

Mechanisms and Immune Dysregulation in Arsenic Skin Carcinogenesis

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ABSTRACT

Long-term exposure to arsenic is associated with cancers of lung, urinary bladder, kidney, liver and skin. Arsenic carcinogenesis might result from oxidative stress, altered growth factors, chromosomal abnormality, immune dysregulation, and aberrant epigenetic regulations. Bowen's disease (As-BD) is the most common form of arsenic-induces skin cancers and is characterized by chronicity, multiplicity, and predisposition in sun-spare skin. However, only about 1% of the population exposed to arsenic developed skin cancers, indicating the host immune response plays an important modulatory role in skin carcinogenesis. In this review, we review the pathomechanisms of arsenic skin carcinogenesis and the immune interactions. Arsenic affects innate and adaptive immune responses through CD4+ T cells, monocytes, macrophages, and Langerhans cells. In skin of As-BD, CD4+ T cells undergo selective and differential apoptosis via Fas-FasL interaction. Numbers and dendrites of Langerhans cells are reduced in As-BD lesions. There is a defective homeostasis and aberrant trafficking of Langerhans cells. Such information is essential to understand the molecular mechanism for arsenic carcinogenesis in both skin and in internal organs.

Keywords: Arsenic, Bowen's Disease, Skin Cancer, Innate Immunity, Langerhans Cells

1. Introduction

Arsenic is a ubiquitous element on the earth. People may expose to arsenic in several ways through drinking, inhalation, and direct skin contact. Drinking of water with arsenic remains the major route of human exposure [1], leading to development of cancers of skin, lungs, and liver in many countries, including Bangladesh, Taiwan, West Bengal of India, Chile, Mexico, and China [2]. Industrially, arsenic is used to generate paints and insecticides. Arsenide is also a critical constituent in semiconductors that is used for electronic chips and computers. In addition to its carcinogenic property, arsenic exposure is also associated with vascular diseases, including stroke, ischemic heart diseases, and peripheral vascular disease [3]. In contrast to its notoriously adverse health effects, arsenic has been used for treatment of lymphoma and leukemia and it still remains the drug of choice for acute promyelocytic leukemia.

It is estimated that around 10% of population exposed to arsenic will develop skin abnormalities, including variegated hyper-/hypo-pigmentations, arsenic keratosis, Bowen's disease, and invasive skin cancers. Only about 1% of exposed population develops skin cancers. Long-

term arsenic exposure results in impaired immunity in susceptible individuals, which may account for the development of cancers in vulnerable individuals. Personal genetic variability, immune system, and the interaction of both might differ, leading to differential susceptibility and cancer immunity in the process of arsenic carcinogenesis.

Based on its oxidative status, arsenic exists in two inorganic chemical forms. Arsenite (AsIII) is a trivalent form while arsenate (AsV) is a pentavalent form. Trivalent arsenite is about 2-10 times more toxic than pentavalent arsenate. In tissues, arsenic is methylated by methyl group supplied by s-adenosylmethionine (SAM). Compared to inorganic forms, the methylated metabolites are less genotoxic [4] and are excreted more quickly in urine [5,6]. After ingestion, inorganic arsenic is obtained by erythrocytes and then distributed systemically to multiple organs, including lungs, liver, and skin [7,8]. In transit from blood to tissues, arsenate is reduced to arsenite. In the liver, arsenic is methylated into mono-methylarsenic acid (MMA V), which can be further reduced to monomethyl arsonous acid (MMA III). A further methylation reaction modifies MMA III to dimethylarsinic acid (DMA V) [9]. In the process of methylation

process, several reactive oxygen species (ROS) are generated [10,11]. WHO recommends safe groundwater arsenic concentration up to 50 µg/L but proposes a provisional arsenic standard at 10 µg/L [12]. The government regulation for arsenic contents in drinking water depends on countries but the standard generally is more stringent, for example, up to 10 g/L in Taiwan, Japan, and U.S.

One of the most systematized epidemiological studies for health effects of arsenic is conducted in Taiwan and it has led the basis of many epidemiological risk assessments over the last 40 years worldwide [6]. In the past decades, we have been investigating on the arsenic carcinogenesis with particular focus on skin not only it is readily accessible but also it might provide a model of chemical carcinogenesis and immune interaction. This review discusses the pathomechanisms of arsenic skin carcinogenesis with special focus on the interactions of immune system and arsenic-induced cancers.

2. Proposed Mechanisms of Action in Arsenical Carcinogenesis

Although arsenic is documented as a weak mutagen, the International Agency for Research on Cancer (IARC) has categorized arsenic as a human carcinogen [13]. The mechanism of arsenic carcinogenesis remains uncertain. However, oxidative stress, chromosomal abnormality and altered growth factors may contribute to arsenic carcinogenesis [9,14,15]. It has been suggested that arsenic might act as a co-carcinogen or a promoter in carcinogenesis by mode of action studies [16]. However, recent studies showed perinatal maternal exposure to arsenic results in spontaneous cancer developments in off springs, suggesting that arsenic might also act in the initiation in two stage chemical carcinogenesis [17]. The effects of arsenic exposure in early life development include epigenetic effects, via DNA hypomethylation, endocrine effects (most classes of steroid hormones), immune suppression, neurotoxicity, and interaction with enzymes critical for fetal development and programming [18].

Arsenic tends to bind to the thio-group (-SH) of proteins, targeting regulatory or structural proteins [19,20]. Approximately 200 proteins could be targeted by the bindings and interactions of arsenic-thio group [21]. Among these proteins, the proto-oncogene c-Jun is well investigated. By binding to thio-groups, arsenic can block Jun N-terminal kinase (JNK) phosphatase activity, resulting in an over activation of JNK, which activates proto-oncogene c-Jun, inducing c-Jun/c-Fos (AP-1)-mediated gene upregulations [22-24]. These upregulated genes include cell cycle regulation, and apoptotic signaling, all of which are strongly linked to arsenic carcinogenesis. Moreover, we have shown there is a quantitative impairment of phosphorylation of keratin 1 and keratin 2 in the process of chronic arsenism, suggesting that keratins, containing plenty of thio groups, are the cellular

targets of arsenic [25]. Through oxidative stress induced by arsenic, genomic mutations might develop, leading to initiation in carcinogenesis. Several lines of compelling evidences revealed the oxidative DNA damages in the target organ of arsenic-exposed animals and humans. In fact, clinical studies in arsenic-induced Bowen's disease (As-BD) uncovered the correlations between increased 8-OHdG levels and the arsenic concentration in the lesional skin [26], indicating the importance of oxidative stress in arsenical skin carcinogenesis. Mechanistically, *in vitro* studies showed low concentrations of arsenic (< 5 µM) can generate ROS, which in term increases the transcription of the nuclear factor kappa B (NF-KB) [24,27-30], that eventually promotes cell proliferation [31].

The second possible mechanism in arsenic carcinogenesis is through genomic instability and chromosome abnormalities. Arsenic is repeatedly reported to induce chromosome abnormalities and aberrant sister chromatid exchanges [32-34]. In human fibroblasts and CHO cells, arsenic induced chromosome abnormalities and induces sister chromatid exchanges at high and low concentrations, respectively [35,36]. These chromosomal abnormalities were highly associated with arsenic-induced oxidative DNA damages [26,37] and might link to arsenic carcinogenesis. Arsenite exposure induced micronuclei (MN) formation [38], which indicates cellular response to DNA damages. An increased frequency of MN was also detected in exfoliated bladder cells, buccal cells, and lymphocytes from arsenic-exposed humans [39-41]. Chien et al showed that arsenite results in tumorigenicity of HaCaT cells in nude mice by increased frequency of MN [42].

The third possible etiological factor leading to arsenic carcinogenesis is through abnormal DNA repair and epigenetic regulations. Arsenic was able to inhibit DNA repair systems in the steps of nucleotide excision repair [43-45], DNA ligase III activity, DNA base excision repair [46,47] and DNA strand break rejoining [48]. Many key DNA repair regulatory proteins were inhibited by arsenic, including DNA ligase I, DNA ligase II, DNA ligase III, DNA polymerase β, 6-methyl-guanine-DNA methyltransferase, and poly (ADP-ribose) polymerase (PARP) [14,47,49]. Agents messing up with those DNA repair proteins can lead to genetic mutations. Along with its effect in DNA repair, arsenic also potentiated the mutagenicity of other carcinogenic factors (such as UV, X-rays, and chemical agent) [50-53]. Moreover, arsenic affected global histone methylation and also DNA methylation, indicating that arsenic also affects epigenome machinery to influence gene expressions involved in carcinogenesis [54]. In most cases, arsenic induced DNA hypomethylation, probably through the inhibition of DNA methyltransferases [55]. However, it has been reported there is a hypermethylation in promoter of gene

p53 and p16 in people exposed to arsenic [56]. Arsenic at very low concentrations (below 1 μ M) can inhibit both DNMT1 and DNMT3A in HaCaT cells [57]. Indeed, recent studies showed perinatal exposure to arsenic results in DNA methylation globally in GC-rich (guanine and cytosine) regions [58].

3. Hophysiology of Arsenic Skin Cancers

Arsenic tends to accumulate in ectodermal tissues including the skin, hair and nails. Skin lesions are most common and most accessible in arsenic-induced pathologies [59-61]. Variegated hyper- and hypo-pigmentation and punctate palmar-plantar hyperkeratosis are all hallmarks of chronic arsenic exposure. The hyperkeratosis may appear as a regular thickening or as discrete nodules. A dose relationship has been found for the arsenic concentrations in well water and the occurrences of hyperpigmentation and hyperkeratosis among the people living in the endemic areas [62,63]. Furthermore, Tseng *et al.* found a dose-response relationship between arsenic levels in drinking water and skin cancers by a comprehensive epidemiological survey five decades ago [62]. Among skin cancers, the most common arsenic-induced skin cancers are Bowen's disease, followed by basal cell carcinoma and squamous cell carcinoma [62].

Bowen's disease is a carcinoma *in situ* of the skin resulting from UV or arsenical exposure [2,59,62,64]. Clinically, arsenic-induced Bowen's disease is different from classical (UV-induced) Bowen's disease by its multiplicity and its propensity in sun-spare skins [2,62,65]. There are abnormal cellular proliferation and apoptosis in arsenic-induced Bowen's disease (As-BD) as presented with increased epidermal thickness and individual dyskeratotic keratinocytes, respectively [2,59]. After decades of development, As-BD can penetrate through basement membrane and become invasive squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and combined forms of the skin cancer [2,62, 66,67]. Individuals with As-BD are considered a risk for development of malignancies in the lung and urinary bladder [67-70]. It was estimated that As-BD started within one decade, invasive skin cancer after scores of years [71], and lung cancers after 30 years following the chronic arsenic exposure [66]. Therefore, the characteristic clinical and histopathological features of As-BD serve as a model to understand the different stages of chemical carcinogenesis.

Microscopically, p53 protein was greatly expressed in As-BD as compared with non-arsenical BD [72-74]. Arsenic can induce p53 accumulation via an ATM-dependent pathway [75,76]. The over-expressed p53 in As-BD lesions was a mutant form [77,78], of which most of the p53 mutation sites are located on exon 5 and exon 8. Furthermore, the mutation types of p53 gene mutation in As-BD were different from those in UV-related skin

cancers [79], indicating the differences in the pathogenesis of As-BD and UV-induced Bowen's disease. Although the connection between p53 mutation and arsenic exposure was not clear, the effect of arsenic on p53-related pathways was well recognized. Studies have shown that arsenic exposure resulted in G2/M cell cycle arrest and DNA aneuploidy, both of which are regulated by p53 [80-82].

There are coexisting hyperproliferative and dyskeratotic (apoptotic) keratinocytes in As-BD lesions [31]. The effects of arsenic on keratinocytes depend on the concentrations of arsenic. At lower concentrations ($\leq 1 \mu$ M), arsenic induced keratinocyte proliferation and enhanced both NF-KB and AP-1 activity [31]. The proliferation is dependent on the mitochondrial biogenesis (manuscript in preparation). At higher concentrations ($\geq 5 \mu$ M), arsenic induced keratinocyte apoptosis by Fas/Fas ligand (FasL) pathway. Since promoter regions of FasL contained binding sites for AP-1, arsenic-activated Fas/FasL signaling may associate with arsenic-induced AP-1 activation [83-85].

4. Arsenic Influences Immune Regulation and Immune Responses

Intact and functional immunity is important in tumor surveillance of skin cancers. This is evidenced by the fact that patients with renal transplant and HIV infection have higher risk to develop skin cancers. Depends on cell type, tissue, and species, arsenic influenced immune system and its responses differentially in many aspects [86-88]. Arsenic may provoke immune responses by inhibition of regulatory or suppressor cells. For example, arsenic affected function of regulatory T lymphocytes in humans [89]. Arsenic *in vitro* enhanced immune response by deleting the precursors of suppressor T cells from normal spleen cells [90].

Arsenic affected many different kinds of cells in the immune system, leading to dysregulated immune responses. *In utero* exposure to arsenic impaired child thymic development and enhanced morbidity to respiratory infection [91]. The increase in respiratory infection by influenza was also shown in arsenic-exposed mice [92] and was associated with alternation of immune response genes in the lungs, such as IL-1beta, IL-1R and a number of toll-like receptors [93]. In addition to its adverse effects on the infection, arsenic can alter the systemic immunity. In patients with As-BD, there was a markedly reduced in contact hypersensitivity (CHS) reaction to DNCB in the skin [94], accompanied with reduced spontaneous and phytohemagglutinin(PHA)-induced IFN-gamma and TNF-alpha productions. The decreased CHS response to DNFB was also shown in the mice fed with arsenic-containing water [95]. We reported that arsenic induces CD4+ cells apoptosis by affecting the autocrine TNF-alpha loop [96,97]. Furthermore, there was a de-

crease in numbers of T cells and the expression of IL-2R on them from patients with As-BD [94,98]. We also showed that T cells from arsenic-exposed people were anergy to PHA stimulation but were exaggerated to arsenic treatment [96]. A recent study showed T cell proliferation to Concanavalin A (Con A) was markedly reduced in people exposed to arsenic and there was a parallel decrease in the levels of TNF-alpha, IFN-gamma, IL-2, IL-10, IL-5, and IL-4 [99]. In arsenic-exposed children, arsenic burden was also associated with a reduced proliferative response to PHA stimulation. CD4+ cells were selectively decreased with CD8+, B, and NK cells remained unaffected in proportion. IL-2 but not IL-4, IL-10, or IFN-gamma was decreased in PHA-activated peripheral blood mononuclear cells [100]. In mice, T cell-dependent humoral immune response was extremely sensitive to suppression by arsenic and assessment of humoral immune responses should be considered in evaluating the health effects of arsenic containing agents [101]. Collectively, arsenic inhibits systemic T cell activation and proliferation via TNF-alpha axis. Macrophages were also potential targets of arsenic in humans [102]. Macrophages from people exposed to arsenic showed loss of cell adhesion capacity, decreased in NO production, and impaired phagocytic ability [103]. Monocytes from children exposed to arsenic produced less superoxide anion and nitric oxide[104]. Arsenic also affected phagocytic ability of neutrophils and degranulation via Syk activation[105].

In the cell level, arsenic has dual effects on cell proliferation in lymphocytes. Arsenic compounds at low concentrations enhanced DNA synthesis in PHA-stimulated proliferation of human lymphocytes, whereas arsenic at higher concentrations inhibited cellular proliferation and induced apoptosis [96,106,107]. As occurred in fibroblasts and CHO cells, arsenic has been shown to induce aneuploidy [108,109], sister chromatid changes [110-112], other chromosomal abnormalities [32] in lymphocytes. Mechanistically, arsenic influenced T cell receptor activation by increasing basal and induced phosphorylation of Lck and Fyn (first kinase associated to TCR complex) [113]. Metabolites of arsenic can also interfere with cell division via tubulin disruption, leading to aneuploidy [114]. A major cellular source of methyl group, S-adenosyl-L-methionine can reverse micronucleus formation induced by sodium arsenite and other cytoskeleton disrupting agents in cultured human lymphocytes [115].

In contrast to the scarce studies studying effects of arsenic on normal lymphocytes, there are a lot of studies investigating arsenic induced apoptosis in cells from lymphoma or leukemia, which coincides with the use of arsenic trioxide in acute promyelocytic anemia and multiple myeloma. Arsenic induced normalization of differentiation of promyelocytes in acute promyelocytic leukemia, of which arsenic remains the drug of choice.

Phosphoinositide 3-kinase/Akt inhibition increased arsenic trioxide-induced apoptosis of acute promyelocytic and T-cell leukemia [116]. Arsenic induced apoptosis through activation of Bax in hematopoietic cells [117]. Furthermore, arsenic trioxide (As) and interferon (IFN)-alpha coordinately induced cell cycle arrest and apoptosis that is modulated by bcl-2, bax, p53, and NF-kappaB [118,119]. Thus, the effects of arsenic on T cells development may act as a double-sided sword and appear to be cell-specific and concentration-dependent.

5. Altered Skin Associated Lymphoid Tissue in Arsenic-Induced Bowen's Disease

In patients with As-BD, there was a markedly reduced in contact hypersensitivity reaction to DNCB in the skin [94], accompanied with reduced spontaneous and PHA-induced IFN-gamma as well as TNF-alpha production. Both GM-CSF and TGF-alpha were found in the epidermis at clinically normal sites within 10 weeks after arsenic treatment *in vivo* and also from arsenic-treated keratinocytes [120-121]. Arsenic can enhance keratinocytes to express TGF- α , GM-CSF, IL-6 and IL-8 [120-122]. These growth factors and cytokines expression may induce cutaneous tumorigenesis via AP-1 and NF-KB regulation [123]. Although a clear link has been established for impaired T cell proliferation by arsenic, the causative role of impaired T cell activation and predilection of T cell apoptosis with the cutaneous carcinogenesis has seldom discussed. There was a decreased proportion of peripheral CD4+ cells in the peripheral blood from arsenic-exposed humans as compared to that from control subjects; the CD4+ cells from As-BD patients were less vulnerable to arsenic-induced apoptosis, due to defected TNF-R1 expression. Those residual CD4+ cells were less susceptible to arsenic-induced apoptosis. However, when those CD4+ cells infiltrated into the As-BD lesions, FasL from As-BD in the epidermis induced selective CD4+ cell apoptosis (**Figure 1**). This additional tumor evasion phenomenon present in the cutaneous environment provided a reasonable explanation for persisting nature of arsenic cancers in the skin despite the moderate dermal inflammatory infiltrates [124].

It is evident that cell-mediated immunity is depressed in patients with arsenic-induced Bowen's disease [94]. Langerhans cells (LC) are known to be one of the professional antigen presenting cells for T lymphocytes. They play a pivotal role in the presentation of tumor-associated antigens. Others and we have reported there was a progressive decrease in numbers of Langerhans cell in the order of normal skin, normal appearing skin in As-BD, and As-BD lesion. [125-127]. However, how arsenic alters LC migration and polarizes Th responses remains unknown. Using an epicutaneous protein sensitization model in mice, we have found that arsenic exposure enhanced LC migration to draining lymph nodes, and

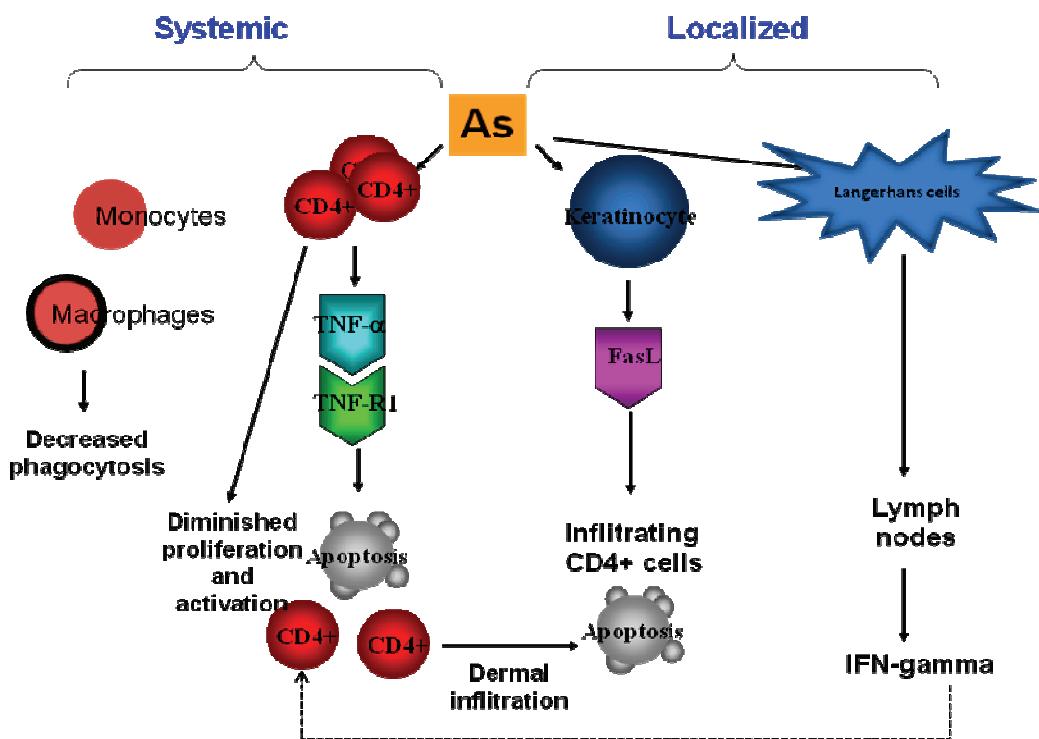


Figure 1. Proposed altered systemic and cutaneous immune responses in arsenic carcinogenesis. Arsenic inhibits T cell proliferation, induces T cell apoptosis, decreases monocyte/macrophage phagocytosis in the systemic circulation. In the skin, CD4+ T cells are vulnerable to apoptosis by FasL from epidermal keratinocytes. Langerhans cell is decreased in numbers in the epidermis and its trafficking to lymph nodes is enhanced

that enhanced LC migration to draining lymph nodes, and that the chronic nature of As-BD might result from enhanced Th1 responses with dysregulated LC trafficking (manuscript in preparation).

6. Conclusions

Bowen's disease is the most common form of arsenic-induced skin cancers. As-BD is characterized by its chronicity, multiplicity and predisposition in sun-spare skin. Patients with As-BD are often defected in their cellular immunity (**Figure 1**). CD4+ T cells are quantitatively reduced in people with As-BD. CD4+ T cells from arsenic-exposed individuals are less susceptible to apoptosis due to an impaired TNF-alpha-TNFR loop. However, once CD4+ T cells gain access the As-BD lesions, FasL from epidermal keratinocytes in As-BD induces selective CD4+ cell apoptosis. Notably, there is also a decrease in numbers and aberrant trafficking of Langerhans cells in As-BD. Thus, arsenic differentially affects systemic and localized immunity in arsenic skin carcinogenesis. In chemical carcinogenesis, the attribute of chemical immunology should be considered.

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