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Insights into the Genotoxic Effects of Heavy Metals in Human Diseases

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ABSTRACT

Genotoxic agents—particularly heavy metals such as arsenic, lead, cadmium, and mercury—pose significant threats to human health by inducing DNA damage and promoting genomic instability. These agents affect both somatic and germ cells, contributing to a wide range of health outcomes, including various cancers, neurodegenerative disorders, infertility, and heritable genetic diseases. Genotoxicity interferes with essential cellular processes such as DNA repair and cell cycle regulation, leading to cascading biological effects that compromise cellular function and overall organismal health. Understanding the underlying mechanisms of genotoxic stress is critical for identifying molecular targets, developing reliable diagnostic biomarkers, and designing effective strategies for disease prevention and treatment. This underscores the urgent need for rigorous monitoring and mitigation of genotoxic exposures, particularly in rapidly industrializing regions where environmental contamination is on the rise. This review highlights the critical effects of genotoxicity on cellular response mechanisms and its contribution to the progression of human diseases.

KEYWORDS: Environmental Contamination, Pollution, Industrialization, Heavy Metal, DNA Damage, Disease, Cancer

In today's industrialized and technology-driven era, human exposure to hazardous substances has risen dramatically due to widespread industrialization, urbanization, and modern agricultural practices. These developments have introduced numerous synthetic and naturally occurring toxicants into the environment, transforming contamination into a global concern rather than a localized issue. Hazardous agents, such as food additives, pesticides, industrial chemicals, radiation, microbial byproducts, and heavy metals, are now commonly found in the air we breathe, the water we drink, the soil we cultivate, and the food we consume. Unfortunately, many of these compounds enter commercial use without undergoing complete toxicological studies, creating regulatory vulnerabilities that promote chronic human exposure to genotoxicants, substances capable of causing DNA damage and disrupting the genome.

Genotoxic substances can be broadly classified into four major categories based on their mode of action and origin. Chemical agents, including alkylating compounds, nitrogen mustards, intercalators, and base analogues, disrupt the fidelity of DNA replication and induce mutations by directly modifying nucleotides or interfering with DNA structure. Physical agents such as ionizing radiation (X-rays and gamma rays) and non-ionizing radiation (ultraviolet light) are known to cause DNA strand breaks, chromosomal fragmentation, and other forms of structural damage that compromise genomic stability (Blank and Goodman, 2011; Miyakoshi, 2013; Almaqwashi et al., 2016). Heavy metals—notably cadmium, arsenic, chromium, lead, and mercury—contribute to genotoxicity through mechanisms including the generation of reactive oxygen species (ROS), inhibition of DNA repair enzymes, and the formation of DNA–protein crosslinks, which collectively interfere with genomic maintenance (Errol et al., 2006; Tchounwou et al., 2012). Lastly, Microbial toxins such as aflatoxins and bacterial genotoxins can induce both oxidative and alkylative DNA damage. These toxins impair replication fidelity and DNA repair, leading to the accumulation of mutations and contributing to the initiation and progression of carcinogenesis (Grasso and Frisan, 2015).

These diverse sources of genotoxic exposure highlight the urgent need for stringent toxicological evaluation, regulatory oversight, and public health measures to mitigate long-term genomic risks.

Cellular Responses to Heavy Metal Genotoxic Stress

Genotoxic effects encompass a broad range of DNA alterations, including single- and double-strand breaks, base modifications, DNA cross-linking, abasic site formation, and chromosomal rearrangements (Figure 1). Genotoxic agents, also known as genotoxins, are classified into three types based on their biological effects: carcinogens, which promote uncontrolled cell proliferation and tumor formation; mutagens, which alter DNA sequences and may cause heritable mutations; and teratogens, which disrupt embryonic development and cause congenital anomalies (Purchase, 1994; Kaina, 2003; Kastan and Bartek, 2004; Cavalieri et al., 2012).

Upon exposure to genotoxic agents, especially heavy metals, cells activate a complex array of molecular defense mechanisms to maintain genomic stability. These include DNA damage recognition and repair systems such as base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and homologous recombination (HR). When damage is irreparable, cells initiate apoptosis to eliminate damaged

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cells, thereby preserving tissue function (Torgovnick and Schumacher, 2015; Roos et al., 2016; Srivastava et al., 2016).

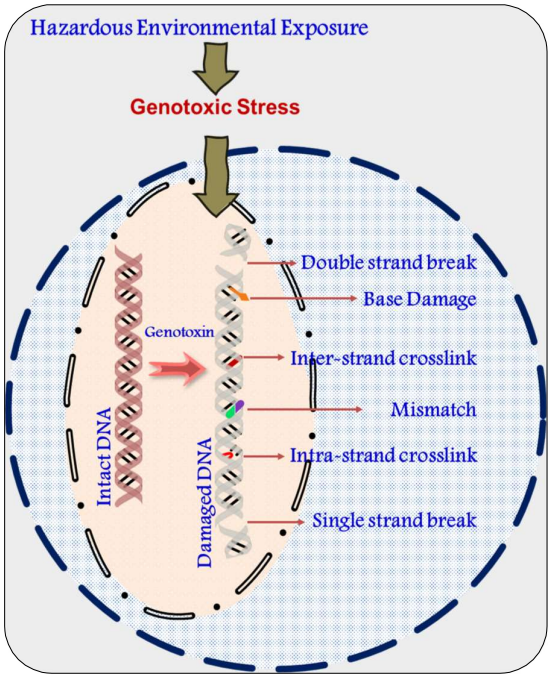

Figure 1. Genotoxic agents induce a range of DNA alterations,

Heavy metal exposure often activates DNA-damage sensors such as ATM and ATR kinases, which phosphorylate CHK1, CHK2, and p53, leading to cell cycle arrest and allowing time for DNA repair or triggering apoptosis if repair fails (Shackelford et al., 1999; Kastan and Bartek, 2004). In parallel, heavy metals induce oxidative stress through the overproduction of ROS, like superoxide anions, hydrogen peroxide, and hydroxyl radicals, which damage nucleic acids, proteins, and lipids and disrupt mitochondrial function. Although cells deploy antioxidant enzymes such as SOD, catalase, and GPx and non-enzymatic antioxidants like glutathione (GSH), chronic exposure to metals like cadmium, arsenic, and lead can overwhelm these systems, resulting in oxidative DNA lesions including 8-oxoguanine (Cooke et al., 2003; Evans et al., 2004; Jomova and Valko, 2011; Sytar et al., 2013).

Heavy metals also activate inflammatory signaling pathways such as NF-κB, which governs cytokines like IL-6 and TNF-α, contributing to tissue damage and carcinogenesis. Simultaneously, activation of MAPK pathways, including ERK, JNK, and p38, regulates cellular stress responses and apoptosis (Wang and Shi, 2001; Matsuoka and Igisu, 2002; Waisberg et al., 2003; Beyersmann and Hartwig, 2008; Milnerowicz et al., 2015).

At the epigenetic level, arsenic and nickel inhibit DNMTs and HDACs, while cadmium and chromium alter histone modifications, leading to gene silencing or activation of oncogenes (Mishra et al., 2010; Fragou et al., 2011; Srivastava and Ahn, 2015; Srivastava et al., 2016; Srivastava et al., 2016). These changes may persist across cell generations and contribute to long-term disease risks, including cancer and developmental disorders.

To evaluate the genotoxic potential of environmental substances, a variety of in vitro and in vivo assays are used. The Ames test detects point mutations in specific bacterial strains, while the comet assay (single-cell gel electrophoresis) quantifies DNA strand breaks. The micronucleus test identifies chromosomal fragments or entire chromosomes excluded from daughter nuclei during mitosis. In vivo models, such as rodents and zebrafish, provide systemic insights into genotoxicity, developmental impacts, and tissue-specific responses (Rojas et al., 1999; Tice et al., 2000; Jha, 2004; Barbosa et al., 2010; Srivastava et al., 2012; Srivastava and Srivastava, 2016). Emerging tools like omics technologies (transcriptomics, proteomics, and epigenomics) and high-content imaging offer comprehensive insights into cellular responses to heavy metal-induced genotoxicity.

Complementing these, metabolomics, by profiling small molecules in biological samples, offers a functional snapshot of biochemical and physiological changes, revealing early indicators of toxicity and disease risk (Nicholson et al., 1999; Waters, 2010; Bouhifd et al., 2013; Bouhifd et al., 2015; Zhao and Hartung, 2015)

Heavy metals significantly disrupt key metabolic pathways essential to cellular homeostasis. Glycolysis and the tricarboxylic acid (TCA) cycle are commonly impaired, resulting in reduced ATP production and energetic stress. Fatty acid β-oxidation is also inhibited, leading to lipid accumulation, mitochondrial dysfunction, and oxidative stress. Additionally, heavy metals promote lipid peroxidation, which compromises membrane integrity and cellular viability. A critical pathway affected by heavy metal exposure is one-carbon metabolism, which supports nucleotide biosynthesis, redox balance, and methylation reactions critical for epigenetic regulation (Hall and Gamble, 2012; Kruman and Fowler, 2014). For example, cadmium exposure alters urinary levels of creatinine, citrate, and various amino acids, signaling renal dysfunction, oxidative stress, and impaired energy

metabolism (Nicholson et al., 2002; Griffin and Bollard, 2004; Bundy et al., 2009). Plasma metabolomic analyses have similarly demonstrated cadmium-induced disruption in lipid and amino acid profiles, consistent with mitochondrial toxicity. Arsenic interferes with folate and methionine cycles, leading to global hypomethylation of DNA and histones. This disruption affects chromatin structure and gene expression, thereby contributing to genomic instability and carcinogenesis (Fragou et al., 2011; Salemi et al., 2017). These metabolomic signatures not only serve as early markers of systemic toxicity but also act as mechanistic indicators linking molecular changes to phenotypic outcomes, supporting their application in biomonitoring and risk assessment of environmental exposures.

Heavy Metal-Induced Disease Progression in Human

Heavy metal-induced genotoxicity poses a significant public health threat, contributing to the pathogenesis of a wide range of chronic and degenerative diseases, including cancer, neurodegenerative disorders, cardiovascular dysfunction, and developmental abnormalities (Table 1). Persistent environmental and occupational exposure to toxic metals, particularly cadmium, arsenic, lead, mercury, and hexavalent chromium, leads to their bioaccumulation in tissues, where they exert cytotoxic and genotoxic effects through multiple interconnected mechanisms.

Table 1: List of a few Genotoxic agents that cause the human disease progression

Genotoxic Agent	Associated Human Diseases
1,3-Butadiene	Leukemia, Lymphoma
Acetaldehyde	Esophageal cancer, Oral cancer
Aluminum	Neurotoxicity, Alzheimer-like symptoms
Arsenic	Chronic lung disease, Hyperpigmentation, Skin cancer, Liver fibrosis
Asbestos (inhalation)	Asbestosis, Mesothelioma, Lung cancer
Benzene	Acute myeloid leukemia, Bone marrow suppression
Beryllium	Chronic beryllium disease, Lung cancer
Cadmium	Kidney damage, Lung cancer, Osteoporosis
Chromium (VI)	Allergic dermatitis, Nasal septum perforation, Lung cancer
Copper	Liver or kidney damage (long-term), Gastrointestinal distress (short-term)
Cyclophosphamide	Bladder cancer, DNA crosslinks
Ethylene oxide	Breast cancer, Lymphoma
Formaldehyde	Nasopharyngeal cancer, Myeloid leukemia
Ionizing Radiation	Leukemia, Thyroid cancer, Breast cancer
Lead	Neurodevelopmental delays, Kidney damage, Hypertension, Anemia
Mercury	Neurological disorders, Immune dysfunction, Kidney failure
Nickel	Lung cancer, Nasal cancer, Dermatitis
Nitrosamines	Kidney tumors, Liver cancer, and Gastric cancer
PAHs	Lung cancer, Bladder cancer, Skin cancer
PCBs	Liver cancer, Chloracne, Immunotoxicity
Perchloroethylene	Bladder cancer, Esophageal cancer
Polluted air / Particulates	Lung cancer, COPD, Cardiovascular disease
Silica (inhalation)	Silicosis, Lung fibrosis, Lung cancer
Styrene	Nasopharyngeal cancer, Genotoxicity in lymphocytes
Vinyl chloride	Liver angiosarcoma, Brain and lung cancers

These metals damage DNA directly, induce oxidative stress, cause epigenetic alterations, and impair DNA repair pathways. Such disruptions result in mutation accumulation, chromosomal instability, cell cycle arrest, premature senescence, and malignant transformation. The DNA damage response (DDR) acts as a critical cellular safeguard, detecting DNA lesions, initiating repair, activating checkpoints, and determining cell fate through survival or programmed death (Hartwig et al., 2002; Roos and Kaina, 2006, 2013; Srivastava et al., 2016). However, chronic or high-dose exposure to heavy metals may overwhelm or disrupt DDR signaling,

tipping the balance toward genomic instability and disease progression.

A major genotoxic mechanism involves the overproduction of reactive oxygen species (ROS). Metals such as cadmium, chromium, and arsenic catalyze Fenton-like reactions or deplete endogenous antioxidants like glutathione and superoxide dismutase (SOD), resulting in lipid peroxidation, protein oxidation, and DNA damage (Valko et al., 2005; Valko et al., 2006; Jomova and Valko, 2011). ROS-induced DNA lesions—such as 8-oxoguanine and thymine glycol, which induce base mispairing, strand breaks, and mitochondrial genome instability, ultimately activating pro-apoptotic signaling (Evans et al., 2004; Hartwig, 2013). Cadmium, while not producing ROS directly, impairs antioxidant defenses and displaces zinc from DNA repair enzymes, thus indirectly facilitating ROS accumulation and oxidative injury (Hartwig et al., 2002; Valko et al., 2006; Jomova and Valko, 2011; Hartwig, 2013)

Heavy metals further contribute to genotoxicity by directly inducing DNA adducts, DNA–protein crosslinks, strand breaks, and telomere attrition. (Evans et al., 2004). (Hoeijmakers, 2009; Jackson and Bartek, 2009) (Tornaletti, 2005; Jackson and Bartek, 2009) (Phillips, 2005). Telomeric DNA, rich in guanine, is especially vulnerable to oxidative attack, leading to telomere shortening, chromosomal fusions, and premature cellular aging, which are hallmarks of cancer and age-related diseases (Jackson and Bartek, 2009).

Additionally, heavy metals disrupt essential DNA repair pathways, further exacerbating genomic instability. Cadmium impairs both base excision repair (BER) and nucleotide excision repair (NER) by inhibiting enzymes such as OGG1 and XPA (Hartwig et al., 2002; Hartwig, 2013). Arsenic interferes with BER by suppressing PARP1, XRCC1, and DNA ligase I, proteins critical for single-strand break repair (Hartwig et al., 2002). Lead and chromium inhibit the mismatch repair (MMR) pathway, which corrects base mismatches and insertion-deletion loops during DNA replication. Mercury targets mitochondrial DNA repair, increasing ROS generation and compromising mitochondrial respiratory function (Jomova and Valko, 2011; Hartwig, 2013). These inhibitory effects on DNA repair systems undermine genomic maintenance and facilitate mutagenesis, carcinogenesis, and other degenerative diseases.

Beyond direct DNA damage and repair impairment, heavy metals act as potent epigenetic modifiers. Arsenic and nickel induce global hypomethylation and site-specific hypermethylation of critical gene promoters, including tumor suppressors such as *p16INK4a*, *MLH1*, and *BRCA1* (Beyersmann, 2002; Salnikow and Zhitkovich, 2008; Arita and Costa, 2009; Brocato and Costa, 2013). Cadmium and chromium also alter histone modification patterns (acetylation, methylation, phosphorylation), leading to chromatin remodeling and dysregulated transcription (Beyersmann, 2002; Salnikow and Zhitkovich, 2008; Martinez-Zamudio and Ha, 2011; Chervona and Costa, 2012). Moreover, heavy metals modulate the expression of non-coding RNAs, particularly microRNAs (e.g., miR-21, miR-34a), which play essential roles in cell cycle control, apoptosis, and inflammatory responses (Chervona and Costa, 2012). Importantly, these epigenetic alterations may be heritable via the germline, raising serious concerns about transgenerational health impacts.

The carcinogenic potential of heavy metals is further supported by epidemiological and experimental evidence. Chronic exposure to cadmium, arsenic, and chromium is associated with increased risks of lung, liver, bladder, prostate, kidney, and skin (Beyersmann, 2002; Waisberg et al., 2003; Valko et al., 2006; Arita and Costa, 2009; Jaishankar et al., 2014). These metals activate oncogenic signaling pathways such as NF-κB, MAPK, and PI3K/AKT, promote epithelial–mesenchymal transition (EMT), and enhance angiogenesis, which facilitates tumor progression and metastasis (Matsuoka and Igisu, 2002; Valko et al., 2005; Colotta et al., 2009). Moreover, loss-of-function mutations and epigenetic silencing of DDR genes such as TP53, ATM, and BRCA1/2 are frequently observed in heavy metal-associated cancers (Carney et al., 1998; Rotman and Shiloh, 1999; Roos et al., 2016).

The central nervous system is particularly susceptible to heavy metal-induced genotoxicity. These metals can cross the blood–brain barrier and accumulate in neurons, leading to oxidative stress, mitochondrial dysfunction, neuroinflammation, and synaptic disruption (Crespo-López et al., 2009). Lead and mercury have been linked to cognitive impairment, behavioral abnormalities, and neurodevelopmental delays in children (Jomova and Valko, 2011). In adults, cadmium and arsenic exposure are implicated in Alzheimer's disease (AD) and Parkinson's disease (PD) through mechanisms involving amyloid-β aggregation, tau phosphorylation, and dopaminergic neuron degeneration (Crespo-López et al., 2009).

Reproductive toxicity is another major consequence of heavy metal genotoxicity. Cadmium induces sperm DNA fragmentation and testicular apoptosis, while arsenic disrupts meiotic progression and fetal DNA methylation (Hartwig et al., 2002; Valko et

al., 2005; Valko et al., 2006; Diamanti-Kandarakis et al., 2009; Sweeney et al., 2015). Maternal exposure to lead or mercury during pregnancy has been associated with low birth weight, neural tube defects, and impaired neurocognitive development in offspring (Mendola et al., 2002; Kasperczyk et al., 2004; Brender et al., 2006). These adverse effects stem from both direct genotoxic damage during organogenesis and epigenetic reprogramming, potentially affecting offspring health over the long term.

The immune system, dependent on DNA rearrangement for lymphocyte diversity, is also a key target of genotoxic stress. Heavy metals interfere with V(D)J recombination, clonal expansion, and immunoglobulin production (Dietert and Piepenbrink, 2006; Dietert, 2009). Lead, cadmium, and mercury reduce thymocyte proliferation, induce apoptosis in B and T cells, and impair hematopoietic stem cell function (Crespo-López et al., 2009; Mishra, 2009; Maqbool et al., 2017). These effects contribute to immunodeficiency, increased susceptibility to infections, and the development of hematological malignancies such as leukemia and lymphoma, particularly in populations with chronic exposure (Lawrence and McCabe, 2002).

Heavy metal-induced genotoxicity significantly affects cardiovascular and metabolic health. Cadmium, lead, and arsenic induce DNA damage in endothelial cells, contributing to vascular inflammation, hypertension, and atherogenesis (Kasperczyk et al., 2004; Vaziri, 2008; Messner and Bernhard, 2010; Ellinsworth, 2015; Kukongviriyapan et al., 2016). Mitochondrial genotoxicity impairs cardiomyocyte function, compromising energy metabolism and promoting cardiomyopathy (Varga et al., 2015). These metals also disrupt lipid and glucose metabolism, leading to obesity, insulin resistance, and chronic low-grade inflammation—hallmarks of metabolic syndrome and type 2 diabetes (Vaziri, 2008; Tellez-Plaza et al., 2013).

Conclusion and Future Perspectives

Recent and past studies consistently demonstrate that genotoxic agents, encompassing physical, chemical, and environmental factors, play a central role in inducing genomic instability, which adversely impacts human health through various biological pathways. Genotoxic effects manifest in both somatic and germ cells, with serious implications. In somatic cells, such alterations are strongly associated with the initiation and progression of cancer and other degenerative disorders. In germ cells, genotoxicity can result in infertility, inherited genetic disorders, and complex multifactorial diseases, thereby posing transgenerational health risks. The genotoxicity induced by heavy metals and other agents triggers a cascade of molecular events that compromise essential cellular processes, including DNA replication, repair mechanisms, and cell cycle regulation. These disruptions can lead to persistent genomic instability, chronic inflammation, and ultimately, cellular transformation or programmed cell death. Understanding the intricate molecular responses to genotoxic stress, particularly the cellular DNA damage response (DDR), is critical for elucidating disease mechanisms and identifying potential molecular targets for therapy.

In summary, heavy metal-induced genotoxicity remains a major global health concern, contributing to a broad spectrum of human diseases. Continued advancements in molecular biology, epigenetics, and toxicogenomics are vital for deepening our understanding of how genotoxic agents operate. Such insights will inform the development of improved diagnostic tools, effective preventive strategies, and novel targeted therapies aimed at mitigating the harmful impacts of environmental and occupational genotoxicants.

Conflicts of Interest: The author declares no conflicts of interest.

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