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Chronic Arsenic Toxicity and Cancer

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ABSTRACT

Arsenic pollution in ground water has been envisaged as a problem of Global concern. Chronic arsenic toxicity (arsenicosis) due to drinking of arsenic contaminated ground water is a major environmental health hazard throughout the world including India and Bangladesh. Chronic exposure to arsenic in drinking water can cause increased risk of skin, lung, kidney, bladder cancer, liver disease and chronic respiratory problems. The exact molecular mechanism of arsenic induced carcinogenesis is still less understood. Both arsenite and its metabolites can have a variety of genotoxic effects, which may be mediated by oxidants or free radical species. All of these species also have effects on signaling pathways leading to proliferative responses. There are interesting differences in the activities of inorganic and organic species both in terms of target organ carcinogenicity and genotoxic and toxic mechanisms. A scientific consensus has not yet been reached on the many suggested modes of arsenic carcinogenesis that exist in the literature. These include modes that are predominately genotoxic (i.e.,chromosomal abnormalities, oxidative stress, and gene amplification) vs. more nongenotoxic (i.e., altered growth factors, enhanced cell proliferation and promotion of carcinogenesis, and altered DNA repair). Likewise, the dose-response relationship at low arsenic concentrations for any of these suggested modes is not known.

Key-words: Arsenic, Chronic exposure, Cancer.

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Introduction

Chronic arsenic toxicity or arsenicosis is a condition that is caused by consuming, absorbing or inhaling more than the optimum levels of arsenic, which is a semi-metallic element that is capable of forming an array of poisonous compounds. It is present in ground water all over the world. Arsenic pollution in ground water has been envisaged as a problem of Global concern. Many aquifers in various regions of the world are contaminated with arsenic (As) at concentration above 50 μg/l. Of these, the most noteworthy occurrences are in West Bengal (India), Bangladesh, Taiwan, Northern China, Hungary, Mexico, many parts of the USA, Chile and Argentina. Chronic arsenic toxicity (arsenicosis) due to drinking of arsenic contaminated ground water is a major environmental health hazard throughout the world including India and Bangladesh. In India, significant arsenic contamination in groundwater was detected in the year 1983 in West Bengal, when some villagers were diagnosed to be suffering from arsenicosis due to drinking of arsenic contaminated water. [1].

Lot of research on health effects of chronic arsenic toxicity in humans has been carried out. The symptoms of chronic arsenic toxicity (arsenicosis) are insidious in onset and are dependent on the magnitude of the dose and duration of its exposure. Further, there is a wide variation in the incidence of chronic arsenicosis in an affected population. Even not all members of an affected family show clinical symptoms of arsenicosis. Pigmentation and keratosis are the specific skin lesions characteristic of chronic arsenic toxicity. However, it was also found to be associated with various systemic manifestations including cancer. Chronic exposure to arsenic in drinking water can cause increased risk of lung, kidney, bladder cancer, liver disease and chronic respiratory problems. However, there is overwhelming evidence that consumption of elevated levels of arsenic through drinking-water is causally related to the development of cancer at several sites, particularly skin, bladder and lung [2-5].

This paper explores the relationship of arsenic exposure with cancer development and summarizes current knowledge of the potential mechanisms that may contribute to the neoplastic processes observed in arsenic exposed human populations.

Materials and Methods

An extensive systemic review of various studies was done to study the effect of Chronic arsenic poisoning on liver. This systematic review was conducted using electronic databases to report on long term effect of chronic arsenic toxicity. To find relevant studies various databases was used including PubMed, and the Cochrane Library. All types of relevant studies were included like journal articles, reports and book chapters, because of limited information regarding the topic of interest. Moreover, the research question could be answered by any type of study. All titles and abstracts were screened first, followed by a full-text review of relevant review articles, including meta-analyses, and published studies based on original data and then all the suitable references were added to the list of articles.

Results and Discussion

The evidence of carcinogenicity in humans from exposure to arsenic is based on epidemiological studies of cancer in relation to arsenic in drinking water. Ecological studies, cohort studies and case-control studies from many countries observed that arsenic was potentially carcinogenic for skin cancer, urinary bladder cancer and lung cancer due to chronic exposure [6]. Among 4865 cases of arsenicosis studied in arsenic affected villages in West Bengal State of India, 212 (4.35%) cases of skin cancer and 38 (0.78%) internal cancers were detected [7]. Ingestion of inorganic arsenic in humans has been associated with an increased risk of nonmelanoma skin cancer and also to an increased risk of bladder, liver, and lung cancer. Even there is evidence of different mechanisms in the development of lung cancers through different exposure routes.EPA has classified inorganic arsenic as a Group A, human carcinogen [8-11].

Various studies were conducted to establish dose-response relationships between cancer risks and the concentration of inorganic arsenic naturally present in water supplies. Similar large population studies in an area of Taiwan with high arsenic levels in well water (170-800 micrograms/L) were used. It was estimated that at the current EPA standard of 50 micrograms/L, the lifetime risk of dying from cancer of the liver, lung, kidney, or bladder from drinking 1 L/day of water could be as high as 13 per 1000 persons. For average arsenic levels and water consumption patterns in the United States, the risk estimate was around 1/1000 [12].

Arsenic is not directly mutagenic, but there are evidences that it is genotoxic. The mechanism of genotoxic action of arsenic may result from generation of ROS, inhibition of DNA repair, and altered DNA methylation that may lead to genomic instability. Arsenic expresses its genotoxicity by inducing effects including deletion mutations, oxidative DNA damage, DNA strand breaks, sister chromatid exchanges, chromosomal aberrations, aneuploidy, and micronuclei. Arsenic related other effects of genotoxicity include gene amplification, transforming activity, and genomic instability. These genotoxic effects of arsenic are observed *in vitro* in mammalian cells and *in vivo* in laboratory animals and humans and researchers observed chromosomal aberrations in lymphocytes in workers exposed to arsenic. Trivalent arsenicals, both inorganic and organic, are more potent genotoxins than the pentavalent arsenicals. [13]. In spite of its incidental therapeutic properties, the International Agency for Research on Cancer (IARC) has classified arsenic as a carcinogen,for which there is sufficient epidemiological evidence to support a causal relationship between exposure and cancer. At present nine different possible modes of action of arsenic carcinogenesis are discussed: chromosomal aberrations, oxidative stress, altered DNA repair, altered DNA methylation patterns, altered growth factors secretion, enhanced cell proliferation, promotion or progression of tumor, gene amplification, and finally, suppression of p53 gene.

Hypothesis regarding the cause of cancer due to arsenic.

A scientific consensus has not yet been reached on the many suggested modes of arsenic carcinogenesis but there are some hypothesis relating to mechanism of carcinogenesis as stated below.

1. Oxidative stress: Oxidative stress is one of several proposed mechanisms of action for arsenic-induced toxicity and carcinogenesis [14]. Reactive oxygen and nitrogen species are generated by several potential mechanisms in cells, animals, and humans that are exposed to arsenic [15] and can alter cellular redox status by depleting thiols such as glutathione and by modulating thioredoxin reductase [16]. Oxidative DNA damage is observed in animals and humans exposed to arsenic [9, 10]. Also, reactive oxygen species are known to be able to alter signal transduction pathways like EGFR (Epidermal Growth Factor Receptor) signalling pathway, PI3K/AKT signalling pathway and the Nrf2-KEAP1 signalling pathway that regulate gene expression [14, 15]. Different oxygen concentrations and accumulation of iAs species, endogenous reducing agents, and ferritin, among others factors in different tissues leads to variation of mechanisms of iAs carcinogenicity in different tissues. As lungs are exposed to the highest oxygen tensions in the body, and DMA [III], and its derivates (including ROS) are excreted through the lung, so this organ is frequently affected by iAs-induced carcinogens [16]. Inorganic arsenicals change the expression of genes related to stress, which produce some proteins or activate enzymes, including: heme oxygenase, heat shock protein-60, -70 and –90, DNA damage inducible protein GADD 45 and DNA excision repair protein ERCC1.Down regulation of certain cytochrome P450 enzymes and activation of the c-Jun/AP-1 transcription complex occurred with arsenic treatments. Increases in caspase-1,TNF-alpha and the metal-responsive transcription factor MFT-1 is also evident. All these events are responsible for arsenic cytotoxicity in some types of cells, for example in the human liver cancer cells (HepG2). This effect is potentiated by atrazine. [17]

2. Mitochondrial Damage: Arsenic-associated mitochondrial dysfunction, mitochondrial DNA (mtDNA) depletion, and induction of mtDNA deletions may contribute to the carcinogenicity in humans. So mitochondria might be an important target of arsenic-induced genotoxicity. On the other hand, since mitochondria is a major source of intracellular ROS, arsenic-mediated disruption of its function can lead to an increase in intracellular ROS levels and subsequently, to an increased mutagenic potential, either directly or by decreasing DNA repair capacity . Relationships between mitochondria and arsenic-mediated effects are supported by observations such as suppression of arsenic-induced apoptosis in HeLa cells by the antioxidant action of N-acetyl-cysteine, which prevents mitochondrial membrane depolarization. Alternatively, arsenic can act directly through condensing mitochondrial matrix and opening of permeability transition pores [16].

3. Alteration of DNA methylation : Inhibition of activity of p53 human tumor suppressor gene leading to significant hypermethylation of p53 & p16 gene in As induced skin cancer. This hypermethylation is dose response dependent. p53 function in cell cycle arrest, apoptosis, inhibition of tumor growth and preservation of genetic stability having correlation with cancer cases in 50% of all cancers[18,19,20]. To determine the role of methylation in such carcinogenesis, the degree of methylation of p53 and p16 gene in DNA was studied from blood samples of people chronically exposed to arsenic and skin cancer subjects. Significant DNA hypermethylation of promoter region of p53 gene was observed in DNA of arsenic-exposed people compared to control subjects. This hypermethylation also showed a dose-response relationship. Further, hypermethylation of p53 gene was also observed in arsenic-induced skin cancer patients compared to subjects having skin cancer unrelated to arsenic, though not at significant level. However, a small subgroup of cases showed hypomethylation with high arsenic exposure. Significant hypermethylation of gene p16 was also observed in cases of arsenicosis exposed to high level of arsenic. In man, arsenic has the ability to alter DNA methylation patterns in gene p53 and p16, which are important in carcinogenesis [21].

4. Arsenic-induced epigenetic alterations.Arsenic biotransformation depletes SAM resulting in aberrant DNA methylation.Arsenic detoxification requires the use of S-Adenosyl methionine (SAM) as a methyl donor; consequently, arsenic-related epigenetic effects mainly derive from deprivation of the cellular pool of methyl (-CH3) groups. Although cellular levels of SAM itself are not likely affected, a high demand of SAM due to chronic arsenic exposure will affect the availability of the cellular pool of methyl groups. Since SAM is the major methyl donor for DNA-methyltransferases (DNMT), depletion of methyl groups can lead to global hypomethylation and changes in chromatin remodeling. Such epigenetic modifications have been shown to promote malignant transformation in a variety of cell types, including lung. Arsenic has been shown to induce global hypomethylation, as demonstrated by reduction in LINE-1 methylation and total 5-methyldeoxycytidine content in lymphoblastoid cells [15].

5. Mutation of p53 gene Mutation of p53 gene is often found in As exposed patients with pre carcinomas and carcinomas.Inactivation of the p53 tumor suppressor is a frequent event in tumorigenesis. In most cases, the p53 gene is mutated giving rise to a stable mutant protein whose accumulation is regarded as a hallmark of cancer cells. Mutant p53 proteins not only lose their tumor suppressive activities but often gain additional oncogenic functions that endow cells with growth and survival advantages [22].A study was conducted in an arsenic endemic area of Taiwan to study the role of p53 tumour suppressor gene in the carcinogenesis of arsenic-related skin cancers where tumour samples were collected from 23 patients with Bowen's disease, seven patients with basal cell carcinomas (BCC) and nine patients with squamous cell carcinomas (SCC). The result showed that p53 gene mutations were found in 39% of cases with Bowen's disease (9/23), 28.6% of cases with BCC (2/7) and 55.6% of cases with SCC (5/9) [23,24].

6. **Defective DNA repairand comutagenic effect** The mechanism of arsenite comutagenesis with alkylating agents is based on the reaction with DNA to form a variety of adducts, in which some favor primarily the base oxygens while the others favor the base nitrogens. These DNA adducts are excised by specific DNA glycosylases. Some investigators suggest that the absence of normal p53 functioning, along with increased positive growth signaling in the presence of DNA damage, may result in defective DNA repair and account for the comutagenic effect.[17]

7. Arsenic induces epithelial-to-mesenchymal transition: A study using human bronchial epithelial cells (HBEC) demonstrated that chronic arsenic exposure of P53-knock down cells induced malignant transformation accompanied by epithelial-to-mesenchymal transition (EMT) [15].

8. Induces chromosomal abnormalities including changes in structure and number of Chromosomes and sister chromatid exchanges. Inorganic As is known to damage chromosomes. Due to little evidence of covalent binding between iAs and DNA structures, it has been proposed that much of the DNA damage observed during iAs exposure is indirect, occurring mainly as a result of ROS induction which generates DNA adducts, DNA strand breaks, cross links, and chromosomal aberrations. Depending on which cell cycle phase exposure occurs, as a consequence DNA oxidation, iAs can result in gross chromosomal aberrations including DNA strand breaks [14].

To assess the risk from environmental and occupational exposure of arsenic, in vivo cytogenetic assays have been conducted in arsenicosis-endemic areas of the world using chromosomal aberrations (CA) and sister chromatid exchanges (SCE) as biomarkers in peripheral blood lymphocytes. In a study, conducted in arsenic-endemic villages of North 24 Parganas (district) of West Bengal, India from 1999 to 2003 a significant difference ($P < 0.01$) in the frequencies of CA and SCE between the cases and control group was observed. Presence of substantial chromosome damage in lymphocytes in the exposed population predicts an increased future carcinogenic risk by Arsenic [25].

9. Histone Modification. Histones proteins enable condensation of double-stranded supercoiled eukaryotic DNA into nucleosomes, which are made up of two copies each of H2A, H2B, H3, and H4 proteins. Arsenic compounds were also shown to induce malignant transformation of human nontumorigenic cell lines through changes to histone H3 acetylation, DNA promoter methylation, and decreases expression of the DBC1, FAM83A, ZSCAN12, and C1QTNF6 genes [26].

10. MicroRNAs :miRNAs are small, noncoding RNA species that orchestrate the expression of genes involved in many key aspects of cell biology. In humans, more than 1400 miRNAs have been identified to date (miRBase data base; Release 17, April 2011).An increasing number of studies show that arsenic exposure can alter miRNA expression levels in vitro and in vivo. Human lymphoblastoid cells exposed to sodium AsIII over six days showed altered expression of five miRNAs (hsa-miR-210, -22, -34a, -221, and -222) [27,28].

Arsenic toxicity can also be enhanced by other environmental carcinogens. For example, arsenic-exposed individuals with a history of smoking and chronic exposure to environments with high fertilizer use may be more susceptible to cancer-prone skin lesions than those without these risk factors, even at the same level of arsenic exposure. UV light can act as a carcinogen with Arsenic in a synergistic mode of action, leading to development of hyperkeratosis. Similar mode of action was also observed between development of skin lesions in men and high levels of arsenic (above 100 μg/L) and tobacco smoking.[28]

Conclusion

The exact molecular mechanism of arsenic induced carcinogenesis is still less understood. Both arsenite and its metabolites can have a variety of genotoxic effects, which may be mediated by oxidants or free radical species. All of these species also have effects on signalling pathways leading to proliferative responses. There are interesting differences in the activities of inorganic and organic species both in terms of target organ carcinogenicity and genotoxic and toxic mechanisms. A scientific consensus has not yet been reached on the many suggested modes of arsenic carcinogenesis that exist in the literature. These include modes that are predominately genotoxic (i.e., chromosomal abnormalities, oxidative stress, and gene amplification) vs. more nongenotoxic (i.e., altered growth factors, enhanced cell proliferation and promotion of carcinogenesis, and altered DNA repair). Likewise, the dose-response relationship at low arsenic concentrations for any of these suggested modes is not known.The complete contradiction between the epidemiological and experimental evidence suggests that arsenic compounds may act as cocarcinogens or comutagens (enhancing agents) rather than primary carcinogens or mutagens.

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