

REVIEW

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Molecular features in arsenic-induced lung tumors

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Abstract

Arsenic is a well-known human carcinogen, which potentially affects ~160 million people worldwide via exposure to unsafe levels in drinking water. Lungs are one of the main target organs for arsenic-related carcinogenesis. These tumors exhibit particular features, such as squamous cell-type specificity and high incidence among never smokers. Arsenic-induced malignant transformation is mainly related to the biotransformation process intended for the metabolic clearing of the carcinogen, which results in specific genetic and epigenetic alterations that ultimately affect key pathways in lung carcinogenesis. Based on this, lung tumors induced by arsenic exposure could be considered an additional subtype of lung cancer, especially in the case of never-smokers, where arsenic is a known etiological agent. In this article, we review the current knowledge on the various mechanisms of arsenic carcinogenicity and the specific roles of this metalloid in signaling pathways leading to lung cancer.

Keywords: Arsenic, Arsenite, Lung cancer, Epigenetic, Reactive oxygen species, Epidermal growth factor receptor, Phosphatidylinositol 3-kinases, NFE2-related factor 2

Introduction

Arsenic is a well-known human carcinogen [1]. This metalloid is widely distributed throughout the Earth's crust and arsenical species tend to remain in solution even at high concentrations (tens of $\mu\text{g/L}$) at near-neutral pH [2]. As a result, arsenic exposure through drinking water is considered the cause of the largest mass poisoning worldwide. In Bangladesh, more than 70 million people are at risk of long term exposure to high levels of arsenic through groundwater [3]. On the other hand, chronic exposure to low-levels of arsenic in drinking water is an emerging risk across different parts of the world, including North America (Figure 1) [4-7]. Paradoxically, arsenic (as arsenic trioxide, As_2O_3) is also used as therapeutic agent in the treatment of acute promyelocytic leukemia [8,9].

Common types of tumors associated with arsenic exposure are found in skin, bladder, liver and lung. Following arsenic exposure, lung cancer has proven to be amongst the most deadly cancer types [13,14]. Lung adenocarcinoma is

the most common type of lung cancer worldwide, however, the most frequent histological subtypes observed in arsenic-induced lung tumors – among both smokers and non-smokers – are squamous cell carcinomas (SqCC) and small cell carcinomas (SCC) [15]. Lung tumors derived from individuals exposed to arsenic also exhibit differential genetic and epigenetic changes when compared to histologically matched tumors derived from an arsenic-free environment. The differential molecular alterations seen in arsenic-induced tumors may not arise from inorganic arsenic, but instead from more damaging arsenic species generated through its metabolism [16]. In this article, we discuss mechanisms that enhance the carcinogenic potential of arsenic, such as its biotransformation, as well as the impact of this carcinogen and its derivatives at a molecular pathway level.

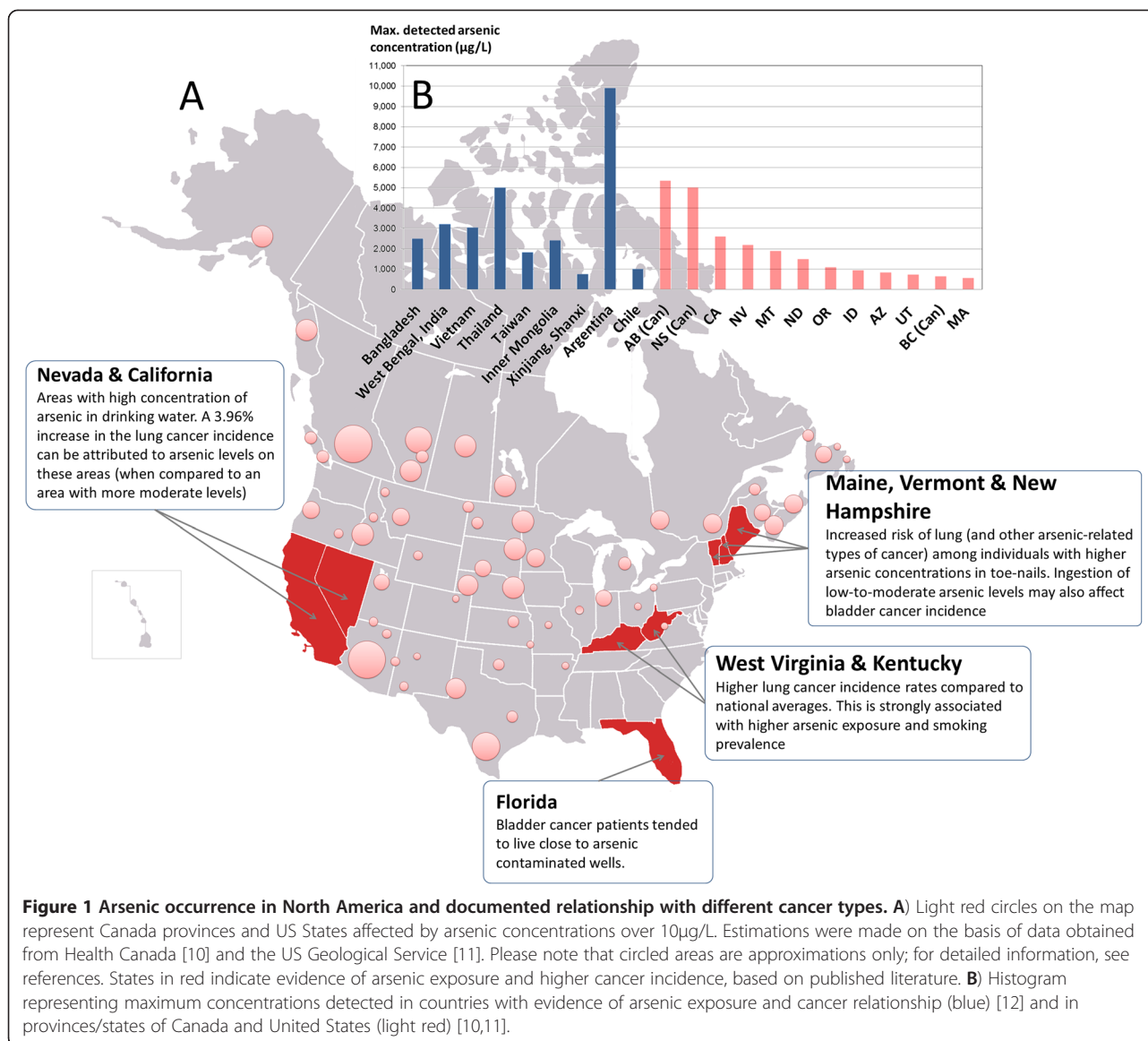
Molecular mechanisms involved in arsenic-induced carcinogenesis

The carcinogenic capacity of arsenic is causally linked to its biotransformation (Figure 2) [17]. Inorganic arsenic is readily absorbed by the gastrointestinal tract when ingested through drinking water [18]. Upon ingestion, arsenic is predominantly found in its pentavalent form

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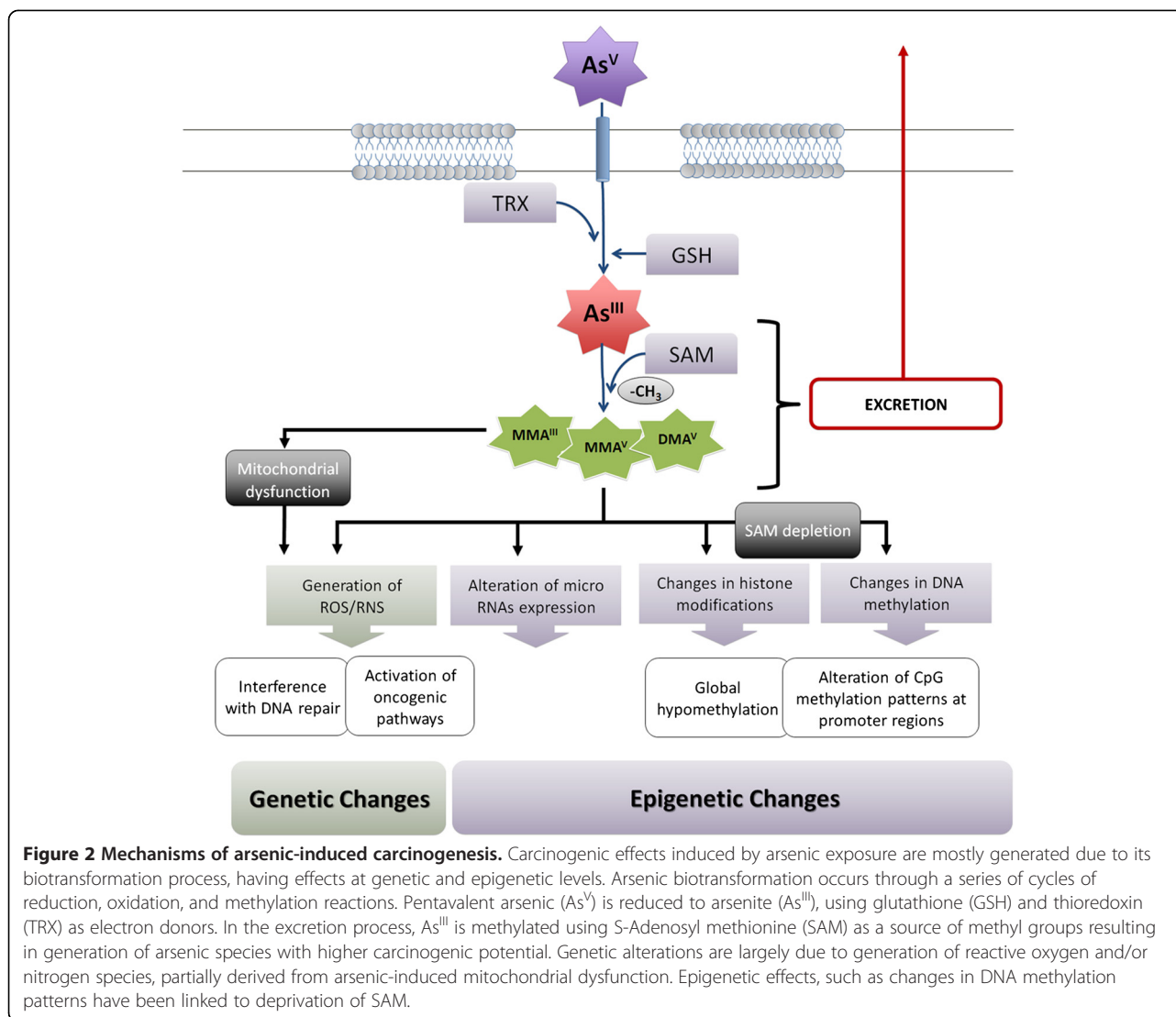
(arsenate, As^V) and enters cells through membrane transporters such as inorganic phosphate transporters (PiT) and aquaporins [19,20]. Inside the cell, As^V is reduced to the more toxic arsenite (As^{III}) in a glutathione-dependent reaction driven by polynucleotide phosphorylase and mitochondrial ATP synthase [21]. As a part of a cellular detoxification process, As^{III} and its methylated conjugates are translocated from hepatocytes into bile as glutathione conjugates [22]. Mono- and dimethylated As^{III} species leaving the liver are highly reactive and have been shown to induce damage in different organs, including lungs. This damage occurs primarily through the generation of reactive oxygen species (ROS) in concert with glutathione depletion [23-25]. Increased toxicity of As^{III} can be attributed to a high covalent reactivity towards thiol groups;

thus, the metalloid often interacts with proteins to induce their inactivation/degradation [20].

Arsenical species induce genetic alterations

Arsenic as a co-mutagen

Inorganic arsenic does not interact directly with DNA and is not considered to be mutagenic at non-toxic doses [26]. However, as previously described, methylated arsenic species and other byproducts generated in the biotransformation process are potent clastogens and mutagens [27,28]. Furthermore, low doses of arsenic can potentiate mutagenic effects through other carcinogens such as UV light, N-methyl-N-nitrosourea, diepoxybutane, X-rays, methylmethane sulfonate and tobacco [29-34].



Arsenic induces DNA damage via generation of reactive oxygen and nitrogen species

Arsenic-induced ROS may be generated by either cycling of As^{III} and As^V [35] or through disruption of the mitochondrial electron transport chain [36] (Figure 2). Most of the known arsenic-related mechanisms of ROS generation involve the latter mechanism. Typically, mitochondrial ROS is generated through monomethylarsonous acid (MMA^{III})-mediated inhibition of mitochondrial complexes II and IV [16], which results in a back-log of electrons and, eventually, electron leakage from complexes I and III [37]. Liberation of electrons from the electron transport chain (ETC) leads to formation of superoxide anion radicals ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^{\bullet}) [19,38]. Arsenic-mediated production of free-radical species has been associated with the formation of DNA adducts, DNA double-stranded breaks, DNA cross linking, chromosomal

aberrations, DNA mutations and DNA deletions (Figure 2) [39-41].

Arsenic can also induce generation of reactive nitrogen species (RNS). The mechanisms involved are not completely understood; however, they are thought to occur in a tissue-specific manner [42]. The increase in amounts of RNS such as peroxynitrite has been shown to cause DNA alkylation, deamination, and oxidative DNA damage [43-47].

Arsenic interferes with DNA repair processes

Arsenic can affect cellular DNA repair capacity, by altering both nucleotide- (NER) and base-excision repair (BER) mechanisms (Figure 2). Arsenic interferes with NER by reducing the frequency of incision steps of the repair process [30], reducing the expression of NER-associated genes and decreasing expression and protein levels of Xeroderma pigmentosum complementation

group C (XPC) [48-50]. In addition, methylated As^{III} species generated by the biotransformation process impair the expression and activity of human PARP1, a promoter of NER that acts in response to DNA damage [51]. Arsenic metabolites also decrease gene expression and protein levels of BER-related components, such as 8-oxoguanine DNA glycosylase 1 (hOGG1), DNA ligase III α (LIGIII α), and X-ray cross complementing protein 1 (XRCC1) [17]. In arsenic-exposed murine lung tissue, the expression of several genes related to BER – such as apurinic/aprimidinic, endonuclease/redox effector-1 (APE1), ligase I, DNA, ATP-dependent (LIG1), 8-oxoguanine DNA glycosylase (OGG1), and poly (ADP-ribose) polymerase 1 (PARP1) – were elevated [52].

Arsenic induces chromosomal and genomic instability

Arsenic-treated cells demonstrate significantly increased micronuclei formation as well as chromosomal aneuploidy, likely by an effect on sulfhydryl groups of tubulin and microtubule-associated proteins and consequential cell spindle assembly disruption [53-57]. Additional studies have shown that the p53-dependent increase in p21 expression observed in normal cells following DNA damage is inhibited in cells exposed to arsenic, leading to cell cycle progression despite heavy DNA damage and genomic instability [58-61]. Similarly, arsenic-induced disruption of PARP1 activity contributes to genomic instability by allowing the survival of cells with significant DNA lesions [51,62]. Studies comparing DNA copy number alterations in arsenic-exposed and non-exposed lung tumor cells indicate the location and frequency of alterations differ between the two cases. Genomes of lung tumors from patients who never smoke, as well as those chronically exposed to arsenic harbor segmental DNA amplifications at 19q13.31 and 19q13.33 and segmental DNA losses at chromosomal locus 1q21, among others [63,64]. Interestingly, genes in 19q13.33, such as Spleen focus forming virus (SFFV), proviral integration oncogene B (SPIB), and Nuclear receptor subfamily 1, group H, member 2 (NR1H2) have been shown to be oncogenic in mouse models [65-67].

Arsenic-induced epigenetic alterations

Arsenic biotransformation depletes SAM resulting in aberrant DNA methylation

Arsenic detoxification requires the use of S-Adenosyl methionine (SAM) as a methyl donor (Figure 2); consequently, arsenic-related epigenetic effects mainly derive from deprivation of the cellular pool of methyl (-CH₃) groups [68]. Although cellular levels of SAM itself are not likely affected, a high demand of SAM due to chronic arsenic exposure will affect the availability of the cellular pool of methyl groups [69-71]. Since SAM is the major methyl donor for DNA-methyltransferases

(DNMT), depletion of methyl groups can lead to global hypomethylation and changes in chromatin remodeling [72,73]. Such epigenetic modifications have been shown to promote malignant transformation in a variety of cell types, including lung [74-76]. Arsenic has been shown to induce global hypomethylation, as demonstrated by reduction in LINE-1 methylation and total 5-methyldeoxycytidine content in lymphoblastoid cells [72]. Importantly, even low-level arsenic exposure resulted in DNA hypomethylation in rat models [77]. Moreover, arsenic-induced SAM deprivation can alter CpG methylation status of promoters for specific genes, such as Deleted In Bladder Cancer 1 (DBC1), Death-Associated Protein Kinase 1 (DAPK), and P53 [68,78-86]. ROS generated during arsenic biotransformation can also interfere with DNA methylation and contribute to aberrant epigenetic modifications and deregulation of gene expression [87].

Interestingly, individuals chronically exposed to high yet non-lethal levels of arsenic exhibit a significantly higher degree of DNA methylation in promoter regions of P53 and CDKN2A compared to non-exposed controls [88]. Lung cancer cell models have also shown that arsenic exposure resulted in P53 promoter hypermethylation and subsequent transcriptional silencing of this gene [78]. Promoter hypermethylation of tumor suppressors CDKN2A and RASSF1A was also observed in lung tumors of mice exposed to inorganic arsenate [75].

Arsenic changes gene expression patterns by altering histone modification

Arsenic-mediated reduction of global levels of H4K16 acetylation, a mark of gene activation, has been demonstrated in cell models [89]. Further, arsenic exposure has been shown to modify H3K4, H3K9, and H3K27 histone methylation patterns in both malignant and non-malignant lung cell lines, leading to a decrease in the expression of genes associated with histone acetylation and DNA methylation changes [80,90]. Arsenic has also been reported to alter the chromatin landscape of arsenic-induced cancer cells through loss of the repressive histone modifications H3 triMe-K27 and H3 diMe-K9 and an increase in the levels of activating Ac-H3 and diMe-K4 at the WNT5A locus – resulting in the ectopic expression of WNT family genes [73].

Arsenic induces epithelial-to-mesenchymal transition and other biological effects through changes in micro-RNA expression

A study using human bronchial epithelial cells (HBEC) demonstrated that chronic arsenic exposure of P53-knock down cells induced malignant transformation accompanied by epithelial-to-mesenchymal transition (EMT) [91]. A reduction in expression of a miR-200 family member was correlated with this exposure, and was shown to occur

through increased promoter methylation. Re-establishment of miR-200b expression alone was capable of entirely reversing and preventing arsenic-induced EMT and malignant transformation [91].

Arsenic exposure can alter miRNA expression levels in vitro and in vivo in other cell types and tissues. For example, in a study using chick embryos, arsenic decreased expression of miR-9, -181b, -124, and -125b. Decrease of miR-9 and miR-181b resulted in expression of their common target Nrp1, leading to cell migration, tube formation and angiogenesis [92]. Arsenite induced overexpression of several miRNAs, including miR-222, in human peripheral blood-derived cells from individuals with insufficient dietary folate. Overexpression of miR-222 was reversed by the restoration of normal folate levels [76].

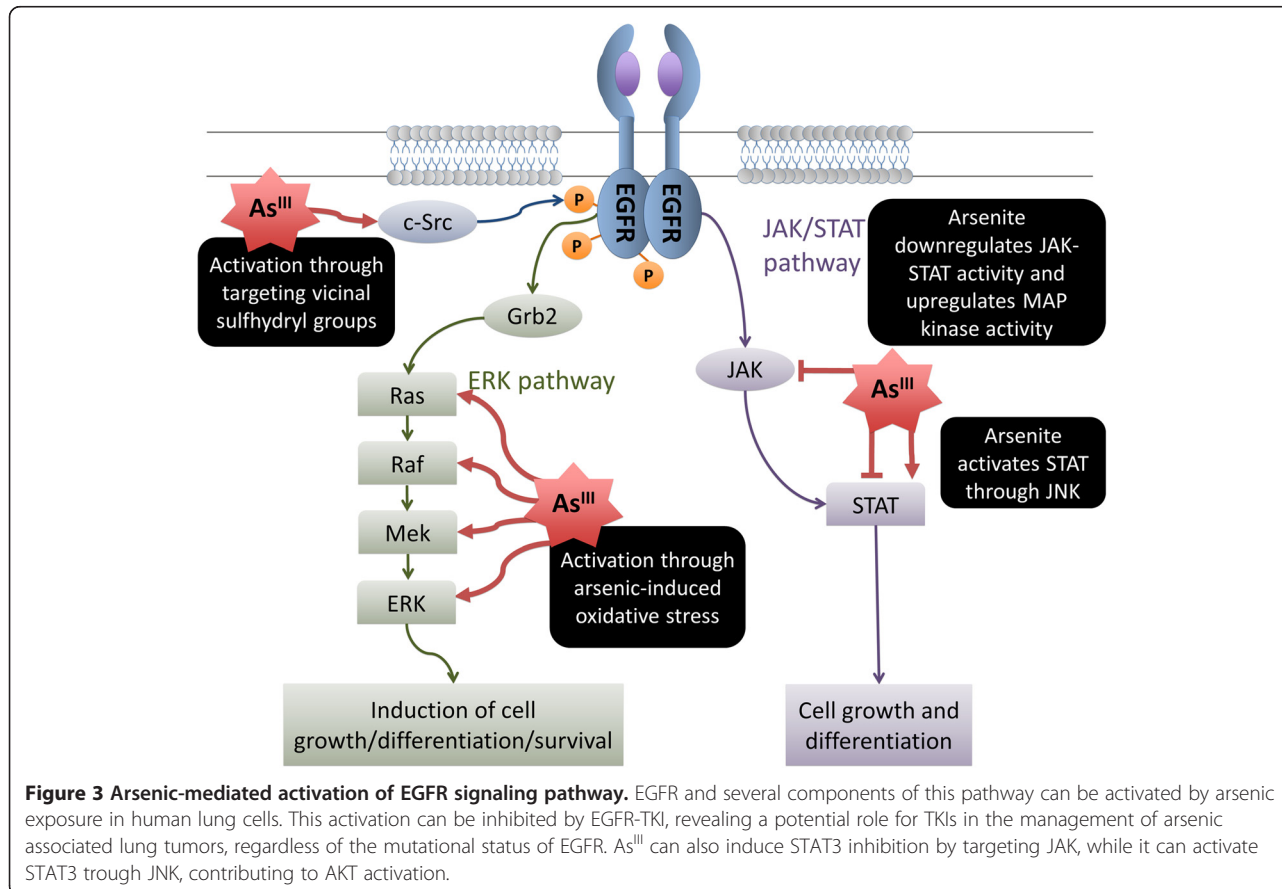
Arsenic targets key pathways associated with lung cancer

Arsenic stimulates the EGFR signaling pathway

Alteration in the EGFR pathway can result from mutation and/or amplification events at the epidermal growth factor receptor (EGFR) locus. The consequence of either genetic event is a structural alteration that destabilizes the auto-

inhibitory loop of EGFR, forcing the receptor into a constitutive and ligand-independent active state [93].

Similar states of EGFR constitutive activation can be induced by even moderate levels of arsenic, similar to those registered in contaminated U.S. drinking water, affecting the lungs and other target organs of arsenic carcinogenesis [94,95] (Figure 3). Arsenic can stimulate c-Src activity, which can then activate EGFR by physical interaction resulting in two unique tyrosine phosphorylation events (Tyr845, Tyr1101), leading to ligand-independent EGFR phosphorylation and constitutive activation [96-98]. Arsenic can also induce activation of components of the EGFR pathway in lung epithelial cells, such as Ras, Raf, Mek and ERK through ROS [94,99,100]. Arsenite inhibits STAT3 through JAK inactivation, and such interference may play a role in arsenic-associated pathogenesis [101]. Conversely, it has been shown that As^{III} activates STAT3 through c-Jun NH2 kinase (JNK), contributing to Akt activation [102]. Arsenic-exposed hepatocellular carcinoma cells display overexpression of EGFR [95], while in leukemia cell lines, As^{III} is capable of activating Rac1 GTPases resulting in downstream engagement of the JNK pathway and increased cell survival and proliferation [103,104]. This arsenic-related induction of EGFR



signaling offers promising therapeutic utility, as inhibitors of EGFR and various other pathway components are already in place or in development [105].

Arsenic and the PI3K/AKT signaling pathway

Signaling through the PI3K/AKT pathway starts with the activation of receptor tyrosine kinases (RTK's) through binding to an extracellular growth factor. Binding of the extracellular ligand to its receptor leads to the dimerization and activation of the RTK [106]. The consequence of RTK activation, is the successive recruitment and activation of PI3K, AKT, and hundreds of target proteins that drive increased cell growth, metabolism, survival, and proliferation [106].

Acute exposure to arsenite can stimulate the PI3K/AKT phosphorylation cascade, leading to cellular transformation characterized by increased proliferation and anchorage-independent growth [107-109] (Figure 4). As^{III} can induce phosphorylation of EZH2 at serine 21 in human bronchial epithelial cells and such phosphorylation of EZH2 requires As^{III}-activated signalling through JNK and STAT3 leading to phosphorylation of AKT [110]. Arsenic-induced activation of AKT may be also associated with its ability to cause the induction of miR-

190. This microRNA acts by repressing expression of the PH domain leucine-rich repeat protein phosphatase (PHLPP) – a negative regulator of AKT signaling [111]. Additionally, it has been shown that activation of the JNK-STAT3 pathway is involved in As^{III}-induced AKT activation [102]. In HBECs, As^{III} can stimulate AKT and the consequent release of vascular endothelial growth factor (VEGF), inducing cell migration through different mechanisms [102,112,113]. During malignant transformation of stem cells, arsenite has also been shown to suppress expression of PTEN, an important inhibitor of PI3K/AKT signaling [114].

Although acute activation of this pathway is thought to be mediated by arsenic-induced ROS, the specific role of arsenic on PI3K/AKT signalling during chronic exposure remains to be clearly demonstrated [115].

Arsenic and the Nrf2-KEAP1 signaling pathway

The transcription factor nuclear factor erythroid-derived factor 2-related factor 2 (NRF2) plays a key role in the activation of oxidative stress response. NRF2 contains a leucine-zipper DNA binding domain capable of binding to both antioxidant response elements (ARE's) and electrophile response elements (ERE's). Under normal conditions,

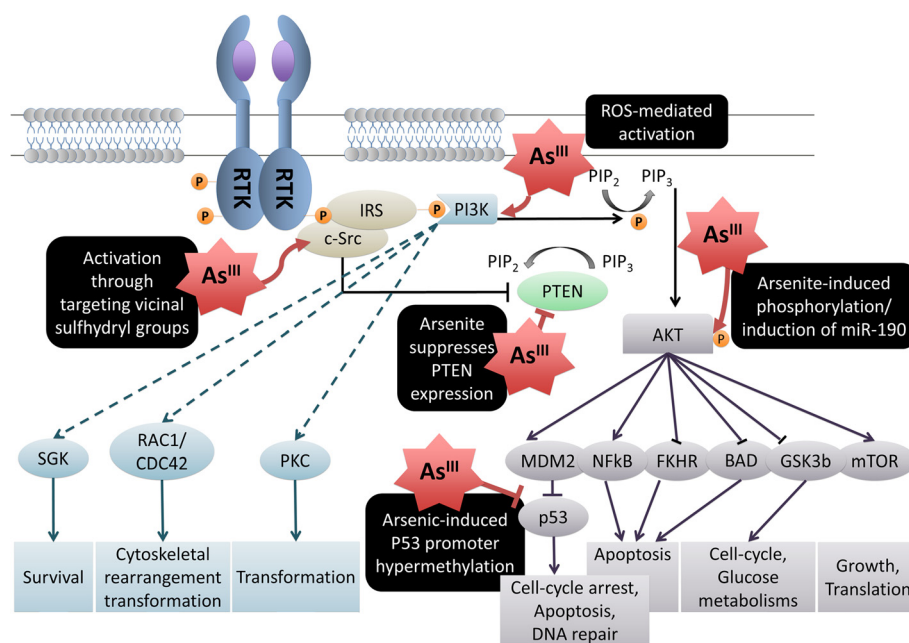


Figure 4 Arsenic-mediated disruption of PI3K/AKT signaling pathway. Depending on the receptor, different proteins can bind to the phosphorylated tyrosine residue of the RTK to recruit PI3K to the plasma membrane. There, the activated PI3K can interact with phosphatidylinositol 4,5-bisphosphate (PIP₂) on the inner side of the membrane, and catalyze its phosphorylation to phosphatidylinositol 3,4,5-triphosphate (PIP₃). PIP₃ activates the kinase AKT, which is capable of phosphorylating a number of target proteins in the cytoplasm and nucleus. Some of the direct targets of PI3K (light blue) and AKT (grey), and their consequences on cell fate are depicted. Arsenic targets sulfhydryl groups of PI3K kinases such as c-Src, also resulting in activation of the PI3K/AKT pathway. As^{III} can also activate AKT independently of PI3K, both through STAT3 and/or induction of miR-190. PTEN is an inhibitor of the pathway that has been shown to be a target of arsenic in stem cells. Among other mechanisms, methylation patterns at the promoter region of the p53 gene have been shown to be modified by arsenic, resulting in silencing of this tumor suppressor.

NRF2 is actively sequestered by KEAP1 and targeted for proteolytic degradation [116]; however, under conditions of oxidative or chemical stress, NRF2 dissociates from KEAP1 and migrates to the nucleus to initiate a stress-related response. The KEAP1 E3-ubiquitin ligase complex is frequently affected by genetic disruption and aberrant expression in non-small cell lung cancer, resulting in NF- κ B activation, is characteristic of lung tumorigenesis [117].

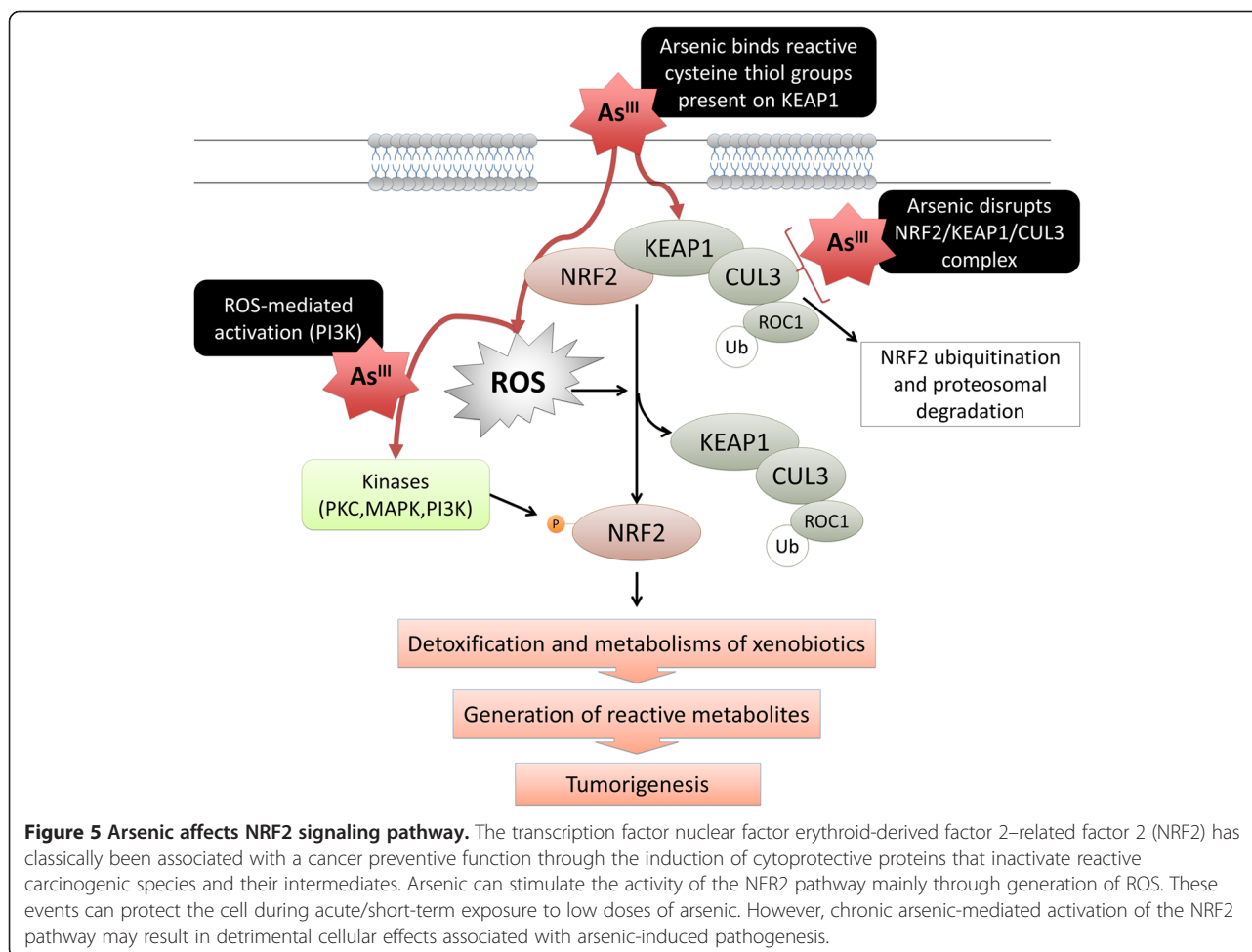
It has been proposed that activation of the NRF2 pathway confers protection against toxic effects induced by both As^{III} and MMA^{III} [118]. Pathological alterations in lung tissue, such as lung inflammatory response, induced by short-term exposure to arsenic can be prevented by NRF2 activation [119]. Arsenite can also stabilize NRF2 by disrupting the NRF2-KEAP1-CUL3 complex (Figure 5) [113]. It is possible that this occurs through the interaction of arsenic with KEAP1, since it has been reported that arsenic is capable of binding to reactive cysteine thiol groups present on KEAP1, thus triggering the dissociation of the complex and inducing constitutive NRF2-dependent signaling [120]. This apparent protective effect of NRF2 against arsenic toxicity

has been observed most often at low doses; however, chronic low-dose exposure may overwhelm the arsenic-mediated NRF2-dependent protection, resulting in over-stimulation of NRF2-dependant genes [121].

Conclusion and future directions

Lung cancer is the leading cause of cancer-related deaths in North America, affecting over 200,000 men and women each year [122]. Arsenic poisoning through contaminated drinking water leading to arsenic-induced lung cancer is a major public health concern; consequently, the mechanisms underlying the carcinogenic effects of arsenic in lung cancer has become an important avenue of research.

Undoubtedly, the biotransformation of As^V into As^{III} and its methylated conjugates plays a crucial role in arsenic carcinogenicity at both genetic and epigenetic levels. Genetic changes are acquired mainly through the induction of ROS during the biotransformation process, while the competition for methyl groups between As^V detoxification enzymes and DMT's contribute to epigenetic abnormalities.



Arsenic species directly modulate several oncogenic pathways – most notably the EGFR, PI3K/AKT and the NRF2/KEAP1 pathways – and these specific pathways possess actionable targets for therapy in lung cancer. A greater understanding of the molecular mechanisms governing arsenic-related lung tumorigenesis may therefore yield promising translatable findings. Deep characterization of arsenic-related tumors and/or cell models at both the genetic and epigenetic levels, and the comparison of arsenic-related and unrelated SqCC tumors may provide such insights. On the other hand, mechanisms associated with anti-tumoral effects of As₂O₃ in the treatment of APL (not discussed in this review) should also be considered in order to increase the understanding of the molecular effects of arsenic in the human body.

In conclusion, arsenic can induce specific alterations affecting pathways that drive malignant transformation in lung cells. Current evidence suggests that arsenic-induced lung tumors represent a unique class of lung cancer, based on histology and underlying molecular characteristics. Further characterization of the mechanisms by which arsenic affects its targets will certainly give support to preventing and/or reducing the effects of arsenic toxicity, especially among those populations chronically exposed to arsenic.

Abbreviations

AsIII: Arsenite; AsV: Arsenate; EGFR: Epidermal Growth Factor; HBEC: Human Bronchial Epithelial Cells; MMAIII: Monomethylarsonous Acid; NRF2: NFE2-Related Factor 2; PI3K: Phosphatidylinositol 3-kinase; ROS: Reactive Oxygen Species; RTK: Receptor Tyrosine Kinase; SAM: S-Adenosyl Methionine; SCC: Small Cell Carcinomas; SqCC: Squamous Cell Carcinomas.

Competing interests

All authors declare no conflict of interest on the topics covered by this review.

Authors' contributions

RH and DBS contributed to manuscript conception and writing. KE and DR contributed to literature search and manuscript writing. SL and WLL contributed to manuscript writing and critically revised the paper. All authors read and approved the final manuscript. VM contributed to study conception, manuscript writing and critically revised the paper.

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