**Arsenic Carcinogenesis and Immune Dysregulation**

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**Abstract:** Arsenic, a metal ubiquitously distributed in the environment, remains an important global health threat. Drinking arsenic-contaminated water is the major route of human exposure. Exposure to arsenic contributes to several malignancies, including skin, respiratory, hepatobiliary, and urinary systems. Cutaneous lesions are the important manifestations in long-term arsenic exposure and arsenical skin malignancies usually herald the development of other internal cancers, making arsenic carcinogenesis a good model to investigate the progression of chemical carcinogenesis. In fact, only a portion of arsenic-exposed humans eventually develop malignancies, likely attributed to the arsenic-impaired immunity in susceptible individuals. Currently the exact pathophysiology of arsenic carcinogenesis remains elusive, although increased reactive oxidative stresses, aberrant immune regulations, and chromosome abnormalities with uncontrolled cell growth might be involved. This review discusses how arsenic dysregulates innate and adaptive immunities in the systemic circulation, along with in the target organs. These findings offer evidences for illustrating the mechanism of arsenic-related immune dysregulation in the progression of carcinogenesis and these may help explain the nature of multiple and recurrent clinical lesions in arsenic skin cancers.

**Keywords:** Arsenic; carcinogenesis; Bowen's disease; drinking water

1. Introduction

Arsenic is one of the common metals. Due to its ubiquitous nature, it poses a significant global health threat. Its name derives from “arsenikon”, the Greek name of yellow pigment. Based on the periodic table of chemistry, arsenic has been classified in the same group as nitrogen and phosphorus. In fact, all of them are essential chemical elements in cells [1]. The typical physical-chemical specific feature of arsenic to interact with biological tissue may result in its various and significant biological effects. Exposure to arsenic results in cancers of several organ systems, such as skin, respiratory, hepatobiliary, and urinary systems. In addition, arsenic exposure may contribute to the occurrence of multiple atherosclerotic vascular illness, such as cerebrovascular event, myocardial infarction, and peripheral vascular diseases [2]. On the other hand, arsenic does have some benefits in treating specific diseases, such as lymphoma and leukemia. For example, arsenic is the drug of choice in patients of acute promyelocytic leukemia due to its biological effects in blast cell differentiation and immune cell activation [3].

Environmental exposure to arsenic can result from natural or anthropogenic routes. It enters human body through several ways, such as oral ingestion, respiration or skin absorption. Oral ingestion with arsenic-contaminated water is the most common source [4]. To date, there remain more than 100 million people exposed to arsenic at levels higher than 50 ug/L through drinking water or via industrial sources [5]. For example, several decades ago in Taiwan, the residents of southern and western coastal areas often drank arsenic-contaminated groundwater and developed arsenical...
DNA base excision repair, and DNA strand break rejoining oxidative DNA damage and mutations by the impairment of nucleotide excision repair, a role in drives individuals form of oxidative DNA damage, First, 8 growth although increa... to arsenic leads to profound biological effects in many organ system and it occurs by the first manifestation of arsenic toxicity. In addition, about 10% of individuals exposed to arsenic cause cutaneous diseases, such as hyperpigmentation, Bowen’s disease, and arsenic keratosis. On the other hand, only around 1% of the individuals develop squamous cell carcinoma, basal cell carcinoma, or other cutaneous malignancies. This phenomenon with individual immune dysregulation might explain why only a certain proportion of susceptible individuals develop adverse health effects.

Bowen’s disease, as squamous cell carcinoma in situ, is the most common skin cancers induced by arsenic. Clinically, typical Bowen’s disease is mainly associated with sun exposure and tends to be solitary, whereas arsenic-induced Bowen’s disease (As-BD) is distributed in sun-protected skin and tends to be multifocal. However, there is no morphological discrepancy between classical and arsenic-induced Bowen’s disease in their pathological features. Variegated hyperpigmentation and punctate keratosis on palms and soles are the most significant clinical characteristic of arsenic-induced skin lesions. These clinical features are often used as diagnostic clues to indicate chronic arsenic exposure. In addition, mucous membrane melanosis and conjunctiva congestion are minor dermatological presentations caused by arsenic exposure.

Arsenic contributes to the formation of two important categories of non-melanoma skin cancers (NMSC), i.e., basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). A high prevalence of NMSCs due to chronic arsenic exposure was noticed in the southwest of Taiwan, where the entire prevalence rate for cutaneous malignancies was 10.6/1000. Additionally, drinking arsenic contaminated water also contributes to arsenic-induced skin malignancies in Bangladesh, China, and India. The association between inorganic arsenic in drinking water and miscellaneous malignancies has been well-confirmed at high exposure–concentration. However, the epidemiologic evidence has suggested a threshold for the connection between inorganic arsenic exposure and malignancies. Based on the epidemiologic evidence mainly generated from the field study in Taiwan, in 2001, United States Environmental Protection Agency (USEPA) and World Health Organization (WHO) produced a more strict criterion for arsenic level in drinking water, by decreasing the acceptable arsenic level in drinking water from 50 to 10 µg/L.

3. Pathophysiological mechanisms of arsenic carcinogenesis

The precise pathophysiological mechanism understanding arsenic carcinogenesis is still unclear, although increasing of reactive oxidative stresses and chromosome dysfunction, with uncontrollable growth aberrant immune developments, might be possible mechanism of arsenic carcinogenesis. First, 8-Hydroxy-2-deoxyguanosine (8-OHdG), a form of reactive oxygen species (ROS) and a major form of oxidative DNA damage, was obtained from urine and skin tissue of arsenic exposed individuals. Low level of arsenic generate ROS, which increases the transcription of NF-kB and drives cell proliferation. In addition, oxidative damages and mitochondrial mutations might play a role in arsenical skin malignancies. Arsenic affects DNA repair machinery, which leads to oxidative DNA damage and mutations by the impairment of nucleotide excision repair, DNA ligase, DNA base excision repair, and DNA strand break rejoining. Rather than the unrecoverable
DNA damage, arsenic also affects a bunch of epigenetic regulations. For example, Chanda et al. showed that DNA hypermethylation of the critical promoter region of the p53 gene and p16 gene was present in the DNA from arsenic-exposed individuals [25]. Zhou et al. suggested a possible mechanism by which arsenic-related carcinogenesis via the dysregulated histone methylations that are involved in gene silencing and activating marks [26]. Liao et al. showed that un-methylation at -56 and -54 bp Cpg in the cyclin D1 promoter presents as a predictor for invasive malignancies from carcinoma in situ in individuals with arsenical cancers [27].

In As-BD lesions, keratinocytes (KC) are the significant biological target. Abnormal cell proliferation and dysregulated energy homeostasis of keratinocytes became important in the mechanism and development of As-BD lesions. Lee et al. reported that arsenic can regulate the prolongation of glycan residues of the membrane glycoprotein, which may be crucial in carcinogenesis of arsenic [1]. Besides, mtTFA up-regulation, increased mitochondrial biogenesis, and augmented mitochondrial functions induce cell proliferation in arsenic-induced skin cancers, indicating that mitochondria become a significant part in the induction of keratinocyte proliferation [22]. Lee et al. further showed that oxidative destruction and mutations in mtDNA might be contributed to arsenical skin malignancy in mitochondrial biogenesis [21]. Moreover, the expressions of cytokeratin 14 (CK14) and the N-terminal truncated p63 isofrom (ΔNp63; proliferation regulator) were enhanced in As-BD, which contribute to abnormal keratinocyte growth in arsenical skin malignancies [28].

4. Immune response in arsenic skin cancers and its involvement in arsenic carcinogenesis

As discussed earlier, not all of the humans exposed to arsenic develop cutaneous malignancies, suggesting that dysregulated immunity caused by arsenic in susceptible individuals contributes to the development of arsenical cancers.

4.1. Overview of skin immunity

The human immune system include two different functional groups: innate and adaptive immunity [29]. These two classifications have distinct characteristics of recognition receptors and differ in the speed at which they respond to a possible threat to the host. The innate immune systems include macrophages and dendritic cells (DCs), which lead to a rapid but not lasting response against the pathogens. On the other hand, T and B lymphocytes were included in the adaptive immune system, which bear particular antigen receptors encoded by rearranged genes of T cell receptors and immunoglobulins. Adaptive immunity develops more slowly compared to that of innate immunity. It can create and sustain memory of immune reaction; thus, it can also provide a rapid and robust reaction facing immunologic challenge. Either the innate or adaptive immune can be categories as cellular or humoral immunity that represents the different of antibodies or immune cells, respectively.

4.2. Arsenic-induced dysregulated immune responses

As-BD, the most common carcinoma in situ due to chronic arsenic exposure, is featured with multiple and recurrent cutaneous manifestations. Besides, it may cause impairment of immunity in susceptible patients [27]. In mice, the production of immunoglobulins, proliferation of T lymphocyte, phagocytosis of macrophages and their nitric oxide release ability were impaired in arsenic-exposed mice [11]. In zebrafish, Nayak et al. demonstrated that arsenic suppresses the overall innate immune system at an acceptable arsenic concentration in drinking water [30]. Monocytes and macrophages are also potential targets of arsenic. Lemarie et al. illustrated that an inorganic trivalent form of noncytotoxic level of arsenic trioxide (As2O3), significantly impairs proliferation of human blood monocyte-derived macrophages in vitro. It was also reported that arsenic induces rapid cell rounding and loss of actin reorganization, mostly via the Ras homolog gene family member A-associated kinase pathway [31]. Other studies have also reported that As2O3 significantly deteriorates the releasing of IL-12 and IL-23 from activated individual dendritic cells and decrease the activation of T-helper (Th)
cells [32]. Moreover, an impaired macrophage function and delayed-type hypersensitivity response were also presented in arsenic-exposed individuals with skin manifestations [33].

In mice, transplacental studies of arsenic revealed that the offspring had a dose-dependent effect of the number of lung, liver, ovary, and adrenal tumors in adulthood [34]. Maternal exposure of arsenic augment oxidative stress in the placenta. In addition, pro-inflammatory cytokines IL-1 , TNF- , and IFN- were increased through the enhancement of oxidative stress [35]. Lymphocyte function deteriorated and may contribute to smaller size of thymic and decreasing function in newborns and infants [36]. In children, it is reported that arsenic exposure decreases the Th1 cytokine levels in plasma and increases total concentrations of IgG and IgE in plasma [37]. All of these immune deregulations could associated with the enhanced risk of immune dysregulation and infections in arsenic-exposed children. In adults, chronic arsenic exposure may lead to the deterioration of macrophage ability and impairment of peripheral blood polymorphonuclear leukocytes [38].

In patients with arsenical cancers, impaired immunity does not only occur systemically, but also in locally in As-BD skin lesions. Our group has presented that arsenic cause selective CD4+ cell apoptosis in the peripheral blood. Once the surviving CD4+ cells are infiltrated into the local skin, the soluble FasL from the keratinocytes trigger tumor-released selective CD4+ cell apoptosis because an increased Fas expression in CD4+ cells. Moreover, we have also reported that vascular endothelial growth factor (VEGF) from cancer cells contributed to dysfunction of Langerhans cell (LC) and impaired antigen presentation along with T-cell activation in As-BD lesions [32]. Abnormal immune activation of LC and CD4+ cells provides a plausible mechanism for the impaired tumor surveillance in As-BD (Figure 1).

![Figure 1](image_url)

**Figure 1.** Aberrant immune activation of Langerhans cells (LCs) and CD4+ cells provides a reliable illustration for the impairment of anti-tumor surveillance in As-BD. In As-BD lesions, keratinocytes (KC) are the significant target. Dysregulated energy homeostasis and aberrant cell proliferation present as crucial role in arsenic carcinogenesis.

5. Conclusion

Long-term arsenic exposure contributes to dysfunction of immunity in susceptible people. As-BD is illustrated microscopically by increasing of cell apoptosis, keratinocyte proliferation, and whole-layered disorintatated, all of which necessitate the involvement of mitochondria which associated with energy generation, ROS production, cell proliferation, DNA damage and mutations, and immune responses. Above presentations illustrate the mechanism of arsenic-related immune...
impairment in the prior step of carcinogenesis and explain the nature of multiple and recrudescent clinical lesions in arsenic skin cancers.

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**References**


