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Arsenic in Groundwater and Its Carcinogenicity

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ABSTRACT: Due to groundwater contamination and runoff from certain mining operations, populations are exposed to detrimental levels of arsenic daily. The effects of arsenic exposure on the human epigenome are extensive, and some are still unknown. It can alter DNA methylation, inhibiting specific tumor suppressor genes and increasing the risk of neoplasia. This can be drawn back to certain crucial factors of DNA methylation, such as CpG Binding Proteins or DNA Methyl-transferases, all of which have shown linkage to carcinogenesis. Arsenic can also cause an overproduction of free radicals and a reduction of antioxidant production, causing oxidative stress. Lastly, it has also been associated with specific chromosomal abnormalities. All of these factors, which will be discussed in further detail, have been shown to contribute to the progression of cancer.

KEYWORDS: Biomedical and Health Sciences, Epigenetics; Arsenic Carcinogenicity; DNA Methylation; Methyl CpG Binding Proteins; DNA Methyltransferases.

Introduction

Arsenic is a naturally occurring and extensively distributed element found in the earth's crust. It comes in a multitude of forms, some of them being organic (Arsenite (AsIII) and Arsenate (AsV)) and others being inorganic (Dimethylarsinic acid (DMA) and Monomethylarsonic acid (MMA)).[1] Organic arsenic is metabolized by being absorbed into the bloodstream and reduced from Arsenate to Arsenite, which then allows for its methylation and detoxification.[2] In its inorganic form, however, arsenic can be extremely harmful to the human body, causing the development of skin lesions, cardiovascular diseases, and cancer.[3] The health defects of chronic exposure to arsenic are relatively well-known. What is little known about Arsenic, however, is its prevalence in our daily lives. It is said that the average daily dietary intake of Arsenic through food ingestion in adults is 40 micrograms.[4] This is in addition to levels of arsenic found in drinking water, which in some areas of the United States exceeds the maximum contaminant level of 10 µg/L.[5] It is worth noting that certain populations are more susceptible to arsenic exposure than others, namely, lesser-developed countries that rely on mining and other industrial processes to fuel their economies. Mining has served as a significant economic resource and has allowed numerous countries to prosper. It provides many employment opportunities and will enable countries that were once economically stagnant to flourish. However, some of its environmental effects must be addressed due to its pervasiveness. Acid Mine Drainage (AMD) is the process of newly exposed iron sulfides oxidizing to create sulfuric acid, a corrosive acid capable of weathering nearby rocks and leaching toxic metals into rivers and streams.[6] Certain populations, having no choice but to drink this contaminated water and not being given enough information by the government to deem the water undrinkable, may be at risk of developing diseases associated with increased arsenic exposure. The International Agency for Research on Cancer (IARC) has identified arsenic and arsenic compounds as carcinogens. This is also applicable to when arsenic is ingested through drinking water, where it has been known to cause cancers of the bladder and lungs.[7] However, in studies regarding the carcinogenicity of arsenic, there have been a few uncertainties about whether arsenic in itself is a carcinogen or whether it works synergistically with other carcinogens. Furthermore, in studies involving laboratory animals, where arsenic is administered as a single agent, it has generally been found to be nongenotoxic. In a study conducted by Xie *et al.*, both organic and inorganic forms of arsenic were administered to mice for a 17-week period. After the initial 4 weeks of administering arsenic, phorbol 12-myristate 13-acetate (TPA), a tumor promoter, was given to the mice. At the end of the 17-week period, global hypomethylation (contributor to carcinogenesis) was found in the mice for all forms of arsenic.[8] Therefore, research in animal models does not demonstrate the carcinogenicity of arsenic as a single agent but rather its ability to serve as a co-carcinogen along with other carcinogenic environmental factors.[9]

One such population that suffers from frequent exposure to carcinogenic environmental factors is that of Mongolia[10]; Mining accounts for 20-30% of Mongolia's national GDP and 90% of its annual exports.[11] Mongolia places great importance on its mining activities but fails to recognize its effect on the welfare of its people. Mongolia has the highest incidence rate for stomach cancer in the whole world.[12] Bangladesh, a country infamous for its "Arsenic Incident" of 1993, discovered arsenic in their tube wells, the primary source of drinking water for rural populations.[13] Bangladesh is ranked second worldwide for Mouth and Oral Cancer incidence rates.[12] It is essential to note that mining is not the sole contributor to arsenic in drinking water. Even countries that don't depend on mining, such as the United States, have unhealthy levels of arsenic in their groundwater.[14] Therefore, this is not only a local phe-

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nomenon but a global one. Cancer is said to be the product of multistage developments and changes in gene expression.[15] This paper aims to identify such developments and how arsenic contributes to their progression. Exposure to arsenic and other toxic metals through mining operations and groundwater contamination increases susceptibility and mortality to certain forms of cancer.

Discussions

Epigenetics:

The term "epigenetics" was introduced in 1942 by embryologist Conrad Waddington, who related the term to the 17th-century concept of "epigenesis" since it was known to show the developmental processes connecting one's genotype to their phenotype.[16] Since then, the definition of epigenetics has evolved into the study of how behavioral and environmental factors can affect genetic processes. These changes, although reversible, are extremely prominent and can go so far as to turn genes "on" or "off," either stimulating or inhibiting genetic functionality.[17] There are different forms of epigenetic alteration, including DNA methylation, histone modification, and non-coding RNA. DNA Methylation, the most extensively discussed form in this paper, involves methyl groups being added to genes in order to repress their activity. When gene expression is suppressed too much or, in some cases, not enough, it can greatly change regular gene development and can lead to unwanted processes. It is important to note, however, that not all methylation leads to gene silencing. When taking place in locations outside promoter regions, methylation does not necessarily lead to gene silencing and may not impact gene expression as extensively.[18] Another form of epigenetic alteration is histone modification, which involves the attachment of chemical groups to histone proteins, making them more closely packed together. This hinders the ability of other proteins to "read" the genes and assist in their development. Lastly, there is a form of epigenetic alteration that takes place using non-coding RNA. While the main role of non-coding RNA is to break down coding RNA to stop the production of certain proteins, it can also recruit proteins to modify histones, again rendering certain genes defective.[17]

DNA Methylation and Cancer:

DNA methylation plays an important role in regulating genes that control cell proliferation, differentiation, and overall development. These alterations can be passed down to daughter cells during DNA replication.[19] DNA promoter hyper-methylation has been linked to the loss of tumor suppressor gene expression, specifically the production of the p53 gene. An article by Esteller *et al*. covers a study regarding the prevalence of DNA hyper-methylation in lung cancer patients. The study tested 22 non-small cell lung cancer patients for aberrant methylation in a couple of tumor suppressor/detoxification genes. 68% of the patients presented with signs of hyper-methylation in all tumor stages. Genes such as tumor protein p53 and p16 genes have been proven fundamental to neoplasm prevention, but all are affected by hyper-methylation.[20] Another study by Kroeger *et al*. observes DNA hyper-methylation in the progression of acute myeloid leukemia (AML). A genome-wide screening was conducted to reveal the methylated CpG sites in AML patients. 23% to 83% of patients with AML showed signs of abnormal methylation at diagnosis, and 47% to 93% of patients with AML showed signs of abnormal methylation at relapse. To assess the correlation between the hyper-methylated genes and cancer progression, a total of 9 genes were tested in a group of AML patients for abnormal methylation. It was found that all patients had at least 1 of the 9 genes methylated at diagnosis and at least 2 of the 9 genes methylated during relapse. In addition, many of the methylated genes played crucial roles in tumor suppression, such as the p15 gene and the CDH13 gene. During AML relapse, a 15% increase in the number of p15 genes methylated was shown. This shows a positive correlation between the hyper-methylation of tumor-suppressor genes and cancer progression.[21]

Another topic related to genetic alteration and DNA methylation is hypo-methylation. There have been studies associating hypo-methylation with oncogenic transformation. One such study is that of Good *et al*. In the study, patients with Triple-negative breast cancer (TNBC) were said to have an over-expression of TET1 DNA demethylase, along with hypo-methylation of up to 10% of CpG sites. Through further study of breast and ovarian cancers, scientists have found a connection between TET1 and hypo-methylation and the activation of cancer-specific oncogenic pathways such as PI3K, EGFR, and PDGF.

Furthermore, after a CRISPR-mediated removal of TET1, there was a significant decrease in the usage of oncogenic pathways and a substantial increase in immune response genes. This suggests a dependence of cancer cell proliferation on TET1 over-expression.[22] Another correlation worth considering is that of hypo-methylation and tumorigenesis. Though it is clear that neoplasm formation is strongly associated with hypo-methylation, the underlying mechanism is still not understood. Some studies, such as that of Tongelen *et al*., relate tumorigenesis to the activation of "cancer germline genes," which are genes of the germ-line that utilize DNA methylation as a method of repression. When affected by hypo-methylation, these genes can stimulate oncogenic pathways and catalyze processes such as cell proliferation, angiogenesis (blood cell formation), and metastasis (malignant growths at a distance from the primary site of cancer).[23] Lastly, there are studies connecting hypo-methylation of the LINE-1 repetitive element to tumorigenesis, such as that of Ehrlich.[24] The LINE-1 repeat promoter has the main function of mediating tumor suppressor deletion. When this gene is methylated, this function is inhibited, and tumor suppressor genes can perform their respective functions. However, when the LINE-1 promoter is hypo-methylated, there is a more rapid and frequent deletion of tumor suppressor genes, which can lead to oncogenic formation. The hypo-methylation of LINE-1 affects the human genome depending on the condition. For example, LINE-1 hypo-methylation significantly affects lymph node involvement in prostate adenocarcinomas. Another instance is hepatocellular carcinoma, which shows the hypo-methylation of repetitive sequences (such as LINE-1) in relation to the reoccurrence of the disease.

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Epigenetic Machinery:

There are other facets to DNA methylation to be considered, such as methyl CpG binding proteins, that can potentially lead to cancer. Methyl CpG binding proteins (MBPs) recognize the CpG sites during DNA methylation. Therefore, they play a major role in identifying where to attach methyl groups. There are three categories into which methyl CpG binding proteins are divided: MBD-containing proteins, methyl-CpG binding zinc fingers, and the SRA domain-containing proteins.[25] The first category, MBD-containing proteins, is further divided into three subdivisions: histone methyl-transferases (HMT_MBD), the MeCP2_MBD proteins, and histone acetyltransferases(HAT_MBD). However, not all members of this group interact directly with CpG sites. HMT_MBD, which has been shown to interact with CpG sites, contains two categories: *SETDB1* and *SETDB2*, affecting chromosomes 1 and 13, respectively. *SETDB1*, on its own, has not been proven to cause cancer but has been associated with proteins that play a significant role in neoplasia. For example, its association with *DNMT3A* has been proven to repress the *p53* gene in breast and ovarian cancer cell lines. *SETDB1* has also been proven to interact with the protein MCAF1. Along with MBD1 (another transcriptional repressor), *SETDB1* and MCAF1 form a complex(*SETDB1*:MCAF1:MBD1). This complex has been shown to result in heterochromatin formation and gene repression.[26] Although the evidence linking *SETDB2* and cancer is limited compared to that of *SETDB1*, there is evidence associating *SETDB2* with a 1-Mb deletion on chromosome 13q, which is related to the progression of lymphocytic leukemia.[26] Another study by Yang *et al.* observes the over-expression of the CXXC zinc finger protein 1 (CFP1) in ovarian cancer tissues and cells. To ascertain the role of CFP1 in ovarian cancer progression, immunohistochemistry was performed on ovarian cancer tissues. A strong CFP1 signal was found in 125 samples; of those, over 30% showed a moderately strong signal, and just over 5% showed a powerful signal. Therefore, the overexpression of CFP1, a CpG-binding protein, can negatively affect DNA methylation, potentially leading to cancer. This evidence is only amplified when considering the high expression of CFP1 in endometroid carcinoma and serous cystadenoma.[27]

There is also the catalyst of DNA methylation, DNA methyl-transferases (DNMTs) to consider. It is no doubt that when considering the consequences of methylation, DNMTs should be analyzed as well. The methyl-transferase family generally has five members: *DNMT1, DNMT2, DNMT3A, DNMT3B*, and *DNMT3L*. *DNMT1* is a maintenance methyl-transferase, identifying a hemimethylated site and establishing the methylation pattern for the *de novo* methyl-transferases. *DNMT3A* and *DNMT3B* focus on un-methylated CpG sites, predominantly active in embryonic stem cells.[28] Since exposure to arsenic has well-established effects on DNA methylation, it is highly plausible that it affects the expression or activity of DNA methyltransferases. Over-expression of these methyl-transferases can cause the methylation of CpG sites within tumor suppressor genes, which represses their activity and can cause tumorigenesis. For example, the over-expression of *DNMT1* can silence tumor suppressor genes *p16*, *CDH13*, and *CDH1*, which can lead to pituitary adenoma.[29] Furthermore, mutations in *DNMT3A* can cause DNA hypo-methylation through *DNMT3A R882* mutation and can potentially lead to acute myeloid leukemia.[30] The process through which hyper-methylation can occur evolves around densely packed CpG dinucleotides known as CpG islands. CpG islands, in the normal methylation process, are usually un-methylated, while dispersed CpG sites are hyper-methylated. When CpG islands, especially those in tumor suppressor genes, are hyper-methylated, it can silence the tumor suppressor gene and lead to neoplasm formation.[31] The carcinogenicity of DNA methyl-transferase over-expression was further proven using animal models. Belinsky *et al*. used a mouse model to observe the role of *DNMT1* in tumor formation. It was found that the reduction of *DNMT1* correlated with the reduction of incidence rates for lung cancer.[32] However, though the correlation between DNMTs and cancer is undeniable, there is a certain contradiction. Husni *et al*. found that the lack of *DNMT3A* can facilitate tumorigenesis.[33] Various other studies have verified that *DNMT3A* deficiency can promote tumor growth and cause overall genomic instability. This calls to question whether *DNMT3A* is an oncogene or a tumor suppressor gene. In some cases, depending on the cancer type, stage, and other factors, *DNMT3A* and other proteins might be considered oncogenes, whereas, in others, they might be considered tumor suppressors. Furthermore, scientists have yet to discover if the other DNA methyltransferases abide by this paradox.[34]

Arsenic and Epigenetic Changes:

Arsenic has been known to cause changes in DNA methylation, possibly hyper or hypo-methylating certain genes. This is shown in a study conducted by Intrasunanont *et al*., which shows the in utero effects of chronic arsenic exposure in newborn babies.[35] The study involved fifty-five newborn babies exposed to levels of arsenic and sixteen newborns that have not been exposed to arsenic. An *in vitro* study was conducted as well. Results showed increased levels of arsenic in the cord blood, hair, fingernails, and toenails in the newborn exposed to arsenic, as well as an increase in promoter methylation of *p53*. (hyper-methylation) In the *in vitro* study, there was a global hypomethylation, showing reductions in repetitive elements such as LINE-1, as well as *p53* hypermethylation once again. This shows that in utero exposure to arsenic could make certain people more susceptible to carcinogenesis. Another study conducted by Enith Nava-Rivera *et al*., discusses the transgenerational effects of arsenic exposure in rats.[36] A group of rats were chronically exposed to arsenic, and four generations of their offspring were observed. Results showed declining levels of concentration, motility, vitality, and morphology in the generations. Exposure to arsenic caused genotoxic damage, aberrant methylation patterns, and an overall decrease in the quality of the sperm. This shows that the epigenetic alterations caused by arsenic not only affect those exposed but also future generations. Chronic arsenic exposure negatively affects the quality of life and endangers future generations, possibly increasing their susceptibility to certain forms of cancer.

Free Radical Production and Oxidative Stress:

Exposure to arsenic has been linked to the increased production of free radicals derived from the superoxide radical and reactive oxygen species (ROS).[37] Free radicals are unpaired electrons that, under certain circumstances, can cause cell damage and oxidative stress. Reactive oxygen species are those that contain oxygen, which easily reacts with other molecules.[38] In addition to this, arsenic has also been associated with the depletion of glutathione and other antioxidants responsible for regulating free radicals.[39] Therefore, the combination of increased free radicals and decreased antioxidants causes oxidative stress. Oxidative stress has many negative consequences, the majority of which encompass the inability of free radicals to perform their usual functions of defending the body against pathogens. This can cause atherosclerosis, diabetes, hypertension, and even cancer.[40] More specifically, ROS has been known to cause DNA strand breaks and damage to nucleotides. Many studies have shown significant DNA oxidation in cancer tissues leading to malignant progression in breast cancer and hepatocellular carcinoma. ROS can also modify regulatory proteins and enzymes in non-cancerous cells, causing carcinogenesis. Furthermore, carcinogenesis, through a study regarding colorectal cancer, has been linked with lipid peroxidation. This was found through thiobarbituric acid-reactive substances in the colorectal cancer patient, which are by-products of lipid peroxidation. This process generates many genotoxic molecules and can alter cellular membrane structure, affecting membrane permeability and recognition by the immune system.[41] Although the correlation between free radicals and cancer is widely unrefuted, some studies link free radical usage to chemotherapeutics, providing a contradictory function to the free radicals. It is well acknowledged that the overproduction of ROS can cause genetic alterations, but these alterations can be lethal to cancer cells. Therefore, ROS has a dual role in both initiating and suppressing carcinogenesis. This is shown through evidence that ROS participates both in the Ras-Raf-MEK1/2-ERK1/2 oncogenic pathway and in the *p38* MAPK tumor-suppressing pathways. So, depending on the cell type, ROS function may vary. [42]

Chromosomal Aberrations:

Exposure to arsenic and arsenic compounds has been found to cause chromosomal aberrations. In a study by Beckman *et al.*, short-cultured lymphocytes of nine workers exposed to arsenic at the Rönnskär smeltery in northern Sweden were observed. Eighty-seven aberrations were found in 819 mitoses.[43] Despite the numerous developmental problems associated with chromosomal aberrations, it has also been linked to cancer. Two predominant factors of cancer cells are aneuploidy (an abnormal number of chromosomes) and structural reorganization of the chromosomes. Aneuploidy has been identified in most tumor cases and half of all leukemia and lymphoma cases. Its underlying cause is an erosion of mitotic fidelity, a condition called chromosomal instability (CIN). This produces alarmingly high losses and gains of chromosomes. Both aneuploidy and CIN have been associated with poor patient prognosis and resistance to chemotherapeutics.[44] There have also been studies, such as that of Moore *et al.*, that have connected arsenic exposure and chromosomal alterations. This connection was determined by examining 123 patients in Argentina and Chile exposed to arsenic. In general, chromosomal abnormalities were higher in those exposed to arsenic. The deletion of chromosome 17p was the most predominant result of the exposure. This study also found an association between these chromosomal alterations and tumorigenesis. The mean number of chromosomal changes increased along with the tumor age and grade, showing a positive correlation between tumor progression and chromosomal abnormalities.[45]

Conclusion

In conclusion, exposure to arsenic can cause a multitude of physiological difficulties and could potentially lead to cancer. Through its effect on DNA methylation, chromosomes, and ROS-mediated oxidative stress, arsenic can permanently alter the human genome. This affects not only those exposed to arsenic but also their offspring. There are, however, ways to remedy this widespread phenomenon. In areas with arsenic in groundwater, populations can use low-arsenic water sources such as purified surface water or rainwater. Testing water for arsenic is also important to distinguish between drinking water and water used for other purposes.[46] Although all the alterations to the genome induced by arsenic have not yet been identified, scientists continue to explore genomic patterns about arsenic and other toxic metals. There are even non-epigenetic effects of arsenic that are yet to be explored thoroughly.[47] When discovered, they can revolutionize epigenetics and etiology, potentially saving many lives.

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