanism of Cd-induced neoplastic transformation of prostate epithelial cells. This appears to highlight genomic alterations associated with Cd exposure that may become more prominent and prevalent with the rising environmental Cd levels.

Cadmium and Mammary Carcinogenesis

Breast cancer in females like prostate cancer in males may also be another consequence of increasing levels of Cd in the environment. In females mammary carcinogenesis has been linked with increased

exposure to Cd (Schrauzer et al., 2008). Interactive effects of selenium and Cd on mammary tumor development and growth in MMTV-infected models has been reported. Mammary gland and the prostate are known to share some tissue ancestry. Thus both breast and prostate cancers may be diseases to watch with the rising environmental cadmium levels.

Cadmium and Transgenerational Events

An unsettling aspect of the rising cadmium levels in the environment is the possible transgenerational effects (Nomura, 2008). Genetic stability and integrity are important in maintaining accurate DNA replication. DNA disruption leads to gene rearrangements, translocations, amplifications and deletions which can contribute to cancer development preceded by genome instability. Transgenerational occurrences are not unlikely given the molecular and biochemical mechanisms of Cd toxicity (Anderson and Brinkworth, 2007; Nomura, 2008).

Cadmium and background Cancer

Exposure to Cd is on the increase and given its involvement in genomic aberrations, raises the probability for cancer manifestation now and in the future. It is most probable that offspring of exposed parents may become of cancer prone age soon and this may be erroneously interpreted as genetic in nature. Follow up studies of workers and populations in polluted areas will be important. For the fast developing industrializing countries combination of increased Cd exposure and co-existent nutritional deficiencies which are also prevalent in these countries may increase the incidence of genome instability and attendant carcinogenesis. Studies have demonstrated that cadmium is a complex carcinogen and that the mechanisms involved in cadmium carcinogenesis are multifactorial. The rising and persistent nature of cadmium in the environment and consequently in biological tissues may have serious consequences for the genome and thus for carcinogenic potential. The increasing persistence of high levels of Cd in the environment has considerable health implications. This implies that populations in the fast developing countries are at great risk of the toxic potentials of Cd, particularly genome instability which had not been hitherto given sufficient attention. As previously indicated, Cd exposure can result in the inhibition of normal DNA damage repair through the mechanisms outlined in cells. Experimental evidence also exists that indicate that Cd inhibits apoptosis and may contribute to the development of a population of apoptosis-resistant cells. These attributes of Cd i.e. persistence in the biological tissues secondary to its persistence in the environment, inhibition of DNA damage repair processes and apoptosis at least put the genome of the populations in fast industrializing countries at great risk. Synergistic interaction between Cd and other toxicants in the environment may further accentuate the potential of genome instability in populations in these countries. The high burden of cadmium content in the cells may prevent the repair of DNA damage secondary to other genotoxic chemicals to which such populations are also simultaneously exposed. In the same vein, Cd-induced inhibition of apoptosis may block the elimination of genetically damaged cells resulting in accumulation in the body and leading to attendant altered genome integrity. As previously seen, Cd may stimulate the proliferation of such genetically injured and apoptosis-resistant cells in those individuals. Thus through these processes Cd may potentiate other carcinogenic substances to contribute to genome instability (multiplier effect) and ultimately lead to the carcinogenic process at no effect level concentrations of those substances.

Further research appears desirable to explore the potential of Cd's contribution to genome inability in countries experiencing greater utilization of cadmium in manufacturing processes and end consumers who contribute to environmental Cd level through inappropriate disposal. Maintenance of genome stability is of fundamental importance for counteracting carcinogenesis. Many human genome instability syndromes exhibit predisposition to cancer. Both nutritional deficiency and toxicity can compromise the integrity of the genome; ineffective DNA damage responses and repair. These observations may be consistent with the report of Huff et al., 2007).

Cadmium Exposure and Chemoprevention

The removal of cadmium from the environment is not pragmatic. Agreeably, its level can be mitigated. A more acceptable approach to protect the population against occult genome instability may be chemoprevention. The potential effect of inorganic micronutrients on alleviating genome instability syndromes warrants all the attention. It is intuitive to explore the possibility that micronutrients may be promising agents for treating genomic instability syndromes through modulation of redox status and genomic stability (Surh, 2003; Yu et al, 2008). This may be a practical approach of preventing cancer, preferably at the preneoplastic stage, using relatively non-toxic dietary chemical entities to halt, reverse or delay the carcinogenic process. A key mechanism of action of chemopreventive agents being restoring genome stability by counteracting oxidative stress and promoting the apoptotic pathway makes them possible antidotes to the rising threat of Cd in the environment. Chemoprevention has been described as a pragmatic approach to contain the consequences of rising environmental Cd levels and concomitant genomic instability which accelerates malignant transformation (Anetor et al., 2008b; Kundu and

Surh, 2008; Cohen and Arnold, 2011).This appears a high priority area for the fast industrializing countries. Bull and Fenech (2008) in agreement with this view have observed that it is becoming increasingly evident that the risk for developmental and degenerative disease increases with more DNA damage, which in turn is dependent on nutritional status; largely the optimal concentration of micronutrients for preventing genome damage. These investigators further observed that that genome damage is also dependent on genetic polymorphism that alter the function of genes involved directly or indirectly in replication and that the development of dietary patterns, functional foods and supplements that are designed to improve genome health maintenance individuals with specific genetic background would be beneficial.

Nutrigenomics: Another Antidote

Though this may remotely be considered aspect of chemoprevention it is specifically aimed at genome protection. Nutrigenomics is the integration of genomic science with nutrition to modulate genetic characteristics. It has been recently broadened to encompass nutritional factors that protect genome damage. This field and its potential has been consistently reviewed by Fenech and his colleagues (Fenech, 2002; 2004; Liu et al, 2005; Bull and Fenech, 2008). It appears a promising field that can be adequately exploited to reverse or prevent occult genome instability.

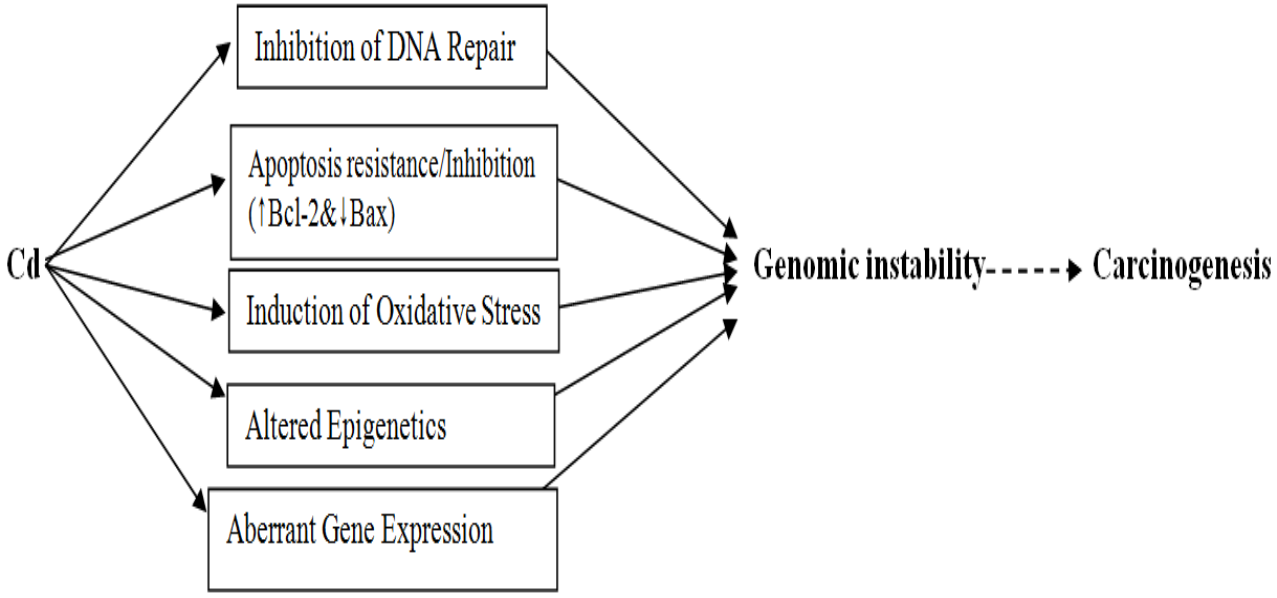

Figure 1: A schematic representation of the mechanisms involved in Cadmium-induced genomic instability.

Miscellaneous Aberrant Genomic Observations

Liu et.al (2005) have shown in plants that Cd pollution in the range 30-120mg/l using random amplified polymorphic DNA (RAPD) profiling that Cd has genotoxic effects. They found that the effects were dose dependent. These observations suggest that even plants are not spared the genomic instability that has been observed in animals and animal components. This implies far reaching significance of the consequences of the rising environmental cadmium levels in the developing countries. Exploring the mechanism of cadmium-induced genomic instability that may lead to carcinogenesis, Singh et al. (Singh et al., 2009) reported aberrant expression of cell cycle and DNA repair genes resulting in increased cell proliferation. The results specifically revealed that short-term exposure to lower doses of Cd significantly increased the growth of TM3 cells, a mouse testicular leydig cell line. In contrast, higher doses were very toxic and lethal to cells. Long- term exposure to higher doses of Cd caused increased cell survival and acquisition of apoptotic resistance. Gene expression analysis demonstrated expression of the anti-apoptotic gene Bcl-2 and reduced expression of the pro-apoptotic gene Bax. Additionally, decreased expression of genes for maintenance of DNA methylation, DNMT1, and DNA repair, OGG1 and MYH was also exhibited by the cells after 24 h exposure. Like the study of Liu et. al (2005), RAPD assay revealed genomic instability in cells with chronic exposure to cadmium, the form of exposure common in the general population. This study shows that among the mechanisms of Cd induced- genome instability include, increased cell survival through increased expression of anti-apoptotic Bcl-2, and decreased expression of pro-apoptotic Bax.

CONCLUSION

It is indisputable that the spate of industrialization in developing countries is contributing substantially to the rising levels of cadmium in the environment. Current understanding suggests that through inhibition of DNA repair mechanisms, inhibitory effects on apoptosis/ resistance, induction of oxidative stress, epigenetic mechanisms and aberrant gene expression this can lead to genome instability in the population. This is a precursor to carcinogenesis and may indeed be at least in part the underlying explanation for the increasing incidence of cancer in these countries. Genome instability though occult should now be considered the critical endpoint of the rising cadmium levels in these countries. This may lead to accelerated malignant transformation of cells. Chemoprevention appears a pragmatic approach to check this inevitable exposure to rising environmental Cd levels. Chemoprevention including nutrigenomics is accepted to be a realistic and fundamental measure to contain the consequences of this rising environmental Cd level. Developing countries must regard this as a priority area to forestall the occult deleterious effect of Cd on the genome and the health of the population. Measures are should be taken to reduce cadmium exposure in the general population in the developing countries to minimize the risk of adverse health effects including genome paresis progressing to genome instability depending on the degree of exposure (dose dependence).

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