Biological Trace Element Research (2022) 200:988–1001
https://doi.org/10.1007/s12011-021-02719-w

Arsenic and Human Health: Genotoxicity, Epigenomic Effects, and Cancer Signaling

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Received: 9 February 2021 / Accepted: 11 April 2021 / Published online: 16 April 2021

Abstract

Arsenic is a well-known element because of its toxicity. Humans as well as plants and animals are negatively affected by its exposure. Some countries suffer from high levels of arsenic in their tap water and soils, which is considered a primary arsenic-linked risk factor for living beings. Humans generally get exposed to arsenic by contaminated drinking waters, resulting in many health problems, ranging from cancer to skin diseases. On the other hand, the FDA-certified drug arsenic trioxide provides solutions for various diseases, including several types of cancers. This issue emphasizes the importance of speciation of the metalloid elements in terms of impacts on health. When species get exposed to arsenic, it affects the cells altering their involvement. It can lead to abnormalities in inflammatory mechanisms and the immune system which contribute to the negative impacts generated on the body. The poisoning originating from arsenic gives rise to various biological signs on the body which can be useful for the diagnosis. It is important to find true biomarkers for the detection of arsenic poisoning. In view of its application in medicine and biology, studies on understanding the biological activity of arsenic have increased. In this review, we aim at summarizing the current state of knowledge of arsenic and the mechanism behind its toxicity including genotoxicity, oxidative insults, epigenomic changes, and alterations in cellular signaling.

Keywords Arsenic · Cancer · Cell signaling · Genotoxicity · Human health

Introduction

Arsenic is a toxic element that ranks 20th in the earth's crust, 14th in seawater, and 12th in the human body in terms of abundance [1–4]. This element can easily enter the ecological cycle through factors, such as dust, rainwater, open waters such as rivers and ponds, and groundwater [3, 5–7]. In general, its entrance to our environments in the biosphere is through geological and anthropogenic (human activities). It can also be transferred to soil and aquatic ecosystems through various biological resources (biogenic) rich in this element [3, 8, 9]. The volcanoes, hot springs, and geysers are natural sources of

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arsenic contamination [9, 10]. Mining, ore dressing, and smelting of non-ferrous metals; production of arsenic and its compounds; petroleum and chemical industries; pesticides, beer, table salt, tap water, paints, pigments, cosmetics, glass, and mirror manufacture; fungicides, insecticides, treated wood, and contaminated food; dyestuff and the tanning industry are major anthropogenic sources of its contamination [3, 11].

Initially, this element spreads with air, food chain, and both surface and ground waters, and then it enters the human body. All biodiversity, especially plants and animals, which constitute important structural components of an ecosystem, get exposed to the toxicity of this element. Especially the pollution in groundwater poses a serious risk for humans worldwide [3, 9, 12–18]. It is also utilized for mining processes. Miners are exposed to this metalloid because of their occupation [19]. People living near mining areas are also at risk due to mining-associated pollution [20, 21].

Some countries suffer from high levels of arsenic (>10 μg/L) in their tap water and soil that is considered a primary arsenic-linked risk factor for various health problems [20]. Approximately 150 million people in more than 70 countries are at risk of arsenic contamination; especially Argentina, Bangladesh, Cambodia, Chile, China, Ghana, Hungary, India, Mexico, Nepal, New Zealand, the Philippines, Taiwan, the USA, and Vietnam [11, 22, 23]. Recently, large amounts of arsenic poisoning have become a major socio-economic and health crisis, especially in South and Southeast Asian countries (affecting over 110 million people) [3, 24, 25]. A famous instance is Bangladesh mass poisoning, where 77 million people are face-to-face with arsenic chronically via highly arsenic polluted drinking waters [26, 27]. Health issues originating from arsenic may not be observed immediately; the consequences may appear 40 years after the exposure stops [28].

There are various paths for humans and animals to face the arsenic pollution; the primary route is heavily arsenic polluted drinking water, which is correlated with diverse health issues (Fig. 1), such as neural, physiological, reproductive, cardiovascular, renal, hepatic, and skin-associated disorders [29]. Exposure to arsenic toxicity in humans can also occur through ingestion, breathing, skin contact, and also genetically, although there is a much smaller source route than normal [30, 31]. It has been reported that the toxicity level on health effects is generally associated with the chemical arsenic type, the time of exposure, and the level of the dose. However, long-term exposure is the cause of many diseases and negative health problems [32, 33].

Arsenic acts on many events inside the human body such as the production of growth factors, the functionality of cell cycle checkpoint elements, apoptosis, DNA repairing, and DNA methylation, immune-related actions, and ROS balance. Changes triggered by arsenic significantly influence the progression of diseases like cancer, diabetes, and cardiovascular disorders [34]. The mechanism of arsenic species functioning is complex and several factors affect the function of arsenicals in the cell covering valence state, the extent of arsenic methylation, electrostatic interplays with the active sites of prominent cellular elements, and pharmacokinetics [35]. Methyl ligation is accounted as the primary biotransformation route for inorganic arsenic species [36]. The metalloid is also known for its ability to trigger epigenetic abnormalities via dysregulation of microRNAs, in addition to alteration of global methylation [37] and histone modifications [38].

Arsenic has mutagenic, genotoxic, and carcinogenic characteristics [39, 40]. It affects DNA by creating DNA adducts and cross-links between DNA and proteins, which are then cut out from DNA and therefore translated into breaks on DNA [41]. The genotoxic potential of this metalloid is primarily based on its capability to create ROS [42]. When coupled with the reduction in the capacity of DNA repairs, arsenic triggers ROS formation leading to negative effects on DNA which creates observed genotoxic effects in humans [43, 44]. The carcinogenicity of arsenic originates from its mutagenicity and its ability to give rise to glucogenesis [45, 46].

In high doses, the metalloid can induce apoptosis. Molecular mechanisms behind arsenic-triggered apoptosis include depolarization of the mitochondrial membrane, formation of cytochrome-C, functioning of caspases, and fragmentation of genetic material [47]. On the way going to apoptosis, arsenic mediates activation of p38, JNK, and caspase-3 depending on the dose of arsenic the cell gets exposed to [48].

Arsenic Speciation

It is a naturally occurring element, widely distributed in the earth's crust, showing metalloid characteristics, and occurs in many minerals either with other elements or as a pure element crystal [3, 11].

Arsenicals consist of two main groups, organic and inorganic arsenic compounds. The organic ones are predisposed to be far more toxic than inorganic ones [49]. Two predominant forms of arsenic are trivalent and pentavalent [50]. As (III) prevents pyruvate dehydrogenase function by connecting to the -SH groups on dihydrolipoamide; as a result, the cellular gain of acetyl coenzyme A (CoA) from pyruvate decreases, which is associated with the reduction in citric acid cycle function and biosynthesis of cellular ATP [51]. As (III) also prevents glucose intake, gluconeogenesis, fatty acid oxidation, following biosynthesis of acetyl CoA [52].

As (V) disrupts phosphorylation reactions [10] by mimicking and taking the places of phosphates in glycolysis and cellular respiration. In the reaction medium, As (V) connects to adenosine diphosphate (ADP) to create ADP-arsenate, which refers to the lack of the high-energy ATP phosphate

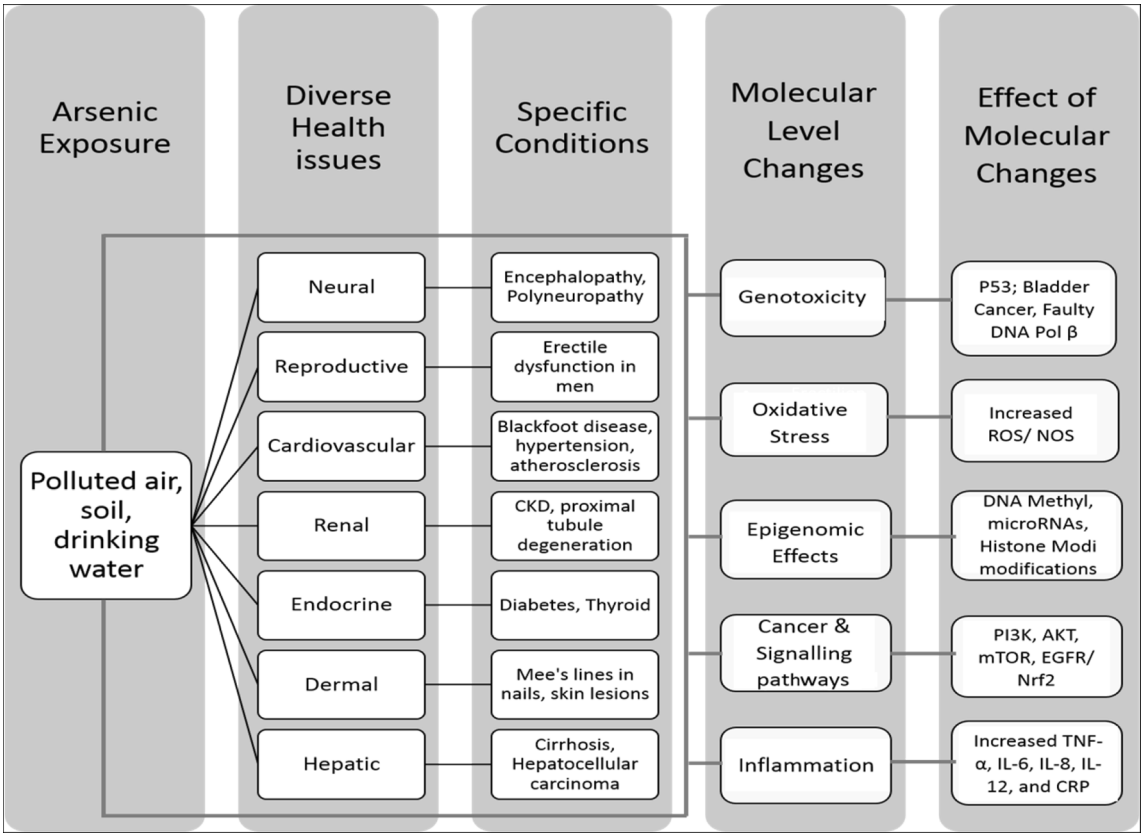

Fig. 1 Human health issues specific to molecular effects of arsenic exposure

linkages. Uncoupling of oxidative phosphorylation happens due to the lack of normal high-energy phosphate linkages [49].

The conversion of arsenates to arsenites is provided via glutathione arsenate reductase, while methylation of arsenates to trivalent arsenicals is succeeded with the help of S-adenosyl methionine (SAM) [36]. Monomethylarsonic acids (MMAs) and dimethylarsinic acids (DMAs) are methyl-ligated derivatives of arsenic. They do not experience a chemical or enzymatic process to be activated but differ from other arsenicals due to their ability to induce unwanted effects on naked DNA [53, 54]. Organic arsenic derivatives produced inside the human body involve monomethylarsonic acid (MMA (V)), monomethylarsonous acid (MMA (III)), dimethylarsinic acid (DMA (V)), dimethylarsinous acid (DMA (III)), and trimethylarsine oxide (TMAO), generated only when an organism is exposed to high doses [55]. Methyl ligation to arsenicals is carried out mainly via arsenic (III) methyltransferase (As3mt) [56]. TMAO is obtained from DMA (V) and MMA (V). DMA (V) is not an attractive target for human As3mt, which explains the rare formation of TMAO in humans. Despite this, DMA (V) and MMA (V) are attractive substrates of rodent As3mt [56]. The consensus about the toxic activity of distinct arsenic species states that arsenite is more toxic than arsenate. Even it is proposed that arsenate toxicity is sourced from translation of arsenate to arsenite [55]. MMA (V), DMA (V), and TMAO are slightly toxic at millimolar doses. As another organoarsenic, arsenobetaine is frequently found in marine products, but it does not show considerable toxicity [57]. Like arsenobetaine, arsenosugars located in foods too are not linked with remarkable toxicity [58]. Methylated thioarsenicals are noted as the arsenicals which exist as bounded with proteins in the form of pentavalent. These are the intermediates responsible for linking methylation and thiolation in arsenic species [59, 60].

Mutageniticity and Genotoxicity

Mutagenicity of this metalloid comes from its ability to interfere with the DNA repairing system [61]. Many genes which are significant for survival, promotion of cancer, apoptosis, signaling events, and growth can be influenced by arsenic-induced chromosomal abnormalities [62]. Arsenic is capable of preventing nucleotide excision as well as base excision repair and mismatch repair [63]. Its mediated blockage of DNA repair is predicted to give rise to a mutation on key tumor suppressor genes like tumor protein P53 (TP53), which increases the risk of bladder cancer [64]. Arsenic-sourced oxidative impacts on enzymes or proteins are also noted due to its high affinity for sulfhydryl groups causing inactivation of vital enzymes [65, 66]. These disrupt the repair system via

either inhibition of ligation or decrease in the expression of DNA repair enzymes like DNA polymerase β [67].

Speciation of this element plays an important role in elucidating its genotoxic ability [68]. When compared to As (III), trivalent mono- and di-methylated forms are more aggressive in terms of genotoxicity and are able to block functions of enzymes [69] as As (III) does [49]. The trivalent methylated arsenic species are reported to be more active compared to the pentavalent forms, contributing mainly to the arsenic genotoxicity [70]. MMA (III) can also lead to electron leaks from the electron transport chain. As a result, activities of mitochondrial complexes I and III are disrupted and ROS, RNS, and some free radicals are generated [71].

Arsenic is capable of creating an oxidative environment inside the cell. Promotion of this oxidative status originates from arsenic-based Fenton type reaction or arsenic-related cellular antioxidative depletion capacity [72–74]. -SH groups on proteins are attractive elements for the binding of trivalent arsenic [75]. This element supports lipid peroxidation by negatively affecting the antioxidant system and amount of -SH groups [76]. ROS sourced from arsenic exposure is proposed to support carcinogenesis, followed by propagation [77]. In a study conducted on human hepatocellular carcinoma cells, it has been reported that there is an ability of arsenic trioxide to induce oxidative stress, caspase-3 activity, and breaks in DNA strands, thus inducing genotoxic DNA damage [78].

Carbonyl derivatives occur among products of protein oxidation. These derivatives are accepted as one of the general biomarkers of protein oxidation [79]. Due to arsenic-induced decrease in antioxidant enzymatic functions and arsenic-triggered increment in free radical formation, there is a rise in the number of protein carbonyls [80, 81]. As an adaptive response to arsenic-induced oxidative stress, a significant rise in activities of glutathione peroxidase (GPx) and catalase (CAT) is exhibited by exposed cells. However, in long-term exposures, cells display a reduction in GPx and CAT functions [82]. The reason being arsenic-mediated depletion of GSH, glutathione reductase (GR), and GPx, which cannot display their activities, ending up with a rise in the level of free radicals and thus oxidative stress [83].

Epigenomic Impacts

Arsenic is capable of acting on some cellular elements at the gene or RNA level during any addition to the protein level and the way the metalloid achieves this can include DNA methylation, microRNAs (miRNA), and histone modifications. It triggers transcriptional repression of hTERT which is the gene that encodes for a subunit of human reverse transcriptase [84, 85]. Consequently, the chromosomal impacts happen due to reduced telomerase function which occurs on chromosomes and can drive cells to genomic instability and cancer or cellular death [85, 86].

DNA Methylation

As3mt uses SAM as a methyl donor and its related reaction gives rise to ROS which contributes to cancer in several organs and some other pathologies [40]. SAM pool becomes smaller due to methylation reactions of arsenic; as such, its depletion can contribute to an altered gene methylation pattern [87]. Any utilization of SAM by arsenic methylator enzymes influences the epigenome [40]. DNA methyltransferase 3 (DNMT3A and B) and DNA methyltransferase 1 (DNMT1) are the main components of DNA methylation. When applied at low concentrations, the metalloid reduces the expression of the DNMTs, which again means a decrease in methylation capacity [38]. Among genes influenced by arsenic-induced epigenetic changes, *p16*, death-associated protein kinase (*DAPK*), and excision repair cross-complementation group 2 (*ERCC2*) are found. *p16* and *DAPK* are two cellular tumor suppressor elements. They get exposed to the promoter hypermethylation, which "turns off" these two genes, while *ERCC2* experiences promoter hypomethylation, via arsenic. By the arsenic-mediated hypomethylation of *ERCC2*, the interaction of ERCC2/Cdk-activating kinase complex (CAK) with transcription factor IIH (TFIIH) is blocked. Consequently, p53 phosphorylation is disrupted, which ends up with impairment of DNA damage recognition [43, 88].

MicroRNAs

In addition to protein level control, p53 is also controlled at the level of the gene. It is known that p53 expression is affected by the presence of miR200b. Arsenic induces downregulation of miR200b, blocking p53, and causes epithelial-to-mesenchymal transition [10], thereby stimulating the suppression of p53 at a transcriptional level resulting in the transformation and discharge of growth factors, GM-CSF, TGF-alpha, TNF-alpha [29].

As opposite to miR200b, miR190 is dose-dependently upregulated via As (III). Overexpression of miR190 ultimately results in the constitutive activation of AKT and its downstream elements. miRNAs seem to be key elements of arsenic-sourced tumor progression [10]. Several studies have been conducted on arsenic-induced dysregulation of miRNAs at the cellular level. In the case of human lymphoblast, TK6 cells treated with 2 μmol/l of Na_3AsO_3 a downregulation of miR-210 and upregulation of miR-22, miR-34a, miR-221, miR-222 have been recorded. It has also been observed that by reversing the arsenic stress on the cells, the miRNA expression is reverted to normal [89]. Similarly, Ling et al. [90] have found an upregulation of miR-21, with subsequent activation of ERK/NF-κB signal pathway in arsenic-induced

transformed human embryo lung fibroblast cells. They have also noted that treating the cells with anti-miR-21 reduced the miR-21 expression thus preventing the activation of the ERK/NF-κB pathway via the increase in the target protein of miR-21, Spryl. Arsenic-induced ERK/NF-κB pathway activation is mediated by miR-21, indicating its role in regulating the signaling pathways.

miRNAs are essential players regulating gene expression affecting cellular processes contributing to the disease development. Dysregulated miRNA expression has been observed in many diseases [91]. In cardiovascular diseases, several miRNAs function as mediators of pathogenic stress-related signaling pathways possibly leading to excessive extracellular matrix production and collagen deposition causing cardiac stress resulting in fibrosis. In cancers, many miRNAs function as oncogenes or tumor suppressors facilitating tumor growth, invasion, and angiogenesis. Moreover, an association between distinct miRNA profile and tumor development, progression, and treatment response has identified miRNAs as potential biomarkers for disease diagnosis and prognosis [91].

The study undertaken by Zeng and Zhag [92] gives an evidence that miR-155e5p regulates the NF-AT1-mediated immunological dysfunction involved in the pathogenesis and carcinogenesis of arsenic. A major finding of these researchers was Krt1 and Krt10, both being markers of hyperkeratosis caused by arsenic, and Krt6c is a potential biomarker that reflects the carcinogenesis of arsenic [92]. Hyperkeratosis is one of the most common skin lesions associated with chronic arsenic poisoning [93, 94]. It is considered a sign of aberrant cell proliferation and is likely a precursor skin lesion for squamous cell carcinoma [95]. In view of this, especially Krt6c can be used as a potential biomarker to reflect the carcinogenesis of arsenic [92].

Although miRNAs' roles in carcinogenesis have been studied, there are several significant areas which should be investigated to understand the full range of influence. Specifically, while examining miRNA expression profiles in different cell lines and tissue types, similarities and differences are found in the expression levels of the miRNAs examined. Keeping in view the diversity of cancer genomes and phenotypes, analysis of genome-wide miRNA expression signatures aids in identifying key miRNAs and networks which have a significant impact on the progression of the disease [91]. According to Sun et al. [96] analysis of nearly 754 miRNAs has revealed that 56 are upregulated and 18 downregulated in the arsenic-exposed group compared to the control. In a West Bengal study conducted on the miRNA profiles on 12 arsenic-exposed individuals, 199 miRNAs were upregulated and 3 downregulated compared to the controls [97]. Both these epidemiological studies stress that the use of the whole genome profiling approach allows for the identification of large numbers of miRNAs which are potentially involved in disease pathogenesis [91]. Even with in vitro and especially in vivo studies, enough experiments have not been carried out on examining the effects of arsenic in the whole genome [98–104]. Shifting the focus from only a few miRNAs to a more thorough miRNA analysis is necessary, as miRNA expression profiles might enlighten mechanisms of action and improve our understanding of the complex biology of cancers and other diseases [91].

Histone Modifications

As (III) application can result in differential impacts on the methylation of H3 lysine [105]. It induces a rise in H3 lysine 9-dimethylation (H3K9me2) by increasing the level of histone-methyltransferase-G9a protein. In cancer, this rise is associated with the silencing of tumor suppressors at the transcription level. H3K9me2 is not the only histone modification affected by arsenic; an increase in H3 lysine 4-trimethylation (H3K4me3) and a reduction in H3 lysine 27-trimethylation (H3K27me3) are like this [38].

In vitro, altered histone H3 acetylation was reported in As (III) and MMA (III) transformed human urothelial malignancies. The changes observed were specific to arsenic, supporting the idea that arsenicals may contribute to tumor initiation via changes on the epigenome [106]. Another study conducted on human bladder epithelial cells has revealed that Monomethylarsonous acid (MMA III) and chronic As3 exposure reduce H4K16 acetylation leading to bladder carcinogenesis [107].

Although there are several reports for arsenic-associated changes in histone acetylation and methylation, only a few reports are connecting histone phosphorylation to arsenic-mediated carcinogenesis [38]. It has been suggested that phosphorylation at H3 is induced by exposure to arsenic and is potentially responsible for the increased expression of oncogenes c-Fos and c-Jun with subsequent activation of a proto-apoptotic factor CASPASE 10 [108, 109].

Cancer and Signaling Pathways

In light of the accumulated scientific data, it is proposed that arsenic-mediated carcinogenesis also originates from the imbalance of significant cellular signaling systems [77]. Exposure of human cells to arsenic induces the activation of the PI3K/AKT/mTOR pathway, ERK, JAK/STAT, and NRF2 pathway as shown in Fig. 2.

PI3K/AKT/mTOR

Several studies have revealed that, under chronic arsenic conditions, there is cellular proliferation, migration, invasion, and anchorage-independency. These endpoints are highly associated with AKT and PI3K functions [110, 111]. PI3K/AKT/

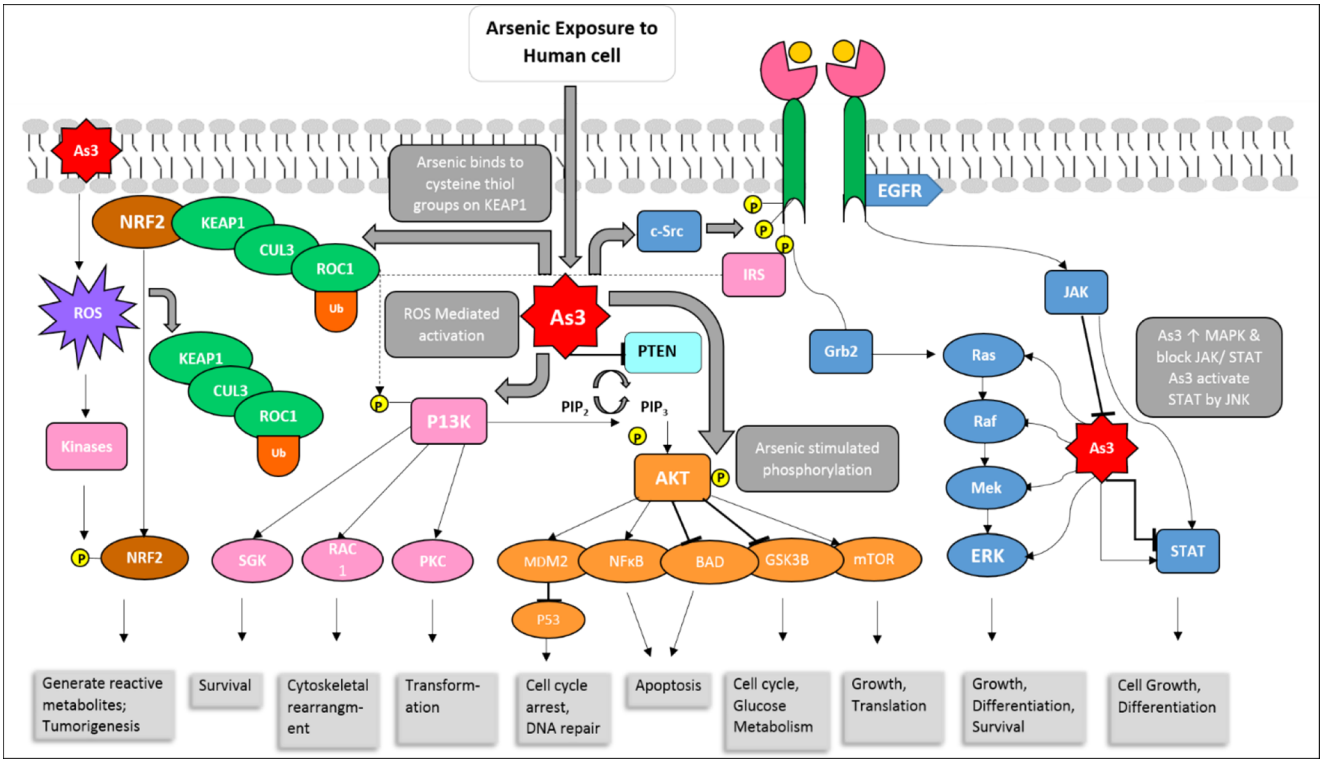

Fig. 2 Arsenic-induced activation of PI3K/AKT/mTOR pathway, ERK, JAK/STAT, and NRF2 pathway. [Arsenic 3(As3), phosphoinositide 3-kinase (P13K), proto-oncogene tyrosine-protein kinase Src (c-Src), insulin receptor substrate (IRS), serum and glucocorticoid-induced protein kinase (SGK), Ras-related C3 botulinum toxin substrate 1 (Rac1), protein kinase C (PKC), phosphatase and tensin homolog (PTEN), protein kinase B (Akt), mouse double minute 2 homolog (MDM2), tumor protein p53, nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), the BCL2 associated agonist of cell death protein (BAD), glycogen synthase kinase 3 beta (GSK3B), mammalian target of rapamycin (mTOR), phosphotidylinositol 4,5-bisphosphate (PIP2), phosphatidylinositol-3, 4, 5-triphosphate (PIP3), growth factor receptor-bound protein 2 (Grb2), Ras GTPase, RAF kinase, mitogen-activated protein kinase (MEK), extracellular signal-regulated kinases (ERK), epidermal growth factor receptor (EGFR), Janus kinase (JAK), signal transducer and activator of transcription (STAT) protein, phosphorylated (P), homeobox-leucine zipper protein (ROC1), Cullin 3 (CUL3), Kelch-like ECH-associated protein 1 (KEAP1), nuclear factor erythroid 2-related factor 2 (NRF2), reactive oxygen species (ROS), ubiquitin (Ub)]

mTOR pathway is commonly disrupted in cancers. This pathway is critical for cellular survival, physiology, and pathology [77]; it can be influenced by mutations in DNA, hepatitis C virus, toxic chemicals involving some non-essential metals/metalloids, and some cellular molecules like interleukin-6 and free fatty acids [112].

As non-essential metals/metalloids, arsenic, cadmium, and mercury trigger malignancy through the PI3K/AKT/mTOR signaling [77]. There is much evidence available proposing that arsenic can do this because of activation of the PI3K/AKT/mTOR pathway to promote proliferation in normal cells, but it shows opposite impacts on cancerous cells. The metalloid drives diverse cancer cells to apoptotic cell death where the efficiency of the operation changes with changing cancer types [77]. As (III) can lead to activation of PI3K/AKT pathway via JNK/ STAT3 signaling induced AKT and via suppression PTEN, a protein blocking PI3K/AKT signaling [10]. During the malignant transformation of stem cells, arsenite has also been shown to suppress the expression of PTEN [113]. In human bronchial epithelial (HBE) cells, As (III) can cause a release of vascular endothelial growth factor (VEGF) by activating AKT. VEGF is known for its ability to stimulate cell migration following distinct procedures [114]. However, differently from the aforementioned arsenicals, arsenic disulfide has been found to block AKT/mTOR signaling, in addition to autophagy and apoptotic cell death, in several osteosarcoma cell lines [115].

EGFR

A probable scenario for arsenic-triggered activation of PI3K/AKT pathway involves stimulation of upstream molecules like epidermal growth factor receptor (EGFR), which is demonstrated to trigger abnormal epithelial cell proliferation [77]. Under normal conditions, EGFR activity is dependent on epidermal growth factor (EGF) binding. Activated EGRF ultimately targets activation of mitogen-activated protein kinase (MAPK) pathways, which are known for their importance in stress responses, inflammatory events, and growth. Arsenic can render c-Src functional, and activated c-Src renders EGFR functional in a ligand-independent manner; consequently, EGFR becomes constitutively active [116]. Later, it

activates Ras/Raf/MEK/ERK signaling. Functioning of Ras/Raf/MEK/ERK signaling ends up with cellular proliferation, migration, and survival [10]. In the case of hepatocellular carcinoma, cells face arsenic overexpress EGFR [117]. Furthermore, the metalloid can render elements of the EGFR pathway functional in lung epithelial cells through ROS. These elements include Ras, Raf, MEK, and ERK [118, 119]. A very recent study has shown how PINK1/Parkin-mediated mitophagy is implicated in arsenic-induced apoptosis of human hepatic cells via activation of ERK signaling cascade [120].

Nrf2

Nrf2 is a transcription factor that guards the cell against oxidative and electrophilic insults. Nrf2 does its job by connecting with small Maf proteins, together with giving rise to transcription of genes having antioxidant response element (ARE) as their regulatory element [121, 122]. NAD(P)H quinone oxidoreductase 1 (NQO1), heme oxygenase 1 (HMOX1), glutamate-cysteine ligase (GCL), and glutathione S transferases (GSTs) are listed under the category of Nrf2-mediated genes [123]. One of how the cell controls the availability of Nrf2 is immobilization via means of Keap1 followed by ubiquitin-dependent proteolysis [121]. In normal cells and cells not fully transformed to malignant form, Nrf2 plays the protective role [124]. Despite this, the constitutive activity of Nrf2 is displayed by diverse cancer cells, providing a growth advantage to fully malignant cells [123, 125]. The growth advantage originates from chemoresistance and augmented cell growth. Chemoresistance sourced from Nrf2 is based on an Nrf2-induced rise in the level of drug-processing elements [124]. Constitutively functional Nrf2 results in cell proliferation via driving glucose and glutamine to biosynthesis and by acting on Pentose Phosphate Pathway [126].

Keap1, as a part of a Cullin-3 E3 ligase, holds Nrf2 for ubiquitination, under non-oxidative and non-electrophilic conditions. Ubiquitin-ligated Nrf2 is destined to get degraded via the 26S proteasome system. Under oxidative and electrophilic conditions, Keap1 detects oxidative factors with the help of its cysteine residues. Once these factors are detected, the interaction between Nrf2 and Keap1 is affected, ubiquitin ligation to Nrf2 fails, the non-ubiquitylated Nrf2 gets stabilized as well as activated, and Nrf2 complexes with small Maf proteins function as a transcription machine for various genes [127].

Both Nrf2 and autophagy display contradictory functions in cancer when compared to normal cells. Cross talk between these two cellular systems occurs by an interaction of p62 with Keap1 [128]. p62 is one of the proteins of autophagic membrane providing substrate specificity to autophagic degradation by clasping ubiquitin-ligated proteins, fated to experience autophagic degradation. The p62 provides stability to the autophagic membrane and assists in surrounding the surface of incoming material [129]. However, when p62 recognizes Keap1, it can sequester it into aggregates of p62 or an autophagic vesicle; but Keap1 can get exposed to autophagic proteolysis inside the autophagosome. This way p62 indirectly renders Nrf2 free, by prevention of Keap1-modulated ubiquitin ligation, to enter the nucleus and causes transcription of ARE genes [128]. The p62 is critically significant for Keap1 turnover because of its role in the degradation of Keap1 [130]. By promoting Keap1 turnover, p62 also protects the integrity of the Nrf2/Keap1 mechanism [131]. Disruption of autophagic function ends up with long-term functional Nrf2, in a p62-related mean [128]. It is important to note that p62 is one of the downstream target genes of Nrf2, and by this downstream relation a positive feedback loop is generated [132].

Trivalent arsenic and trivalent monomethyl arsenic are capable of activating Nrf2. They achieve this by enhancing the connection of Keap1 and Cullin-3 (Cul-3) which impairs dynamic association/dissociation operation happening between Keap1-Cul3. Impairment of Keap1-Cul3 dynamics results in a reduction in ubiquitin ligation to Nrf2, meaning stabilization and activation of Nrf2 [133].

Arsenite-triggered stress-activated p300/CB has been found to provide acetyl ligation to Nrf2. This acetylation positively modulates the binding of Nrf2 to its target region on the DNA [134]. Sodium arsenite triggers activation of Nrf2, independently from cysteines of Keap1, in a way that leads to a decrease in ubiquitin ligation to Nrf2 [135], while arsenic makes Nrf2 functional in p62 by prevention of autophagic flux. After exposure to arsenic, autophagic vesicles arise in amount, and p62, LC3, and Keap1 co-localize to promote constitutive activation of Nrf2 [125, 136]. Sodium arsenite can transform HBE cells by decreasing the amount of Nrf2 and thus its transcriptional targets, NQO1, and HO-1 proteins. In the absence of these proteins, cells are driven into malignant proliferation [137].

Others

Arsenic severely affects some of the signaling molecules such as NO, S-nitrosothiols, AP-1, NFkappaB, and p53. Its mediated damages on these molecules originate from their redox-sensitive character. Additionally, p21 ras is also affected by arsenic via metal-triggered signaling events. Cellular stress induced by the metalloid is sensed with the help of MAPK, JNK, and p38. These three are known to activate a group of genes, called immediate early genes, c-fos, c-jun, and EGR-1, which provide biosynthesis of the heat shock proteins (HSP) and cell transformation [29].

Inflammation and Immune System

Arsenic-related immune issues include weakened immune surveillance system and increased level of infection, autoimmune problems, cancer, and other immune-controlled problems [138]. The recent findings have revealed that this metalloid hinders macrophage activity and aggravates lipopolysaccharide-triggered inflammation, managed by macrophages and monocytes [139]. Inflammation is a famous hallmark for cancer progression. It protects tissues after injury. However, it also gives rise to several diseases involving cancers [140]. As urothelial cells face arsenic, there is a release of inflammatory markers like IL-8, TNF-α, and TGF-β [141]. Chronic low-level arsenic (11–50 μg/L) is demonstrated to promote systemic inflammation. The underlying mechanism is based on the upregulation of pro-inflammatory mediators such as TNF-α, IL-6, IL-8, IL-12, and CRP [142]. Long-term arsenic exposure can impair immune responses against inflammation [143].

There is evidence that inorganic arsenic can repress the immune system to some degree, but tumors related to arsenic, especially the skin, lung, and bladder, do not appear in individuals who are immune-suppressed [38]. Immunosuppressive features of the metalloid are characterized by a decrease in CD4+ level in epidermal keratinocytes [36]. Recently, the role of peptidyl arginine deiminase (PAD2)–induced inflammasome signaling in sodium arsenic–exposed lungs has been investigated showing increased reactivity upon exposure to the metals in mice [144].

Symptoms of As Poisoning

Arsenic can be absorbed by ingestion, inhalation, and penetration via skin, as well as contact with mucous membranes and toxicokinetics depends on the type as well as time of exposure, the physicochemical characteristics of the compound (pKa and solubility), the pathway, and the affected biological species. Nearly 70–90% of the inorganic arsenic is easily absorbed by the gastrointestinal tract after its ingestion, followed by its distribution through the bloodstream to different organs such as the liver, kidneys, lungs, bladder, and secondarily to muscle/nerve tissue. During the absorption and distribution phase, the greatest accumulation of inorganic arsenic is found in the liver and subsequent excretion takes place mainly through urination [145, 146].

The human body contains approximately 0.08–0.02 mg As/kg, mainly concentrated in the liver, kidneys, lungs, bones, and hair. The excessive or prolonged exposure to its compounds results in severe acute or chronic toxicity leading to a range of medical complications termed "Arsenicosis" [147, 148]. In acute As exposures, a metallic taste occurs in the mouth with a slight odor of garlic in the breath and dysphasia, followed by nausea, vomiting, burning in the stomach and esophagus, abdominal pain, and diarrhea. In addition to these, cyanosis, hypoxic encephalopathy, convulsions, acute tubular necrosis, cardiovascular, and respiratory symptoms such as hypotension, pulmonary edema, and heart failure can occur. Death follows in the first few hours from shock or some days later from acute renal or liver failure [148, 149]. Prolonged As poisoning has wide range of clinical features and leads to multisystemic diseases. In chronic As poisoning, the element accumulates in the liver, kidneys, heart, and lungs, muscle tissues, nervous system, gastrointestinal tract, spleen, and other tissues containing keratin. Nearly 2 weeks following As ingestion, deposition starts in the hair and nails, and the highest concentration is observed in the kidneys and liver [148, 149]. It causes myocardial injury, cardiac arrhythmias, and cardiomyopathy by reducing the activity of antioxidant enzymes of the heart, namely superoxide dismutase, catalase, glutathione *S*-transferase, glutathione reductase, and glutathione peroxidase [148, 150]. Toxic polyneuropathy and peripheral neuropathy often occur. Tetraplegia or paresis develops with the prevalence of lesions of peroneal muscles. In rare cases, injuries of the individual cranial nerves: facial, trigeminal, vagus, and sublingual ones have also been reported. Toxic polyneuropathy is usually accompanied by pronounced vegetative trophic disorders: hyperkeratosis, over-exfoliation of the skin on the extremities, hair loss, ulcerative processes on the gums, and vasomotor disorders [148]. The development of clinical symptoms of toxic polyneuropathy initially occurs with symptoms of irritation of the nerve trunks. This leads to sharp pains in the extremities, accompanied by the phenomena of hyperpathia, ataxia, and a marked decrease in vibrational sensitivity. The behavioral changes, obfuscation, and memory loss have also been reported, together with psychoses due to As poisoning [49, 148, 151].

Both inorganic and organic As compounds pass the human placenta in late pregnancy, and accumulate in the fetus. The published work on the effects of As in high doses indicate a risk for pregnancy [148], but the effects in small doses have also been recorded [152]. As-containing compounds cause an abnormal pregnancy outcome in experimental animals at sufficiently high levels, including miscarriages, stillbirths, and infant deaths in communities using drinking water with As concentrations above 50 ppb (μg/L) [148, 153]. Epidemiological studies of areas with high levels of As in drinking waters indicate an association between in utero As exposure and the development of adult diseases cited above together with diabetes [148, 154–157].

Urinary As concentration is used to quantify and monitor its recent poisoning [148]. Analyses of blood, hair, and fingernails samples are also good indicators of exposure. Because of the short half-life of As in blood, hematological estimation is useful in particular in the diagnosis of acute intoxication [148]. Inorganic As incorporates into hair and

fingernails due to its affinity to the sulfhydryl groups in keratin. The metal deposition requires nearly 2 weeks after exposition to appear. In chronic poisonings, As levels found in hair samples are in the range of 0.1–0.5 mg/kg, but in acute poisonings, concentrations reach values between 1.0 and 3.0 mg/kg [148]. Another common clinical manifestation of chronic As exposure is the appearance of Mee's lines in the nails. Hair and nail tests are particularly useful to determine the level of As exposure in the previous 6–12 months; but long hair is needed to define the history associated with exposure [148]. Other key characteristic features are skin lesions, melanosis, keratosis, and pigmentation, often used for diagnosing chronic As poisoning since they usually develop from 5 to 10 years after initial exposure [148].

Arsenic concentration in the blood is not taken into consideration as a trustable biomarker of its exposure whilst urinary concentration is commonly accepted as highly dependable because arsenic is predominantly excreted as a part of urine [49]. It changes heme metabolism; as a result, large amounts of both total porphyrin and coproporphyrin III isomer occur in the urine [158], as the amount of urinary methylated arsenic increases, the risk of skin and bladder cancer increases in parallel [159, 160].

Skin alterations are counted as major indicators of chronic arsenic toxicity [161, 162]. Among the organs, kidneys are most sensitive towards arsenic toxicity [163], and capillaries, tubules, and glomeruli are the major sites associated with renal toxicity [36]. The scope of arsenic poisoning alters with factors like exposed concentration, age, and individual susceptibility [49]. In males, the conversion of MMA to DMA is lower in rate as compared to the females. It is therefore proposed that "male individuals may be more susceptible to arsenic toxicity" [36]. Metallothioneins (MTs) are short polypeptides having a high binding affinity towards heavy metals because of their -SH-rich nature. MTs buffer heavy metals in the serum [75, 164]. Production of MTs can be stimulated in response to trivalent arsenic [75], and HSP production is also stimulated because of arsenic exposure [165, 166].

Conclusions

As is a toxic heavy metal, interrupting in numerous signal pathways. It is renowned for its toxicity, with varying effects on the body and cells in people who are exposed to it, usually through contaminated drinking waters. The mechanism behind the toxicity includes many events like genotoxicity, oxidative attacks, epigenomic changes, and changes in cellular signals [167–169]. It also leads to the abnormalities in the inflammatory mechanisms and the immune system, with further adverse effects in the body. As poisoning causes a variety of biological symptoms in the body, these can be useful for diagnosis. Although the extent of arsenic toxicity varies with various factors such as exposure, age, and individual sensitivity, its concentration in urine is generally accepted as the most reliable biomarker. It was emphasized that as the amount of methylated arsenic in urine increases, the risk of skin and bladder cancer may increase. In addition to these, the skin changes are also counted as major indicators of chronic arsenic toxicity. This review presents an overview of the latest information from the contributions towards the facilitation of detection of reliable biological markers in the treatment of diseases, especially cancer, during arsenic exposure and with a note on the fact related to the understanding of the mechanisms of its toxicity.

Author's Contribution The conception and design of the study: M.O., M.M., and V.A. Acquisition of data, analysis, and interpretation of data: M.O., M.M., V.A., R.A.B., M.E., A.G., B.T.U., M.H., L.N., K.N., A.B., M.A.D., and T.K. Drafting the article: M.O., M.M., V.A., R.A.B., M.E., A.G., B.T.U., M.H., L.N., K.N., A.B., and T.K. Revising the article critically for important intellectual content: M.O., V.A., M.E., M.H., L.N., and K.N. Final approval of the version to be submitted: M.O. and V.A.

Declarations

Conflict of Interest The authors declare no competing interests.

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