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Review Article

Pathophysiology of arsenic-induced adverse health effects

砷引致的不良健康影響的病理生理學

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Chronic exposure to arsenic is associated with cancers of lung, urinary bladder, kidney, liver and skin, as well as vascular diseases, infections, and neurological abnormalities. Arsenic has been declared as a class I carcinogen by the International Agency for Research on Cancer (IARC). Skin cancers are the most common arsenical cancers and usually herald the development of other internal cancers. Although the exact mechanisms of actions of arsenic inside the cells remain to be clarified, the histological changes in arsenical skin cancers and mechanistic studies suggest that aberrant differentiation, proliferation, abnormal apoptosis, dysregulated immune responses, and abnormal mitochondrial homeostasis contribute to the arsenic carcinogenesis. After a brief introduction to arsenic, this review summarises the potential mechanisms involved in the arsenic-induced adverse health effects. Such information may provide further clues to tackling the molecular mechanisms for arsenic carcinogenesis and other adverse health effects.

慢性砷暴露不止與肺癌、膀胱癌、腎癌、肝癌和皮膚癌，還與血管疾病、感染和神經系統異常有著關聯。砷被國際癌症研究機構宣佈爲第一類致癌物。皮膚癌是最常見的砷癌，通常較其他體內癌症早發生。雖然細胞內砷的確切作用機制仍有待闡明，但從砷的皮膚癌組織學變化和機制研究顯示了砷的致癌機轉建基於細胞異常分化、增殖、異常凋亡、免疫反應失調和線粒體平衡異常有關。在簡要介紹砷後，本綜述總結了涉及砷引起的不良健康影響的潛在機制。這些資訊可提供進一步線索來阻斷砷致癌機轉及其他不良健康影響的分子機制。

Keywords: Arsenic carcinogenesis, health hazards, skin cancer

關鍵詞：砷致癌機轉、健康危害、皮膚癌

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Introduction

Arsenic is one of the most common elements in the Earth's crust. Its name originates from the Greek name '*arsenikon*' for yellow pigment. Because of its ubiquitous nature in rocks, hundreds of millions of people in the world, including those in Bangladesh, West Bengal, and Mongolia are

exposed to arsenic through drinking deep well water contaminated with arsenic from strata and rocks. Furthermore, based on its position in the chemical Periodic table, arsenic has similar biophysical properties to the Group 15 elements that also include nitrogen and phosphorus, both of which are major biological elements in animal cells, such as structural and functional proteins, DNA, and RNA. Hence, arsenic tends to interact with the biological tissues and cells resulting in health adverse outcomes including cancers, vascular disease, neurological disease, and infections. On the other hand, arsenic itself has been used to treat certain cancers.

Source of human exposure

Humans may be exposed to arsenic through inhalation, drinking, and less commonly, skin absorption. The most common exposure route of arsenic is through drinking artesian water from deep wells that has been contaminated with arsenic diffused from the rocks into the underground water. Besides the common route of water contamination, in the industry, arsenic is also a common component used in the manufacturing of semiconductor devices, such as gallium arsenide. Arsenic and its compound, particularly the trioxide form, are also applied in the manufacturing of pesticides (lead hydrogen arsenate), herbicides (Agent Blue, sodium cacodylate), wood conservatives (chromated copper arsenate), and insecticides (monosodium methyl arsenate). Historically, ladies used arsenic-containing topical preparations to improve their facial complexion and took arsenic-containing vinegar and chalk to make their skin paler and white. In the past, arsenic was also used in the treatment of sleeping sickness, syphilis, tuberculosis, and skin diseases. Paradoxically, despite its notorious adverse health effects, because of the potent effect of arsenic to induce cell differentiation, arsenic has been approved by FDA to treat acute promyelocytic leukaemia refractory to conventional therapy.

Biological metabolism of arsenic

Inorganic arsenic exists in two chemical forms. Arsenite (AsIII) exists in the trivalent form whereas arsenate (AsV) exists in the pentavalent form. Arsenite is more toxic than arsenate. However, the toxicity order is reversed when the pH becomes acidic. After enteric absorption, inorganic arsenic is circulated to several organs, including the lungs, kidney, liver, and skin. During its transit from blood to tissues, arsenate is reduced to arsenite. In the liver, arsenic is methylated into mono-methylarsenic acid (MMA V), which is further reduced to monomethylarsonous acid (MMA III). A subsequent methylation reaction modifies MMA III to dimethylarsinic acid (DMA V).[1] When arsenic is obtained by the cell, arsenic is modified by the methyl group supplied by s-adenosylmethionine (SAM). Subsequent to methylation, inorganic arsenic becomes less genotoxic and is excreted readily in urine.[2]

The debate about safe level of arsenic in water

Numerous epidemiological studies indicated that arsenic induces cancers of the skin, lungs, liver, and urinary bladders, and central and peripheral vascular disease in a dose-dependent manner. Based on scientific evidence, mostly from epidemiological results in Taiwan,[3] the WHO lowered the previous maximal contaminant level (MCL) of arsenic from 50 ppb to 10 ppb for drinking water. Afterwards, the U.S. National Academy of Sciences supported lowering the MCL of arsenic in drinking water. Recently, there is increasing evidence that chronic exposure to arsenic at lower doses could also induce several health hazards,[4] such as neuropsychological dysfunction and foetal loss. The question of a minimum safe MCL and whether a safe MCL exists remains debatable.

Arsenic-induced adverse non-cancerous health effects

Central and peripheral vascular systems

Chronic exposure inorganic arsenic at high levels has been associated with ischaemic heart disease, cerebrovascular disease, and carotid atherosclerosis. Previous epidemiological studies showed that consumption of drinking water with high levels of arsenic (>100 μg/L) is associated with an increased risk for cardiovascular diseases. A cohort study showed that arsenic-induced QT abnormalities in ECG are associated with atherosclerotic diseases and predict long-term cardiovascular mortality in subjects with previous exposure to arsenic.[5] A recent study in Denmark showed that living in areas where the levels of arsenic higher than 10 mg/L is associated with an increased risk of myocardial infarction.[6] Peripheral vascular diseases are reported to be associated with arsenic exposure by drinking contaminated water. "Blackfoot disease", a folk name of the gangrenous skin vascular disease, was associated with arsenic exposure at high levels from drinking water in Taiwan. Similarly, a recent cohort study done in American Indians found that a mild to moderate exposure of arsenic is associated with decreased ankle brachial index (ABI), an index for peripheral vascular disease.[7] The mechanisms of how arsenic induces vascular diseases are not known, but arsenic may regulate angiogenesis via VEGF and NO production.[8] Individual susceptibility to the vascular occlusive disease may be regulated by the anti-endothelial IgG in the blood from patients exposed to arsenic.[9]

Neurological and neurodevelopmental toxicity

Arsenic is well known to induce neurological and behavioural abnormalities. In addition, it induces adverse health outcomes for neurodevelopment in children.

For high levels of arsenic, epidemiological studies from Bangladesh pointed to possible inverse associations with cognitive function, using arsenic level in urine or blood as exposure and verbal test scores at ages between 5-11 years as an indicator.[10] However, the overall evidence does not consistently show a causal dose-response relationship at low doses in North America.[11]

Infections

In both human and mice, arsenic leads to susceptibility to influenza A infection.[12] Epidemiological studies have shown an increased susceptibility to respiratory infections in infants of mothers exposed to arsenic.[13] Our recent prospective cohort study with thousands of subjects also showed that arsenic increases susceptibility to fungal infections in a dose dependent manner.[14] This susceptibility to infections in vulnerable populations may result from the aberrant immune responses and functional by arsenic. Arsenic differentially affects the activation, differentiation, and apoptosis in different cell components of the immune system.[15] In patients with arsenical cancers, the *in-vivo* delayed hypersensitivity response, a response involved in antigen presenting cells and T cells, is impaired.[16] Further discussions about aberrant immune responses are elaborated below.

Arsenic-induced cancers

Chronic exposure to arsenic leads to cancer development. Skin cancers usually herald other arsenical cancers of internal organs and they are among the most common type of arsenical cancers. Among the arsenical skin cancers, Bowen's disease, a form of carcinoma in-situ, is the most common type. Clinically, arsenic-induced Bowen's disease (As-BD) tends to affect multiple areas of the skin and many of them present in the non-sun exposed areas. As-BD is usually confined to the epidermis for several decades, though a few As-BD lesions may subsequently develop squamous cell carcinoma. Microscopically, As-BD is characterised by full layer epidermal dysplasia, individual dyskeratosis, epidermal acanthosis, and

moderate dermal infiltrates. These pathological changes are attributed to the pathophysiological mechanisms towards abnormal differentiation, apoptosis, and aberrant inflammation.

Abnormal differentiation

Induction of differentiation by arsenic are demonstrated by the fact that low doses of arsenic can induce complete remissions in patients with acute promyelocytic leukaemia, through the induction of differentiation and apoptosis in leukaemic cells. For the epidermal differentiation, our team has shown that p53, one of the critical cellular differentiation molecules, is mutated in the epidermis of As-BD.[17] Moreover, arsenic exposure is associated with G2/M cell cycle arrest and DNA aneuploidy, which is mediated by p53 dysfunction in both cultured keratinocytes and As-BD lesions.[18] The keratinocyte differentiation is accompanied by the transition of the cytokeratin subunits. Through 2-D electrophoresis from the tissue of arsenical cancers, our team showed there are progressive alterations of cytokeratin expression in the process of chronic arsenicism during the transformation from As-BD into invasive arsenical skin cancers.[19] It is interesting to note that energy demand and supply in the cell provide the bases of differentiation. In fact, we showed that DNA damage and mutations of mitochondria, the powerhouse of cell, are mediated by oxidative stress and coupled with the abnormal differentiation of epidermal keratinocytes in As-BD.[20] In addition to mitochondria, protein glycosylation of the cell membrane is involved in the cell differentiation. By wax physisorption kinetics and FTIR imaging, we were the first to show that arsenic regulates the prolongation of glycan residues of membrane glycoprotein through ATP production.[21]

Abnormal apoptosis

Individual apoptosis, as characterised by dyskeratosis microscopically, is a characteristic pathological change in As-BD. It may not be extensive but is clearly present in a scattered fashion in the epidermis of As-BD. Integrin β1, an important molecule located in the basolateral membrane of keratinocyte and important in the process of terminal differentiation and apoptosis, is defective in expression in As-BD.[22] We have shown that arsenic at high doses induces Fas/FasL mediated keratinocyte apoptosis associated with NF-κB and AP1 expression.[23]Clinically, As-BD differs from UV-induced skin cancers by its multiplicity and the occurrence in the non-sun exposed skin. Experimentally, I have shown that arsenic at low doses enhances UVB-induced keratinocyte apoptosis via suppression of Bcl-2 expression and stimulation of caspase-8 activity,[24] suggesting that the synergistic apoptotic effects induced by arsenic may explain the rarity of As-BD in sun-exposed skin.

Enhanced epidermal proliferation

In the tissue level, the enhanced proliferation of epidermal keratinocytes is reflected in the increased epidermal thickness in As-BD. In the cell level, specifically in keratinocytes, we found low doses of arsenic enhance cell proliferation while high doses of arsenic induce cell apoptosis.[24] The cell proliferation is associated with the defective expression of adrenergic receptors,[25] and increased production of IL-8 by keratinocytes. Notably, we showed that the enhanced cell proliferation is regulated by the increased mtTFA-mediated mitochondrial biogenesis, oxygen consumption, and respiratory complexes.[20] The incorporation of imbalanced oncogene/tumour suppressor gene into the mitochondrial-mediated epidermal differentiation could initiate the development of carcinogenesis.[26]

Carcinogenesis

The pathophysiology of how arsenic transforms epidermal keratinocytes remains unclear and may include abnormal proliferation, ROS, deficient DNA repair,[27] and chromosome abnormalities. The chromosome abnormalities, such as sister chromatid changes, have been found in several arsenical cancers and arsenic-treated cells.[28] We reported that arsenic acts specifically on p53 compromised cells to induce chromosome

abnormality, indicating the importance of DNA repair in the spindle assembly and the integrity of chromosome.[29] Reducing ROS using S-adenosyl-methionine actually prevents cells from arsenic-induced aneuploidy, one of the earliest detectable cellular events in the initiation of carcinogenesis.[30] DNA microarray and array CGH in the primary keratinocytes treated with arsenic allows the identification of a cluster of upregulated oncogenes.[27] However, further mechanistic studies are warranted.

Aberrant inflammation

Only 1-5% of people exposed to arsenic develop skin cancers after decades,[31] suggesting that host immune interactions may regulate the process of arsenic carcinogenesis. Patients with As-BD showed a reduction in contact hypersensitivity response (CHS), a cutaneous skin reaction that is provoked by the application of an initiator such as 2, 4-dinitrochlorobenzene (DNCB).[32] Arsenic was shown to activate AP-1 transcription factor by blocking the JNK phosphotase activity.[33] AP-1 is a critical factor in regulating FasL expression since the promoter region of human FasL gene contains an AP-1 binding site. We have reported that in keratinocytes, arsenic induces AP-1 and FasL expression, resulting in apoptosis via Fas/FasL signalling.[23] Furthermore, peripheral CD4+ cells from patients were less vulnerable to apoptosis due to impaired TNF-alpha/TNF-R1 pathway. However, once CD4+ cells infiltrate into the As-BD lesions, FasL from keratinocytes induces the selective CD4+ cell apoptosis.[34]This additional anti-tumour immune phenomenon in the cutaneous environment may explain the frequent occurrence of arsenical cancers in the skin.

In addition to the T cell apoptosis in As-BD, Langerhans cells (LC) are reduced in numbers in As-BD. There is a progressive decrease of LC in the following order: normal skin, normal appearing edge and arsenical skin cancers.[16] The dendritic processes of LC are lost in As-BD.[16] Treatment with DNCB, a potent sensitiser and hapten, augmented the therapeutic response of 5FU in Bowen's disease, suggesting that LC may regulate the disease process in Bowen's disease. In fact, our study showed that arsenic mobilises Langerhans cell migration and polarises Th1 responses in the animal study.[35] In the tissue level, STAT3-VEGF axis in keratinocytes inhibits dendritic cell migration in the microenvironment of As-BD,[36] indicating that cellular interactions between epidermal keratinocytes and dendritic cells play an important role in regulating the disease course of arsenical cancers.

Skin equivalent model

The lack of appropriate animal models for arsenic skin cancers and the disadvantage of a monolayer cultured keratinocyte model in the dynamic cellular interactions in arsenic carcinogenesis had led us to reconstruct an arsenic carcinogenesis three dimensional model that mimics the pathognomonic changes of As-BD at the tissue level in 10 days by a combination of primary keratinocytes, fibroblasts, and peripheral blood mononuclear cells (PBMCs).[37] This tissue model almost completely represents the epidermal thickening, dysplastic changes, and underlying inflammatory infiltrates in the skin of As-BD, allowing us to investigate the arsenic carcinogenesis at the tissue level with cell-to-cell interactions. Not only are the structural changes similar to that in As-BD, our skin equivalent model recreates the abnormal cell cycle and aneuploidy in As-BD. Previous skin equivalent models with immortal keratinocytes (but not primary keratinocytes) using 65 ppb (approximately 1 mM) of arsenic for two weeks induced proliferation but without dysplasia and dyskeratosis.[38] The necessity of incorporating the PBMCs in this model reveals that immune regulation is essential to the development of abnormal differentiation in As-BD and *in vitro* models. Using this model, we showed that arsenic initiated SUV39H2-mediated epigenetic modification of E2F1, which induced centrosome amplification in keratinocytes in two days and induced caspase-8-mediated apoptosis in 10 days.[37]

Animal models of cancers

Despite its well-known carcinogenicity and because of its weak mutagenicity, arsenic alone cannot promote neoplastic disease in classical single- or two-stage murine models.[39] This difference in susceptibility to cancers in humans vs rodents may result from the several log differences in the cell detoxification process. Arsenic hence may act as a promotor rather than the initiator in the carcinogenesis. Without a first hit, such as mutations in the oncogene in transgenic animals, it remains difficult to establish arsenical cancers, particularly in skin cancer. Brief maternal gestational exposure to inorganic arsenic could induce cancers in liver, lung, ovary and adrenal, but not skin cancers, in adult mice after promotional effects of postnatal phorbol ester exposure.[40] The paucity of suitable animal models further stresses the importance of our skin equivalent model in the study of arsenic carcinogenesis.

Conclusions

Arsenic results in many adverse health outcomes, including developmental abnormalities, cancers of different organs, vascular diseases, and infections. Although the exact biological mechanisms and the specific cellular binding elements of arsenic remain largely unknown, the aberrant immune responses, abnormal differentiations, dysregulated apoptosis, and mitochondrial abnormalities may help explain certain processes of arsenic-induced adverse health effects. Incorporation of genome wide analysis with hypothesis driven approaches, animal models, reconstructed skin models, and epidemiological studies may help to tackle the specific mechanisms of actions of arsenic in the animal cells and tissues.

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