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Review

Arsenic-induced Cancers: A Review with Special Reference to Gene, Environment and Their Interaction

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Chronic exposure to the toxic metalloid arsenic, either through occupational or environmental route results in the development of a plethora of dermatological as well as non-dermatological health effects, multi-organ cancers being the most severe ones. Several epidemiological studies have reported the occurrence of different types of cancers in populations exposed chronically to arsenic from different corners of the globe, but the spectrum of symptoms and severity vary widely. Several genetic and environmental factors might play an important causal role for such observed differences, including genetic polymorphisms, dietary habits and socio-economic status of the population. Unfortunately, the paradoxical nature of this carcinogen makes the use of animal model systems unsuitable, since they do not reflect the exact *in vivo* condition of arsenic exposure in human beings. Hence, in this present review, we have attempted to collate the isolated pieces of information available in existing literature depicting the various forms of arsenic-induced cancers, variations and etiology thereof. We have attempted to depict the entire spectrum of carcinogenic outcomes of chronic arsenic exposure and the interactions among several components like, genes (polymorphisms and mutations), environmental factors and dietary factors in the process. The literature reviews are primarily based on the human beings (*in vivo*), but to understand the underlying mechanism, we have also collated the information based on cell line models, and animal models where human data is scanty or unavailable. Thus, here we present a comprehensive review on the current state of research in the field of arsenic-induced cancer and explore the underlying mechanism of arsenic-induced carcinogenicity, along with relevant historical perspective.

Key words: arsenic, diet, gene-environment interaction, cancer

Introduction

Arsenic has been used by mankind since ages immemorial both for constructive as well as destructive purposes. Besides it widespread use in traditional medicine, arsenic has often been the poison of choice for silent killing in case of several cases of royal feuds.

However, in the present days, it is the chronic form of arsenic toxicity, rather than the willful acute poisoning, which plagues the world. Occurrences of chronic arsenic toxicity from different sources have been reported from 70 countries spanning all the 5 continents and renders an imponderable 150 million individuals at risk (1,2). In fact, arsenic has been assigned the status of group I carcinogen by IARC (3) in human beings and ranks 1 on the ATSDR-CERCA priority list of hazardous substances (4).

Chronic exposure to arsenic for long time periods can occur through both occupational as well as environmental routes. In many instances, chronic exposure to this deadly toxicant is a result of working (or from industrial wastes) in mining and smelting industries (5–9). Occupational exposure to arsenic can also occur from working at or near several other kinds of factories where arsenic is used as a raw material or generated as a sludge or waste as in glass factories (10,11), semiconductor factories (12–17), power plants (18,19) and so on. This may also stem from being in constant touch with arsenical pesticides (20–26). However, in majority of the cases, the exposure is environmental in origin, either through drinking of groundwater contaminated from geogenic sources (27–38) or burning of arsenic rich coal (39,40).

Whatever be the source of chronic exposure to arsenic, the results are nearly always detrimental in the extreme. Chronic arsenic exposure leads to the development of classical skin lesions like raindrop pigementation, palmo-plantar hyperkeratosis, hypopigmentation. In addition, arsenic exposure has also been proved to give rise to a plethora of non-dermatological disease outcomes including peripheral neuropathy, conjunctivitis, respiratory problems, liver enlargements and opportunistic infections (41–45). However, the most dreaded outcome of chronic arsenic exposure are undoubtedly

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the multi-organ cancer induced by this toxicant. Since the first reports associating arsenic exposure with cancerous outcomes in 1887 (46), numerous epidemiological studies have proved beyond doubt that chronic arsenic exposure (be it environmental or occupational) gives rise to a wide variety of cancers, including those of skin and also of internal organs like lungs, liver, urinary bladder and kidney. Interestingly, arsenic is regarded as a ''paradoxical carcinogen'' because of its ability to induce cancer in human beings on its own, but not in any other animal model. This makes the study of arsenic-induced carcinogenesis particularly difficult and cumbersome. Most of the data regarding arsenic-induced carcinogenesis are derived from epidemiological studies. Although there are a few reviews reflecting the role of arsenic in specific cancers, there is none to our knowledge, which looks at arsenic exposure with respect to the development of cancers as a whole (including both internal and external cancers). Also, in spite of multifarious studies being performed to elucidate the role of several genes and environmental factors in arsenic susceptibility and carcinogenicity, there has been no adding up of all those work yet which could lead to the spelling out of meaningful conclusions with respect to carcinogenicity of arsenic. Hence, in the present text, we aim to present data from a wide variety of studies to show that arsenic and its metabolites induce a wide variety of cancers in human beings and then to highlight on the role of gene-environment interactions, especially diet and methylation in arsenic-induced cancers.

Arsenic-induced Skin Cancers

Skin is the major site of arsenic toxicity. Prolonged exposure to arsenic manifests itself in the form of several well characterized skin lesions including both non-malignant and malignant forms. These different types of skin cancers, ranging from Bowen's disease to highly metastasizing squamous cell carcinoma, are however, not exclusive to arsenic exposure and may occur under several conditions even in absence of arsenic exposure. In the present section we will review the different types of skin cancers induced by arsenic exposure.

Bowen's disease: Bowen's disease (BD), first described by the American dermatologist Dr. J. T. Bowen in 1912, is an early and mild form of *in situ* carcinoma. It is characterized by reddish undulated skin patches with irregular edges and distinct demarcation lines and usually occurs in sun covered areas in case of arsenic exposure. The epidermis exhibits a striking disorganization, with loss of normal cell polarity and disruption of normal progressive maturation of the epidermal cells and vacuolization of cells are common (47). That arsenic ingestion might lead to BD was suggested as early as 1961 by Graham *et al*. (48). It had also been reported by several other groups such as Imamura et al (49) and Yeh *et al*. (50,51). Arsenic-induced BD has been reported sporadically from several populations including Japanese (49,52–55), Japanese-American population in Hawaii (56), Thai (57), Taiwan (58,59), Finlandnish (60), Turkey (61,62), Korea (63,64), West Bengal, India (65–67), Nepal (68) and South Africa (69).

At the genetic level, arsenic-induced BD (As-BD) is characterized by high levels of genomic instability like most other cancers and exhibit enhanced induction of both chromosomal aberrations (66) as well as micronuclei (67) and also significantly higher sister chromatid exchange and replicative index (70). Interestingly, most of the chromosomal aberrations induced are of chromosome type, i.e., involves both strands of a chromosome, whereas, the incidence of chromatid type of aberrations are similar to that of arsenic-induced non-cancerous skin lesion patients (66). Chromosome type aberrations are extremely potent in activating the protooncogenes and/or suppression of tumor suppressor genes and thus are harbingers of carcinogenic outcomes, and the similar findings are encountered in case of As-BD patients. This point is further illustrated by the fact that considerable number of As-BD patients has a wide range of unique *p53* mutations (in target tissues), mostly in exons 5 and 8 (71). Generation of reactive oxygen species (ROS) is expected to play a significant role in the etiology of As-BD as seen from the elevated levels of 8-hydroxy-2′-deoxyguanosine in the bowen's tissue.

As-BD is different from non-arsenical BD in having unique histology. Studies using immunostaining technique reveal that Langerhans cells are significantly decreased in As-BD along with loss of dendrites compared to adjacent normal skin from the same patients (72,73). Again keratin 16 (marker for hyperproliferation of skin cells) was also found to be highly expressed in the basal and suprabasal cell layers of Bowen's tissue of As-BD patients, but not in case of non-arsenic BD patients (74). Keratin 6 expression was also found to be altered in case of As-BD (75). Additionally, at the molecular level, pathogenesis of As-BD was also found to be different from non-arsenical BD in terms of p53 expression. Enhanced p53 expression was found to be necessary for proliferative potential in case of As-BD (59). Also, the early dysplastic cells of As-BD showed overexpression of Bcl2 compared to normal skin tissue (76). Immunological characterization of As-BD shows that there might be an enhanced recruitment of helper T cells to the site of tumor (73). It is commonly observed that As-BD patients exhibit both cutaneous and systemic immune dysfunctions (77). Studies revealed that As-BD patients had significantly elevated $CD4_+$ cells in the cancerous tissues but significantly decreased in the lymphocytes, along with concomitant induction of Fas expression in $CD4_+$ cells (77). Furthermore, As-BD patients were found to have subnormal cell-mediated

immunity, due to impairment of IL2 receptor expression in lymphocytes via the tumor necrosis factor receptor 1 signaling pathway (78,79).

Basal cell carcinoma: Besides being the most common of all human cancers, basal cell carcinoma (BCC) is also a very common outcome of chronic arsenic exposure. Sporadic BCC occurs predominantly in sun exposed areas of the body, whereas, arsenic-induced BCC is found mostly in the sun covered trunk parts (80) and are usually multiple in number (81). Although, under normal circumstances, fair skinned individuals are more prone to develop BCC, incidences of arsenic-induced BCC have been reported from several countries of the world, encompassing both fair skinned and dark skinned populations. Development of multiple BCC has been reported in arsenic exposed individuals from Canada (82), Oregon, USA (83), Spain (84), China (73), Taiwan (73), Singapore (76,85,86), Australia (87,88), West Bengal, India (45,89), New Hampshire, USA (90), Argentina (91) etc.

BCC is characterized by tumor of basaloma cells of epithelial origin and is non-invasive in nature. Histologically, arsenic-induced BCC and BCC of other origin are similar and consist of transformed basaloma cells with large nucleus and poorly differentiated cytoplasm and are usually associated with elongation of epidermis into the dermal layer (80). This is also associated with decrease in the number of Langerhans cells and disruption of the Langerhans cell dendrites (73). Biochemical analyses showed that at the molecular level, BCC is characterized by a heightened expression of cytokeratins K6, K16 and K17 and a total absence of K1 (75). As in the case of As-BD, BCC also showed elevated expression of p53 and Bcl2. Additionally, Ki-67 was also found to be overexpressed in case of BCC (71,76) compared to normal skin tissue. However, in a study by Castren *et al.* (60) it was shown that mutations in *p53* are not required for this overexpression in case of BCC. Contradictory results were obtained in another study from Taiwan; it was found that almost 30% of the BCC tissues had *p53* mutations, mostly in exons 5 and 8, and these mutations were different from those encountered in case of UV-related skin cancers (71). Interestingly, the level of p53 expression was significantly lower in arsenic-induced BCC tissue when compared to BCC tissue of non-arsenical origin, perhaps due to hypermethylation (87). The risk of development of arsenic-induced BCC has been shown to be genetically modulated as well. In a study on arsenic-exposed population from Europe, XRCC3 codon 241 T variant was proved to confer elevated protection against the development of BCC, whereas, NBS1 codon 185 CC genotype imparted heightened risk of BCC development in men only (92). In another study, the risk of development of BCC was found to be depressed if an individual had at least one A allele at codon 23 of *XPA* gene and at least one Asp allele at codon 312 of *XPD* gene (93).

Squamous cell carcinoma: Squamous cell carcinoma (SCC) is the severest form of skin cancer caused by chronic arsenic ingestion. It is the only invasive form of skin cancer brought about by arsenic exposure which can metastasize and have lethal outcomes. Arsenic-induced SCC can arise *de novo* or from pre-existing BD, and usually develop at the extremities of the body. Unlike sporadic SCC, arsenic-induced SCC often develops at sun protected areas of the body. That prolonged arsenic exposure could lead to the development of SCC was speculated as early as 1948 (94). Since then, occurrences of SCC in cases of chronic arsenic exposure has been reported from several areas of the globe including Canada (82), Oregon, USA (83), Sweden (95), Taiwan (71,75,96), Singapore (76,85,86), Turkey (61), France (97), China (98), West Bengal, India (45), New Hampshire, USA (93), etc. SCC usually appears as small papule at the early stage which, in the later stages might often become crusty and ulcerated (99). It is basically a malignancy of the surface epidermal cells, which gets transformed into poorly differentiated elongated mass of epidermal cells, proliferate, invading the underlying dermal layers and at an advanced stage metastasize into other organs. SCC is characterized by considerable decrease in the number of Langerhans cells as also disruption of the Langerhans cell dendrites and an elevated recruitment of T helper cells to the tumor infiltrates (73). Histologically, there is no difference between arsenic-induced SCC and sporadic SCC (100).

At the biochemical level, SCC is characterized by overexpression of cytokeratins K6, K16 and K17 similar to that in BCC. In addition there is a progressive impairment of K1 and K2 phosphorylation, which is thought to play a key role in the carcinogenic outcome (75). Again, like in BCC, there is also overexpression of p53, Bcl2 and Ki67 in case of SCC (76). This result is also supported by the fact that in a study from Taiwan (71), it was shown that 44% of the arsenic-induced SCC tumor samples had novel *p53* mutations. However, in another study, contrasting results were obtained and p53 overexpression was shown to be a non-requisite step in the pathogenesis of SCC (59). Also, no *p53* mutations were found in SCC tissues from two arsenic-exposed individuals in a study by Castren *et al.* (60), although overexpression of p53 protein was detected, which supports the view that tissue specific *p53* mutations are perhaps not important as far as SCC development is concerned. Single nucleotide polymorphisms in the DNA repair pathway genes were however, shown to be associated with conferring protection to SCC development upon arsenic exposure in a New Hampshire population. Individuals with at least one A allele of XPA codon 23 and those with a combination of at least one

Asn allele at codon 312 and at least one Gln allele at codon 751 of XPD were shown to have significantly lesser risk of development of arsenic-induced SCC compared to those having the wild genotypes (93). The process of SCC development upon chronic arsenic exposure may involve the activation of Nrf2 and subsequent upregulation of MMP-9, keratin-1, keratin-9, involucrin and loricrin expression, as shown by studies on arsenic transformed HaCaT cell line and animal studies (101). Aberrant expression of several cytokeratin genes, including CK1, CK13 and CK15 were also found to be operative during malignant transformation of HaCaT cell line by chronic arsenic treatment (102).

Arsenic-induced Non-dermatological Cancers

Although skin lesions are considered to be the hallmarks of arsenic toxicity, yet, the fact that chronic exposure to this deadly toxicant leads to the development of several varieties of internal cancers is now widely accepted. Several epidemiological studies over the last fifty years and more have repeatedly linked chronic arsenic exposure to malignancies of internal organs, especially lungs, liver and bladder. This section of the review will summarize the literature exploring the relationship between arsenic exposure and non-dermatological cancerous outcomes.

Lung cancer: Although arsenic exposure has long been speculated to be causal to lung cancer, debate regarding its actual role and importance in etiology had been a long lasting one (103). By the middle of the 1970s, a plethora of epidemiological studies were conducted in different parts of the world, which yielded unequivocal results and established firmly the causal role of occupational arsenic exposure towards the development of lung cancer and elevated mortality thereof (104–106). Similar results were obtained from other subsequent studies (107–119). Furthermore, it has been demonstrated that increased lung cancer risk due to chronic arsenic exposure is independent of the exposure route; exposure via ingestion and inhalation leading to similar increment in lung cancer predisposition in the population (120). Several studies have explored the potential synergistic/interactive effect of smoking and arsenic exposure towards in induction of lung cancer. Most of these studies have shown that smokers, exposed chronically to arsenic have a very high risk of developing lung cancer (108,113,121–125). Additionally, it has also been demonstrated that smoking can affect lung cancer propensity in arsenic exposure status, depending upon the GST gene polymorphic status of the individual (125). Chance of development of lung cancer is further increased to a great extent by early childhood or *in utero* exposure to inorganic arsenic (126).

The role of arsenic exposure in lung cancer etiology is not clearly understood. Some evidences indicate that the length of exposure, rather than the intensity might be more important in lung carcinogenesis (107) and that arsenic might play an important role in the later stages of lung cancer development, although, a possibility of its involvement in the early stages was not ruled out (127). The basic mechanism by which arsenic induces carcinogenic outcomes in lung cells seems to be via the generation of reactive oxygen species (ROS). Studies utilizing cultured lung epithelial cells showed significant increase ROS biomarkers. There was also a significant increment in the expression of gamma-glutamylcysteine synthetase (γ-GCS) on arsenic exposure with concomitant increase in the expression of c-fos, c-jun and in DNA binding and transactivation efficacy of AP-1, perhaps in a NF-κB dependant manner (128). The validity of these observations are further strengthened by a later study which demonstrated that cultured human bronchial epithelial cells, BEAS-2B, when exposed to low concentration sodium arsenite, resulted in enhanced cell growth and cyclin D1 expression, mediated by p52-Bcl3 complex formation (129). This induction of ROS in the cellular milieu is hypothesized to be responsible for DNA damage in the form of DNA strand breaks, and formation of DNA-protein crosslinks as demonstrated by using human fetal lung fibroblast cells (130–131). There are some evidences from rodent model which demonstrate that chronic arsenic exposure might also interfere with the methylation status of certain genes and bring about lung cancer (132), although it is yet to be validated in human system. Recent evidences show that DNA losses at chromosomes 1q21.1, 7p22.3, 9q12, and 19q13.31 are frequently associated with arsenic-induced lung tumors (133).

Bladder cancer: Bladder cancer has been associated with chronic arsenic exposure for quite some time. The first report came out as early as 1986, when the results of an epidemiological retrospective study carried out in arsenic endemic region of Taiwan demonstrated that incidence of bladder cancer is significantly associated with ingestion of arsenic laced water (29) and was soon confirmed by another study in 1988 (134). Soon a plethora of studies were conducted in different parts of the world, exploring the relationship between incidence of bladder cancer and chronic arsenic exposure, and the results were unequivocal (111,135–142).

Immunohistopathological studies showed that arsenic-induced bladder tumors were pathobiologically and prognostically identical to non-arsenical bladder tumors (143). At the cytological level, it was found that level of arsenic exposure was directly correlated with the induction of chromosomal instability and that tumors from arsenic exposed individuals might behave much more aggressively than bladder tumors of non-exposed individuals (144,145). There are also some evidences which show that males are more prone to arsenic-in-

duced bladder cancer than females, irrespective of the smoking status (146). Studies on cell line have provided convincing evidence that inorganic arsenic exposure leads to a dose dependant increase of cells in the S phase along with reduction in cell proliferation and hampered DNA replication. This deviation from normal cell cycle was brought about by temporal alterations in the expression of p53 and p21 and their failure to control downstream Cdk2-cyclin E activity (147). It was also shown that Bcl2 and c-fos might be important players in the induction of arsenic-induced bladder cancer, but not for that of non-arsenical bladder cancers (148). Arsenic methylation status of individuals was also found to be associated with the propensity of developing bladder cancers as the ones excreting maximum amount of monomethyl arsenous acid (MMA) were found to be at greatest risk (149). Similar results were obtained from another study which showed that individuals with a high primary methylation index had a higher risk of developing bladder cancer (150). Further studies on human bladder cell lines demonstrated that chronic exposure to MMA leads to hyperproliferation and concomitant reduction in doubling time followed by anchorage independent growth and consequent tumorigenicty (151,152). It was also shown that this MMA-induced transformation was brought about by a complex interplay of several intricately interwoven pathways, including external signal regulated kinase, phosphoinositide 3-kinase, cyclooxygenase 1and cyclooxygenase 2 (153). Again, level of cytokines IL-1, IL-6 and IL-8 were found to be increased in case of chronic arsenic exposure in the same cell line (UROtsa) and was demonstrated to be important from malignant transformation following exposure (154). All these effects are perhaps brought about by the generation of ROS and subsequent lipid peroxidation, protein carbonylation and oxidative DNA damage by trivalent arsenicals (155). The involvement of ROS in the process was further demonstrated by the strong correlation between bladder cancer status and induction of urinary 8-hydroxydeoxyguanosine (156). Epigenetic mechanisms also play an important part in the etiology of arsenic-induced bladder cancer as the promoter hypermethylation of death associated protein kinase (DAPK) gene was shown to be instrumental in the process (157).

Liver cancer: Liver being the seat of arsenic metabolism retains inorganic as also methylated forms of arsenic perhaps for the longest time period inside the body and is thus an ideal target for arsenic-induced carcinogenesis. It has been well documented for a long time that there is a strong association between chronic arsenic ingestion and induction of liver cancer. Literature survey shows that as early as 1968, ingestion of arsenic containing Fowler's solution (used as a medicine) for prolonged periods had been demonstrated to give rise to hemangioendothelial sarcoma of liver (158). Soon after, it was found out that chronic arsenic exposure (be it from medicinal or environmental) could also give rise to angiosarcoma of the liver (159–162). These sporadic observations necessitated large scale well designed epidemiological studies to link liver cancer incidence with chronic arsenic intake. Several studies were conducted in different parts of the world and bear testimony to this association (29,30,80,109,110,141,163–165).

The mechanisms by which chronic exposure to arsenic brings about malignant transformation in the liver tissue are difficult to study in human beings. Consequently, most of our current ideas are based on experiments carried out in rodent models using unrealistically high doses of arsenic like 85 ppm (166), which are not to be found under normal ambient conditions in the nature. Hence, the results obtained from such studies are subject to close scrutiny as far as carcinogenesis in human liver is concerned. However, a few studies have been carried out in exposed human liver tissues and human liver cell lines, which could be more reliable in elucidating the role of arsenic exposure to such carcinogenic outcomes. In one study, using transriptomic technique on biopsy samples from liver tissues from arsenic exposed individuals, it was shown that transcription of around 60 genes are aberrantly altered compared to unexposed controls. These include genes encoding for cell-cycle regulation and proliferation, the apoptosis-related genes, the DNA damage related genes, and the genes encoding for cellular regulators and growth factors (167). Perhaps the most potent mechanism involved in such arsenic induced malignant changes in hepatocytes is the generation of oxidative stress and consequent oxidative DNA damage as visualized by studies on HepG2 cell line (168).

Kidney cancer: Several epidemiological studies have demonstrated the association of chronic arsenic intake with heightened incidence of kidney cancer. Dose response relationship between induction of kidney cancer in both exposed males and females were shown in Taiwan population in 1989 (30). The results were corroborated from similar studies on chronically exposed population from Japan (54), Taiwan (109,110,164,169), Chile (137) and India (170).

Study regarding the mechanism of arsenic-induced kidney carcinogenesis in human system is almost nonexistent and the meager amount of evidence we have is all based on studies in non-human mammalian systems. It has been shown that chronic exposure to arsenic leads to the expression of several stress proteins in the kidney (171) and that mitochondria might be the major target in kidney carcinogenesis owing to the oxidative stress generated by chronic arsenic exposure. It was further shown that human embryonic kidney cell line when treated with low dose of inorganic trivalent arsenic leads

to aberrant alteration in the expression of a plethora of genes including those involved in stress response, proto-oncogene, signaling molecules, transcription factors, chemokine receptors and proteolytic enzymes, leading to complex cellular injury (172).

Role of Diet in Arsenic Carcinogenicity

Of the several probable environmental factors that might have an impact on arsenic toxicity, susceptibility and carcinogenicity, the role of diet is perhaps the most important. Several studies have probed into different aspects of diet on arsenic toxicity and the results show beyond a trace of doubt that nutritional status of the individual often plays a key role in determining the degree of proneness to the toxic effects of chronic arsenic exposure. Malnutrition was demonstrably associated with a higher prevalence of arsenic-induced skin cancer (173). Again, fasting was shown to have a profound effect on arsenic metabolism and speciation as a significantly higher amount of methylarsonate was found to be excreted in the urine of fasting individuals (174). In fact, the interaction of arsenic exposure and diet can act at two different stages as has been elegantly summarized in a review by Vahter (175); viz., by modulating arsenic-induced oxidative stress and by modulating arsenic metabolism. Epidemiological studies have been conducted which shows that dietary factors, especially those involved in one-carbon metabolism, such as folate, methionine and homocysteine are important modulators of arsenic methylation, toxicity and carcinogenicity (176–178). Presence of these factors in diet helps in alleviating the toxic effects or arsenic exposure. Folate has been shown to increase arsenic-induced genomic DNA methylation in peripheral blood leucocytes in exposed population (179). Interestingly and anomalously, however, in one study, it was demonstrated that the arsenic methylation pattern was normal in pregnant woman from arsenic exposed population in Bangladesh, in spite of the prevalent malnutrition (180).

Generation of reactive oxygen species (ROS) is considered to be one of the most potent mechanisms for arsenic-induced toxicity and carcinogenesis (reviewed in 181,182). Hence, it is expected that a diet rich in antioxidants would be helpful in combating the toxic and carcinogenic effects or chronic arsenic exposure. Several antioxidative agents have been tried out to modulate the toxic effects of arsenic exposure, although, most of the studies have used rodent models. However, only a few studies have been conducted using human cell lines and human subjects and the results show that antioxidative agents are effective in alleviating arsenic toxicity. Vitamin A could alleviate the genotoxic effects of arsenic exposure in peripheral blood lymphocytes (183,184). Ascorbic acid treatment was shown to protect HL66 and U266 cells for arsenic-induced toxicity as measured by cell viability, colony formation and apoptosis assays (185). Similarly, treatment with plant flavonoids silymarin and quercetin were found to reduce arsenic-induced heat shock protein 70 kDa expression, lipid peroxidation, and gamma-glutamyl-transpeptidase activity, which are the hallmarks of arsenic-induced oxidative stress (186). On the other hand, natural anthraquinone derivatives can enhance the cytotoxic effects of arsenic as seen on a study using human esophageal carcinoma derived cell line EC/CHUK1 (187). Aqueous extract of garlic reduced intracellular reactive oxygen species (ROS) level in human malignant melanoma cells (A375), human keratinocyte cells (HaCaT) and in cultured human normal dermal fibroblast cells and consequently could attenuate arsenic-induced cytotoxicity (188). Similar alleviating effects were found for other antioxidants including black tea polyphenols (189), curcumin (190,191), folate (192), melatonin (193), plasma alpha tocopherol (194) etc.

Selenium plays a special role in arsenic toxicity and susceptibility; the two metals show an antagonistic behavior in the body. Selenium was shown to have protective effects against arsenic-induced clastogenicity in cultured human lymphocytes (195). These results were further corroborated by a study on smelter workers exposed chronically to arsenic, where, the chromosomal aberration rate of cultured lymphocytes was lowered about 46.1% after treatment with selenium 150 g/d for 21 days (196). Such observations have been reinforced by epidemiological studies. Nail selenium content of individuals chronically exposed to arsenic was inversely associated with arsenic-induced OGG1 expression, which is a hallmark of oxidative stress (197). In addition, it was also found that at any given arsenic exposure level, the risk of premalignant skin lesions was consistently greater among participants with blood selenium lower than the average level (198). The mechanisms for such mutual detoxification are not perfectly understood although, it has been hypothesized that arsenic and selenium increase the biliary excretion of each other and consequent excretion from the system (reviewed in 199). Also, it has been shown that low selenium status is associated with retention of higher amount of inorganic arsenic in the body and a lower biotransformation into dimethylarsinic acid (200).

Conclusion

Thus, to sum up, chronic exposure to arsenic in human beings leads to a host of different types of dermatological and non-dermatological cancers. The individual susceptibility to such cancers are however controlled by a plethora of several low penetrant genes, mutations and polymorphisms thereof and their complex interplay with several environmental factors, notable of them being the dietary factors, which modulate arsenic

biotransformation and the oxidative stress induced by inorganic arsenic and its methylated metabolites.

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