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Arsenic and cancer: evidence and mechanisms

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Abstract

Arsenic is a potent carcinogen and poses a significant health concern worldwide. Exposure occurs through ingestion of drinking water and contaminated foods and through inhalation due to pollution. Epidemiological evidence shows arsenic induces cancers of the skin, lung, liver, and bladder among other tissues. While studies in animal and cell culture models support arsenic as a carcinogen, the mechanisms of arsenic carcinogenesis are not fully understood. Arsenic carcinogenesis is a complex process due its ability to be metabolized and because of the many cellular pathways it targets in the cell. Arsenic metabolism and the multiple forms of arsenic play distinct roles in its toxicity and contribute differently to carcinogenic endpoints, and thus must be considered. Arsenic generates reactive oxygen species increasing oxidative stress and damaging DNA and other macromolecules. Concurrently, arsenic inhibits DNA repair, modifies epigenetic regulation of gene expression, and targets protein function due its ability to replace zinc in select proteins. While these mechanisms contribute to arsenic carcinogenesis, there remain significant gaps in understanding the complex nature of arsenic cancers. In the future improving models available for arsenic cancer research and the use of arsenic induced human tumors will bridge some of these gaps in understanding arsenic driven cancers.

Keywords

arsenic; cancer; carcinogenesis; DNA damage; mechanism

INTRODUCTION

Over millennia, humans have harnessed the unique properties of arsenic for medicinal, agricultural, commercial, and decorative purposes. At the same time, humans have been subject to the stealthy toxicity of arsenic as an odorless and tasteless, intentional or unintentional, poison. Our complicated relationship with arsenic continues to this day.

Therapeutic uses of arsenic have been documented for thousands of years in traditional Chinese medicine and early western medicine. Two forms of arsenic were included in the

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Shennong Materia Medica in 200 BCE and Hippocrates is believed to use arsenic pastes to treat skin disorders (Au, 2011; Hughes et al., 2011; Paul et al., 2022; Chen & Costa, 2021). In 1786 Thomas Fowler reported on the medicinal effects of his arsenic solution for a broad range of infectious diseases and skin and blood disorders, in addition to other health conditions. The noted antimicrobial properties of arsenic led to the development of Salvarsan in the early 1900s as an effective treatment of syphilis garnering a Nobel prize for Paul Ehrlich in 1908. In the past, various forms of arsenic, including those used in traditional Chinese medicine and Fowler's solution, were employed as cancer therapeutics especially for cancers of the blood and skin (Au, 2011; Hughes et al., 2011; Paul et al., 2022; Chen & Costa, 2021). The FDA approved arsenic trioxide as a chemotherapeutic for leukemia in 2000 bringing an ancient drug into the modern era.

Other arsenic compounds have been beneficial as rodenticides, pesticides for agricultural crops and wood preservatives (Hughes et al., 2011; Bencko and Foong, 2017). Arsenic-based pigments were used in paints, fabrics and wallpapers based on a coveted emerald green color (Hughes et al., 2011). However, the medicinal and non-medicinal uses of arsenic revealed human toxicities based on unintended exposures. Widespread use of lead arsenate as a pesticide in apple and cherry orchards ultimately led to an official ban in the United States in 1988 (Hughes et al., 2011). The lasting legacy of this use is evident in millions of acres of land contaminated with lead arsenate. Chromated copper arsenate continues to be used as a wood preservative for non-residential purposes and organic arsenicals remain in restricted use as broad-spectrum herbicides. The potential for further contamination of soils and water by inorganic and organic arsenic compounds is under periodic review by the US Environmental Protection Agency (EPA).

Arsenic toxicity has been exploited for political gains through strategic poisonings leading to the often quoted statement labeling arsenic as the "king of poisons and poison of kings". Modern toxicological focus largely centers on the human health consequences of medicinal, occupational and environmental exposures to arsenic. Studies on health effects of human exposures through natural or anthropogenic arsenic contamination in soils and water led to adoption of drinking water standards worldwide currently at 10 ppb. Despite efforts to limit arsenic exposures, it is estimated that 200 million people or more are exposed to toxic levels of arsenic worldwide (Costa 2021). This chapter will focus on arsenic carcinogenicity and cover human population evidence for arsenic as a carcinogen, mechanisms of arsenic carcinogenicity, the carcinogenic potential of different forms of arsenic and conclude with a brief discussion of areas for future research.

SECTION 1: HUMAN STUDIES

Arsenic is a worldwide health concern due to prevalence in the environment and established human toxicity (Podgorski, 2020; Agency for Toxic Substances and Disease Registry (ATSDR), 2007; ATSDR, 2016; Naujokas et al., 2013). Arsenic is present in rocks, soil and water, and background environmental levels may be increased by mining, burning of fossil fuels, and application of agricultural pesticides and herbicides (Gundert-Remy et al., 2015). In recognition of its toxic potential, arsenic is at the top of the ASTDR Priority List (https://www.atsdr.cdc.gov/spl/index.html). Occupational exposures are limited by the US

Occupational Safety and Health Administration to 10 μg/m^3, and recommended drinking water exposure limits of 10 μg/L (10 ppb) have been established by the EPA and the World Health Organization (WHO) (WHO, 2011; EPA, 2014).

The majority of human population studies focus on chronic arsenic ingestion through drinking water as the predominant exposure route (Andrew et al., 2003; Banerjee et al., 2007; Podgorski, 2020, ATSDR, 2007, ATSDR, 2016; WHO, 2011). Many parts of the world have high levels of arsenic in groundwater and aquifers with populations that use these water sources for household needs. One arsenic prediction model based on household groundwater-usage statistics estimates that between 94 and 220 million people may be exposed to high arsenic concentrations (Podgorski, 2020). Indeed, many seminal health studies have focused on populations in areas of the world with high levels of arsenic in water sources including, but not limited to, Bangladesh, India, Taiwan and Chile (ATSDR, 2007; ATSDR, 2016; Banerjee et al., 2017; Farzan et al., 2021; Moore et al., 2002). Some studies have established the relationship between arsenic levels in water and arsenic in biological specimens such as urine, hair and nails (Mahata et al., 2003; Maki-Paakkanen et al., 1998; Ruíz-Vera et al., 2019).

More recently, greater attention has been paid to food as a source of arsenic exposure (Oberoi 2014; Gundert-Remy 2015; Arslan et al., 2017; Wong et al., 2022). Food crops may contain elevated arsenic levels through irrigation with arsenic-containing water, cultivation in arsenic contaminated fields, or use of agricultural products containing arsenic (Gundert-Remy et al., 2015; Wong et al., 2022). Rice has become a notable concern due to arsenic's uptake and accumulation in this plant compared to other common grains such as wheat (Karagas et al., 2019). There is evidence of greater urinary arsenic in individuals reporting higher rice consumption compared to those with low rice consumption even in areas of low arsenic drinking water exposure (Gossai et al., 2017).

The relationships between arsenic exposure and cancer are clear. Cancer is one of the health effects of concern; arsenic is classified as a Class I human carcinogen by the International Agency for Research on Cancer (IARC) with strong experimental and human population evidence to support arsenic carcinogenicity (IARC, 2004; Moore et al., 2002; Srinivas et al., 2019; Tam et al., 2020). The strongest evidence for organ-specific arsenic carcinogenicity is in skin, lung, bladder and kidney with evidence for arsenic contributions to other cancers (WHO, ATSDR, 2007, ATSDR, 2016; Palma-Lara et al., 2020) (Figure 1).

Skin Cancer

Various non-cancerous skin lesions are associated with long term exposure to inorganic arsenic including changes in pigmentation, plantar-palmar hyperkeratinization and hyperkeratotic warts and corns (ASTDR, 2007; Hunt et al., 2014). These skin changes are most common in areas with high arsenic levels in drinking water and are viewed as sensitive indicators of chronic arsenic exposure (ASTDR, 2007; Hunt et al., 2014; Cheng et al., 2016). Skin lesions and cancer appear to be more prevalent at exposures to drinking water levels in excess of 50 μg/L and evidence linking arsenic to skin cancer is less conclusive at lower arsenic levels (Boffetta et al., 2020, Lamm et al., 2021; Karagas et al., 2015). Recent

findings suggest that ingestion of arsenic containing foods in the diet such as rice may also contribute to skin cancer risk (Karagas et al., 2019; Gossai et al., 2017).

The most common tumors associated with arsenic exposure are keratinocytic tumors including squamous cell carcinomas, which may develop from hyperkeratotic warts or corns, and basal cell carcinomas (ASTDR, 2007; Karagas et al., 2015; Palma-Lara et al., 2020). There is less consistent evidence for arsenic-associated melanoma although it has been reported in Bangladesh (Choudhury et al., 2018), but not in the United States (Langston et al., 2022; Bedaiwi et al., 2021; Yager et al., 2016) or there are too few studies to draw firm conclusions (Matthews et al., 2019).

Lung Cancer

Epidemiological evidence indicates increased incidence of lung cancer in workers exposed to arsenic in the copper mining and smelting industry and ingestion through contaminated water (ASTDR 2007; Smith et al., 2012; Steinmaus et al., 2014; Palma-Lara et al., 2020). Studies conducted in Chilean cohorts born during periods of low versus high arsenic exposure from water reveal increased incidence of several cancers, including lung cancer, associated with the high exposure period (ASTDR, 2010; Smith et al., 2006). Similarly, mitigation efforts to decrease arsenic ingestion from contaminated water in Taiwan led to reduction in lung cancer rates (Su et al., 2011). No associations were identified for lung cancer and arsenic in soil in Taiwan despite reported associations between lung cancer and other metals in the same soils (Huang et al., 2013). These findings and others support the conclusion that lung cancer is increased upon chronic exposure to arsenic in drinking water (ASTDR, 2007; Kuo et al., 2017a; Su et al., 2011; Chen et al., 2010; Heck et al., 2009). There is evidence for dose dependence (Chen et al., 2010); however, the associations are less strong at low arsenic exposures (Shao et al., 2021; Tsuij et al., 2019)

The most common type of lung cancer associated with arsenic exposure is squamous cell carcinoma (Kuo et al., 2017; Heck et al., 2009; Taeger et al., 2009). The correlation between arsenic and squamous cell carcinoma was more pronounced at higher exposure levels; adenocarcinoma and small cell carcinoma of the lung were not associated with arsenic level in the drinking water in a Taiwan population (Kuo et al., 2017) although other investigators reported increased adenocarcinoma and small cell carcinomas of the lung with arsenic exposure (Chen et al., 2010; Guo et al., 2004). A study of former German uranium miners exposed to arsenic found that the arsenic-related type of lung cancer differed in miners based on evidence of silicosis. Arsenic was associated with increased squamous cell carcinoma in miners without silicosis. In contrast non-small cell lung cancer was related to arsenic exposure in miners with silicosis (Taeger et al., 2009) suggesting that other underlying factors may influence the specific lung cancer arising because of arsenic exposure.

Bladder Cancer

Population studies identify a clear relationship between elevated arsenic levels in drinking water and bladder cancer (IARC, 2004; ASTDR, 2007; Smith et al., 2012; Krajewski et al., 2021). A recent study found evidence for oxidative DNA damage in residents exposed to arsenic from artesian well-water in Taiwan and concluded that arsenic exposure and

DNA damage predicted the risk of bladder cancer (Tsai et al., 2021). In the US, arsenic concentrations in drinking water were positively associated with bladder cancer in both men and women (Mendez et al., 2017; Baris et al., 2016) and a spatial cluster analysis of bladder cancer mortality identified significant hot spots. Further study concluded that there was a significant association between bladder cancer mortality and arsenic intake from well water (Amin et al., 2019; Baris et al., 2016). Notably, well water is not subject to federal regulation and may exceed the EPA recommended maximum contaminant level. As with other arsenic-associated cancers, there is not uniform agreement on risks linked to lower exposures (Kayajanian, 2003) although a meta-analysis suggested that exposure to 10 μg/L of arsenic in drinking water may double the risk of bladder cancer (Saint-Jacques et al., 2014). Arsenic ingestion through food is also considered a potentially important source of exposure that may contribute to bladder and other cancers (Gundert-Remy et al., 2015; Oberoi et al., 2014; Karagas et al., 2019).

There are several studies that indicate arsenic exposure may influence bladder cancer progression and clinical outcomes. Comparisons of clinicopathological characteristics in bladder cancer patients from an arsenic contaminated region versus two reference areas found significantly greater proportions of locally advanced and high-grade tumors in the arsenic-exposed patients (Fernandez et al., 2020). Patients from areas of high arsenic exposure in Taiwan versus low arsenic exposure found worse prognosis in the patients from areas of high arsenic and this was most pronounced in the disease-free survival of early-stage disease (Chang et al., 2021). Similar findings were reported for patients in West Bengal, India where measured arsenic accumulation in bladder tumor tissue was associated with advanced tumors, poor prognosis and disease recurrence after treatment (Ghosh et al., 2021). These observations may be related to distinct mechanisms of arsenic carcinogenesis (Zhou et al., 2021; Palma-Lara et al., 2020) as described in Section 2.

Additional Cancers and Cancer Risk Due to Prenatal and Early Life Exposure

Although the evidence for arsenic-associated cancers is strongest for skin, lung and bladder tumors, there are other cancers that are linked to arsenic exposure. There is significant evidence for arsenic induced kidney cancer (Smith et al., 2012; Krajewski et al., 2021; Saint-Jacques et al., 2014; Ferreccio et al., 2013a; Naujokas et al., 2013; Palma-Lara et al., 2020; Chen and Costa, 2021) and liver cancer (Naujokas et al., 2013; Palma-Lara et al., 2020; Chen & Costa, 2021; ASTDR, 2010). There is more limited evidence for increased gastrointestinal tract (Krajewski et al., 2021; ASTDR, 2010), laryngeal (Smith et al., 2012), prostate (Lamm et al., 2021) and breast cancer (Moslehi et al., 2020) risk with elevated arsenic exposure (Abuawad et al., 2021). In the case of breast cancer, it appears that genetic factors may play an important modifying role in arsenic-associated risk (Moslehi et al., 2020).

Gestational and early life exposure to arsenic is associated with a variety of long-term health effects including increased risk of cancer in humans (Smeester and Fry, 2018; Martinez and Lam, 2021). Studies conducted in Northern Chile provide strong evidence for the cancer consequences of prenatal and early life arsenic exposures. In 1958, the levels of arsenic in drinking water increased nearly 10-fold to 870 ppb and remediation efforts in the 1970s

reduced arsenic in drinking water to near pre-1958 levels. This led to human cohorts with different levels and timing of arsenic exposure (Smith et al., 2012). Increased mortality rates were observed for bladder, laryngeal, lung, kidney, liver and other cancers (Smith et al., 2012; Ferreccio et al., 2013b; Steinmaus et al., 2014). Long latency patterns of 25 years or more after early life exposure have been reported for liver, kidney and bladder cancers, often accompanied by evidence for higher incidence and cancer mortality in children and young adults (Yuan et al., 2010; Marshall et al., 2007; Liaw et al., 2008). These findings point to arsenic cancer risks that can persist decades after exposure in early life stages. Given evidence from experimental animal models that prenatal arsenic exposure elevates cancer development (Martinez and Lam, 2021; Waalkes et al., 2007), arsenic exposures across the entire lifespan are a concern.

Modifying Factors of Arsenic Carcinogenesis

Arsenic is one of a limited number of metals or metalloids that is metabolized to methylated forms (Roy et al., 2020). Biotransformation of inorganic arsenic to mono and dimethyl forms (MMA and DMA, respectively) occurs through the enzyme arsenic methyltransferase (AS3MT) and arsenic is excreted as a mixture of inorganic and methylated forms (Roy et al., 2020, see also Section 3). Population studies suggest that the different forms of arsenic are not equivalent in carcinogenic potential. Studies of the proportion of inorganic and methylated arsenic species found that individuals with high urinary inorganic percent or low DMA present were more likely to develop bladder cancer (Chung et al., 2013) and a meta-analysis found that bladder and lung cancer were increased significantly with increasing MMA percent in the urine (Melak et al., 2014). Positive associations between percent urinary MMA and cancers of the breast and skin in addition to lung and bladder also have been reported (Abuawad 2021; Gamboa-Loira et al., 2017; Huang et al., 2018). There is increasing evidence that polymorphisms and expression levels of AS3MT may lead to differences in arsenic metabolism (Delgado et al., 2021) and are important factors in arsenic-related cancer risk and outcomes (Song et al., 2020; Huang et al., 2018; Lin et al., 2018; De la Rosa et al., 2017).

Co-exposures of arsenic and DNA damaging agents can amplify carcinogenesis with the greatest evidence in human populations for skin, lung and bladder cancers. The risk of arsenic-associated skin lesions that can be precursors to cancer was greater with sun exposure (Chen et al., 2006). Furthermore, arsenic exposure and smoking increase risk of lung and bladder cancers with evidence for significant arsenic dose effect (Tsuda et al., 1995; Karagas et al., 2004; Chen et al., 2010; Chen et al., 2004; Koutros et al., 2018; Ferreccio et al., 2013b). These population-based findings are consistent with experimental findings of arsenic co-carcinogenesis (Zhou et al., 2021). Cumulatively, the evidence derived from studies of human populations exposed to arsenic indicate that arsenic is a human carcinogen both as a single agent and the carcinogenic effects can be modified by multiple factors including genetic polymorphisms and toxic co-exposures.

SECTION 2: MECHANISMS OF ARSENIC CARCINOGENESIS

The diverse range of cellular effects of arsenic exposure create a complex landscape for studying arsenic carcinogenesis. Many processes affected by arsenic exposure are interconnected further complicating our understanding of arsenic's effects. This section will discuss key mechanisms of arsenic carcinogenesis focusing on oxidative stress, the role of DNA damage and repair in genotoxicity, epigenetic changes, and how arsenic interacts with proteins to affect major pathways of carcinogenesis.

Oxidative Stress

Oxidative stress is a cornerstone of arsenic toxicity and carcinogenesis. It plays a role in DNA damage, repair inhibition and cellular mechanisms related to cell stress and cell death. Arsenic induces elevated levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that are damaging to macromolecules in the cell including DNA and protein (Ding et al., 2005; Wang et al., 2013) (Figure 2). Oxidative stress due to arsenic exposure is initiated by intracellular metabolism of arsenic, which involves glutathione (GSH) as a necessary mediator. GSH depletion during arsenic metabolism may result in reduced ability to ameliorate damaging ROS, both endogenous and those produced by the direct effects of arsenic in the cell. Arsenic metabolism also produces additional reactive intermediates. For example, the dimethylarsenic peroxyl radical, which is formed in the metabolism of dimethylarsenic acid, a methylated form of inorganic arsenic, further requires antioxidant remediation, and this intermediate has been shown to induce DNA damage (Flora et al., 2007; Yamanaka, 1994; Yamanaka et al., 1995). Specific forms of arsenic and their effects on oxidative stress are discussed in Section 3.

In general, reactive species arise due to the reduction of molecular oxygen to form superoxide radical anions ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), hydroperoxyl radicals (HOO•), singlet oxygen (O_2), and peroxyl radicals (ROO•) (Wiseman and Halliwell, 1996). Arsenic facilitates the formation of these species by targeting several different processes. The role of arsenic in production of ROS is observed in the mitochondria where it causes dysregulation of the electron transport chain (Hosseini et al., 2013). Arsenic inhibits succinate dehydrogenase activity responsible and altering the balance of oxidative phosphorylation and O_2 production which perpetuates formation of additional ROS while also altering mitochondrial membrane potential (Hosseini et al., 2013; Yen et al., 2012). Mitochondria also contain elevated levels of sulfhydryl containing enzymes due to their redox-prominent role making many enzymes in the mitochondria molecular targets of arsenic exposure (Netto et al., 2002). Arsenic induced ROS also leads to formation of oxidative DNA damage, which can be measured as 8-hydroxy-2'-deoxyguanosine (8-OHdG) (Chayapong et al., 2017; Ding et al., 2005; Kessel et al., 2002). NADPH oxidase (NOX), which is activated by arsenic and stimulates increased generation of ROS, is one mechanism of increase DNA damage through oxidative stress (Cooper et al., 2022).

Arsenic causes various forms of cellular damage, which enhances the formation of radicals in the cell, adding to oxidative stress. For example, arsenic exposure leads to the formation of oxidized lipids, which can be used as a biomarker for arsenic-induced oxidative

stress. Lipid peroxidation contributes to protein damage and compromised mitochondrial permeability forming a cycle of increased damage to macromolecules and ROS (Li et al., 2020; Mahajan et al., 2018; Nutt et al., 2005).

Arsenic generates RNS including nitric oxide (NO•), which further interacts with another product of arsenic exposure, $O_2^{\cdot -}$, to produce peroxynitrite ($ONOO^-$), which can affect DNA and proteins (Pace et al., 2017). $ONOO^-$ induces the nitration of tyrosine in proteins potentially altering their function. $ONOO^-$ also can cause S-nitrosation of cysteine residues in proteins, which was demonstrated in a study on the DNA repair protein, PARP-1 and was inhibited by the production of ROS and RNS after exposure to arsenic (Zhou et al., 2019). Additionally, $ONOO^-$ interacts with guanine forming 8-nitroguanine, which is used as a biomarker for RNS production (Kawanishi and Hiraku, 2006). Levels of arsenic exposure have been correlated with increased levels of 8-nitroguanine in epidemiology studies (Navasumrit et al., 2019; Phookphen et al., 2017). Arsenic-induced ROS and RNS increase oxidative stress leading to direct and indirect damage to DNA, proteins, and signaling pathways involved in maintaining genomic integrity. These effects are further discussed in the following sections.

Genotoxicity

Arsenic carcinogenesis is a complex process. However, the current body of research suggests genotoxicity arising as damage to genetic information is a key driver of arsenic-induced cancers and is a result of combined induction of DNA damage, inhibited DNA repair, and aberrant cell division. Genotoxicity begins with damage to genetic material. There is sufficient data showing arsenic exposure results in various forms of DNA damage including DNA double- and single-strand breaks and other lesions such as 8-nitroguanine and 8-OHdG as discussed above (Ding et al., 2005; Dong and Luo, 1993; Dutta et al., 2015; Okayasu et al., 2003). However, arsenic does not directly interact with DNA to cause damage, and there is a lack of strong evidence of arsenic forming adducts with DNA. Instead, studies show arsenic induced oxidative stress is responsible for the majority of DNA damage after arsenic exposure (Kumar et al., 2016). Studies show RNS and ROS inhibitors and pre-treatment with antioxidants attenuate DNA damage after arsenic exposure suggesting oxidative stress is a major contributor in arsenic-induced DNA damage (Ding et al., 2005; Lynn et al., 1998; Nesnow et al., 2002). This effect was also observed in arsenic-exposed human populations (Biswas et al., 2010) and animal studies (Balakumar et al., 2012; Kadirvel et al., 2007)

DNA double strand breaks are a particularly lethal form of DNA damage and if left unrepaired result in cell death. Arsenic-induced DNA double strand breaks have been identified in a number of studies (Guillamet et al., 2004; Mouron et al., 2006; Okayasu et al., 2003; Xie et al., 2014). If mis-repaired, these DNA double strand breaks in sites of key tumor suppressor genes may lead to changes to the genetic material and carcinogenesis. This result is also true of single-strand breaks and the formation of intra-DNA adducts and crosslinks with proteins and other cellular molecules (Bau et al., 2002; Dong et al., 1993; Mouron et al., 2001; Wang et al., 2001). DNA adducts and DNA-protein adducts may also contribute to the formation of DNA double strand breaks if mis-repaired (Bau et al., 2002, Wang et al., 2001). Several studies show arsenic exposure results in crosslinking of

proteins, including DNA repair proteins, with DNA potentially inhibiting repair processes and contributing to genomic instability (Garman et al., 1997; Gebel et al., 1998; Mustra et al., 2007). In another study arsenic-induced DNA-protein crosslinks were observed with gross chromosomal changes including sister chromatid exchanges, a hallmark of genomic instability (Mouron et al., 2005).

Genomic instability is a common driver of cancers and is associated with exposure to many metals including arsenic (Mitkovska et al., 2020; Wu et al., 2019; Wise and Wise, 2012). DNA damage and dysregulation of cell division induced by arsenic ultimately leads to gross changes to genetic material including formation of micronuclei (Basu et al., 2004; Navasumrit et al., 2019), both numerical and structural chromosome instability (States, 2015), and microsatellite instability (Wu et al., 2017). Numerical chromosome instability associated with arsenic exposure has been observed in both human populations (Dulout et al., 1996), cell culture models (Eguchi et al., 1997; Salazar et al., 2010; Sciandrello et al., 2002), and animal studies (Kashiwada et al., 1998). Numerical chromosome instability can arise due to uncoupling mechanisms involved in cell division, such as changes in mitotic checkpoints and centrosome dysregulation, and is considered a driving force of carcinogenesis (Sansregret and Swanton, 2017). Arsenic induces prolonged mitotic arrest resulting in aneuploidy (Eguchi et al., 1997; Yih et al., 1997). Other studies have shown arsenic disrupts centrosome function (States et al., 2002; Suzuki et al., 2009), which can be carried down through cell populations even after removal of arsenic suggesting these changes may be permanent and heritable (Sciandrello et al., 2002). Another endpoint of altered cell division is the formation of micronuclei, which form as a result of lagging chromosomes and chromosome fragments, and these events have been observed in arsenic-exposed cells (Moore et al., 1996), workers (Lewińska et al., 2007; Vuyyuri et al., 2006), and in populations exposed to arsenic in drinking water (Tian et al., 2001; Warner et al., 1994).

Structural chromosomal changes including chromatid exchanges, ring structures, and dicentric chromosomes have been identified in arsenic-exposed human populations (Banerjee et al., 2007; Ghosh et al., 2006; Mahata et al., 2003). Other studies have identified chromatid gaps associated with arsenic exposure and urine levels (Maki-Paakkanen et al., 1998). Importantly for carcinogenesis, increases in chromosomal aberrations have been associated with arsenic-induced cancers and pre-cancerous lesions. For example, chromosome aberrations were found in patients with arsenic-induced Bowen’s disease (Ghosh et al., 2007), arsenic-induced stomach cancer (Boffetta et al., 2007), and were higher in bladder cancer patients with arsenic exposure than those without (Moore et al., 2002).

Telomere maintenance and stability is closely tied to maintaining genomic stability. Several recent studies in an arsenic exposed human population found exposure was associated with altered telomere length, which is also attributed to enhanced chromosomal instability and cancer (Chatterjee et al., 2018; Villarreal et al., 2019). Guanine bases are a target of arsenic-induced oxidative damage. Thus, telomeres, rich in guanine, are a target of arsenic exposure. For example, Coluzzie et al., 2014 showed telomeric changes, included enriched DNA damage and shortening, occurred because of arsenic-induced oxidative stress. These telomeric changes may contribute to compromised protection provided by telomeres in

maintaining chromosomal integrity. Other studies have identified arsenic-induced oxidative stress as a source of telomere attrition and structural chromosome instability arising as end-to-end fusions, and these effects were reduced by the addition of antioxidants (Liu et al., 2003). Epidemiology studies have confirmed arsenic exposure is associated with decreased telomere length and increased risk of skin carcinomas (Farzan et al., 2021; Grau-Perez et al., 2019; Srinivas et al., 2019) while other studies have shown the opposite (Gao et al., 2015).

The literature supports genomic instability represented as structural and numerical chromosome instability and alterations to chromosome maintenance (telomeres) as a prominent mechanism of arsenic-induced carcinogenesis. While these changes are evident the mechanisms of how they arise are important in understanding arsenic carcinogenesis. Changes in cell division were discussed above in association with numerical chromosome instability. However, structural chromosome instability is most associated with DNA damage (discussed above) and failure of robust DNA repair pathways as discussed below.

DNA repair

Arsenic induces a variety of DNA lesions, each with distinct repair pathways (Figure 3). Inhibited DNA repair after arsenic exposure is considered a driving mechanism of genomic instability and arsenic-induced cancers and research in this area has uncovered detailed cellular mechanisms of arsenic carcinogenesis. Mechanistic studies show arsenic affects critical repair factors in pathways of DNA repair including excision repair pathways, nucleotide excision repair (NER), base excision repair (BER) and strand break repair pathways, homologous recombination (HR), and non-homologous end joining (NHEJ).

Excision repair mechanisms are used to remove oxidative damage to nucleotides. Non-bulky damage to DNA bases, such as arsenic-induced 8-oxoguanine and apurinic and apyrimidinic sites, are repaired by BER. BER has been shown to be essential in repairing oxidative damage after arsenic exposure (Lai et al., 2011). Meanwhile BER genes were found to have decreased expression in HaCaT cells exposed to arsenic exposure (Ding et al., 2021). Specifically, human 8-oxoguanine DNA glycosylase I (Ebert et al., 2011), DNA polymerase β, and APE1 (Sykora and Snow, 2008) were found to have suppressed or altered expression and activity in human lung cells after arsenic exposure contributing to repressed BER function.

NER is responsible for repairing bulky type DNA lesions and is particularly important when considering arsenic as a co-carcinogen. NER repairs bulky lesions such as cyclobutane DNA photoproducts induced by ultraviolet radiation (UVR) and DNA adducts as a result of polyaromatic hydrocarbon (PAH) exposure. Arsenic alters NER through several mechanism. Individuals exposed to arsenic in drinking water were found to have decreased expression of DNA repair genes across in cell culture and human populations (Andrew et al., 2003; Andrew et al., 2006). Studies focused on NER after arsenic exposure have identified specific protein targets of arsenic including XPC, XPA, and ERCC1 (Holcomb et al., 2017; Huestis et al., 2016; Muenyi et al., 2011; Nollen et al., 2009; Zhou et al., 2014). Other mechanisms of arsenic-inhibited NER include inhibited protein function. Arsenic inhibits the activity of DNA ligase III and DNA ligase I (Hu et al., 1998). Extensive studies have also found zinc finger proteins in the NER pathway, including XPA are targeted by arsenic exposure altering

their function and are further discussed in Section 3 below (Huestis et al., 2016; Zhou et al., 2014). In addition to direct protein effects, polymorphisms in NER genes were found to be associated with non-melanoma skin cancer and arsenic exposure (Applebaum et al., 2007).

If NER or BER fail to repair DNA damage, double strand breaks can arise. These breaks are repaired by NHEJ or HR as a final attempt to repair the damage and maintain genomic integrity. However, studies show that both NHEJ and HR are impaired by arsenic exposure. Notably Morales et al., 2016 found arsenic shifted repair to the more error-prone alt-NHEJ pathway from the high-fidelity HR repair pathway potentially resulting in mis-repaired DNA double strand breaks and increased genomic instability. Arsenic has been shown to affect HR repair by altering recruitment of HR repair factors including BRCA1 and RAD51 (Zhang et al., 2014). Arsenic increased sumoylation of Mus18, an endonuclease involved in cyclobutane pyrimidine dimers (CPDs) and 6,4'PP HR repair, resulting in compromised DNA damage response (Hu et al., 2017). PARP-1 may play a role in double strand break repair due to changes to PARylation and therefore recruitment of DNA double strand break repair factors. PARP-1 also plays a role in BER, NHEJ, single strand break repair, and as a zinc finger protein has been shown to be a primary target of arsenic exposure, which will be discussed in Section 3.

Epigenetic changes

While studies have identified DNA repair deficiency as a mechanism of arsenic carcinogenesis, epigenetic regulation contributes to changes in DNA repair after arsenic exposure. Decreased gene expression is an established effect of arsenic exposure and studies show arsenic alters DNA methylation patterns across the genome with some sex differences (Bailey et al., 2013; Broberg et al., 2014; Nohara et al., 2011). Increased methylation of promotors involved in DNA repair has been associated with modified expression after arsenic exposure and was observed across different repair pathways. For example, BRCA1, ERCC2, MLH1, and OGG1 all had increased promoter methylation after arsenic exposure often associated with decreased expression (Hossain et al., 2012; Paul et al., 2014; Selmin et al., 2019; Wang et al., 2021). These studies support the finding that DNA methylation is associated with persistent genomic instability (Mauro et al., 2015). Confirming the importance of these finding are studies showing altered methylation patterns in populations exposed to arsenic (Bhattacharjee et al., 2018; Intarasunanont et al., 2012).

DNA methylation may be affected by the metabolism of arsenic, which involved methylation steps. Long term arsenic exposure has been associated with DNA hypomethylation as a result of depleted S-adenosylmethionine (SAM) (Reichard et al., 2007). While the mechanisms are not fully understood, SAM depletion results in decreased DNA methyltransferase activity, which may contribute to this effect (Du et al., 2018). Depletion of SAM and methylation activity may also affect histone methylation.

Posttranslational histone modifications, including methylation and acetylation, play an important role in gene expression. Arsenic has been shown to affect each of these posttranslational modifications creating a complicated landscape for understanding how they alter gene expression and accessibility and recruitment of DNA repair factors to sites of DNA damage. One study found the altered balance of H3K9me2, H3K36me3

and H4K20me2 after arsenic exposure may lead to decreased repair ability at sites of DNA damage (Li et al., 2016). Directly related to expression of DNA repair genes, arsenic increased H3K9me2 was found to reduced expression of genes involved in BER (Ding et al., 2021). Other studies show global histone methylation patterns after arsenic exposure are a contributing factor in malignant transformation (Ge et al., 2018) and cell transformation (Qiu et al., 2021). Zhang et al., 2020 found histone demethylase JDHM2A is responsible for regulating H3K9 dimethylation after arsenic exposure as a potential mechanism.

Arsenic altered levels of histone acetylases may also contribute to changes in gene expression, especially of DNA repair genes. H3K18ac was downregulated after arsenic exposure and this effect was notable in the promoter regions of NER protein genes (Zhang et al., 2020). Arsenic may also inhibit accessibility to repair sites of DNA damage through decreased histone acetylation. For example, arsenic decreased global H4K16Ac, notable for its role in relaxing chromatin, with concentration and time (Jo et al., 2009). Mechanisms of altered histone acetylation, including the effect of arsenic on histone acetyltransferases following arsenic exposure has been linked to zinc finger protein interactions (Tam et al., 2017).

Epigenetic alteration of gene expression is also affected by arsenic-induced changes in microRNAs, which have been linked to inhibited DNA repair, increased sensitivity to oxidative stress, and cellular transformation, and have been proposed to be used as biomarkers of arsenic exposure (Sturchio et al., 2014). Various cohorts of arsenic exposed people around the world have been evaluated for changes in microRNA expression to understand which microRNAs may be playing a role in disease progression (Al-Eryani et al., 2018a; Banerjee et al., 2019; Beck et al., 2018; Ruiz-Vera et al., 2019). Specific microRNAs have been linked with arsenic-induced skin lesions and cancers. For example, Banerjee et al., 2017 found miR-21 contributes to skin lesion and cancer in chronically exposed individuals.

Cell culture studies have looked closely at the role of specific microRNAs altered by arsenic exposure in targeted pathways of cancers. A study of prolonged exposure to arsenic used HaCaT cells as a model for skin cancer and identified dynamic changes in microRNA expression at different stages of exposure and transformation (Banerjee et al., 2022). Looking at specific microRNAs, Gonzalez et al., 2015 found arsenic upregulated miR-21, miR-200a, and miR-141 expression, and determined a likely association with pathways of melanoma progression. Another cell culture study found miR-200b was associated with malignant transformation of bronchial epithelial cells (Wang et al., 2011). These studies have investigated associations between microRNAs and cellular transformation and carcinogenesis. Others have focused on earlier processes in arsenic carcinogenesis. For example, arsenic altered microRNAs were implicated in targeting specific pathways such as the TP53 pathway, implicated to have early effects contributing to carcinogenesis (Al-Eryani et al., 2018b). An *in vivo* study in rats found arsenic-responsive microRNAs are likely involved in pathways of oxidative stress, specifically related to genes that regulate GSH levels (Ren et al., 2015).

MicroRNA studies in human populations and in experimental models have been used to understand how they may affect DNA repair. For example, Wei et al., 2018 found miR-145 was upregulated in individuals exposed to toxic levels of arsenic, and this effect was replicated in a cell culture model where it was found to target expression of ERCC2, potentially having a negative impact on DNA repair. From these studies it is likely microRNAs play a role in pathways of arsenic-induced carcinogenesis and modulating expression DNA repair genes.

Protein Effects

Arsenic-dependent changes to protein expression were discussed above. However, arsenic also affects protein directly. Recent studies have focused on how arsenic affects protein folding signaling pathways and protein function. For example, arsenic induced endoplasmic reticulum protein folding stress, which contributed to autophagy defects but not oxidative stress suggesting this effect is independent of ROS (Dodson et al., 2018). Endoplasmic reticulum protein folding effects have been observed in other arsenic studies as well and is associated with autophagy (Wadgaonkar and Chen, 2021).

While arsenic-altered protein expression and processing contribute to carcinogenic mechanisms, studies show arsenic can interact with zinc finger proteins causing inhibited function, and as briefly mentioned in Section 1, has a significant effect on zinc finger protein interactions. Zinc finger proteins are highly sensitive to oxidation due to thiol groups that play a central role in their function (Krishna et al., 2003). This structure is protected and maintained by a zinc ion, which coordinates a combination of 4 cysteine and histidine residues within the zinc finger domain. Zinc fingers can be found in several arrangements of cysteine and histidine including C2H2, C3H1, C4 and more complex structures like C4C4 ring domains (Klug et al., 2010; Razin et al., 2012). These structures are largely responsible for protein binding nucleic acids and with other proteins (Eom et al., 2016; Fu and Blackshear, 2017).

The mechanisms of arsenic disruption of zinc finger proteins involves the direct displacement of zinc by arsenic within the zinc finger domain. However, different forms of arsenic bind the specific zinc finger orientations depending on the ratio of cysteine and histidine. In general, arsenic has a lower binding affinity for protein with one or two cysteines compared to those with three or four (Asmuss et al., 2000; Kitchin and Wallace, 2006a; Kitchen and Wallace, 2006b). However, while arsenite and arsenic trioxide show a preference to bind to C3H1 and C4 zing finger domains methylated arsenic can bind to all three C2H2, C3H1, and C4 types (Zhou et al., 2014). Details of specific forms of arsenic in carcinogenic mechanisms is discussed in Section 3. Arsenic is similar enough to zinc to competitively displace it from the zinc finger, but in doing so induces a conformational shift within the domain altering how the protein functions (Quintal et al., 2011). The selectivity of different forms of arsenic to bind zinc finger domains with specific combinations of cysteine and histidine also suggests binding selectivity and may impact specific carcinogenic mechanisms differently.

Arsenic displacement of zinc has significant implications for protein in many cell regulatory pathways affecting DNA repair and gene expression (Huestis et al., 2016; Zhou et al.,

2020a). Many studies have focused on the impact of arsenic on zinc finger proteins involved in DNA repair (Cooper et al., 2014; Ding et al., 2017; Tam et al., 2020; Zhou et al., 2011; Zhou et al., 2015). After DNA damage, repair proteins must form complexes around the damage site, which requires binding to the damaged DNA. DNA-binding proteins use zinc fingers for this purpose, and therefore if disrupted, can destabilize DNA repair complexes at sites of damage and inhibit repair. The DNA repair protein PARP-1 is a C3H1 zinc finger DNA binding protein shown to be a sensitive target of arsenic exposure inhibiting its function (Ding et al., 2009; Walter et al., 2007). This disruption interferes with DNA binding and recruitment of other DNA repair factors involved in different pathways of repair including NER and BER (Chaudhuri et al., 2017). Arsenic was also found to bind and displace zinc in XPA, a critical DNA repair factor in NER (Huestis et al., 2016).

Arsenic may impact DNA repair by modulating access to sites of DNA damage. Zhang et al., 2014 found arsenic was able to bind to RNF20 and RNF40 RING finger domains causing a conformational shift in these proteins. The RNF20 and RNF40 RING fingers are responsible for the monoubiquitinating histone H2B and promoting access of DNA double strand break repair factors to sights of DNA damage (Zhang et al., 2014). Indeed, Recruitment of DNA repair factors including the HR repair protein, RAD51, to sites of double strand breaks was impaired after arsenic exposure. Similarly, arsenic was found to bind the FANCL E3 ubiquitin ligase and RING finger protein, altering recruitment of DNA repair factors to sites of DNA interstrand crosslinks (Jiang et al., 2017). These studies demonstrate arsenic can impact the function of different types of zinc finger proteins. Additionally, this interference affects different mechanisms of DNA damage repair and recruitment highlighting the dynamic and vast effect arsenic can have on cellular processes.

Signaling Pathways

Altered signaling after arsenic exposure contributes to checkpoint control, DNA repair response, and cell survival changes linking them together. Many pathways altered by arsenic exposure are interconnected and likely affect multiple mechanisms of arsenic carcinogenesis. One study using arsenic as a case study predicted top pathways associated with arsenic exposure include stress response, apoptosis, cell cycle, and protein signaling pathways such as MAPK, Jak-STAT, and p53 (Davis et al., 2008). MAPK signaling disruption has been observed in cell culture studies to increase cell invasiveness (Tingting et al., 2010). Predictions on arsenic's effect in signaling pathways including JNK, EGFR, AKT, PI3L, mTOR, and Nrf2-Keap1 have been extensively validated in other studies as well (Chen et al., 2013; Kang and Lee, 2008; Fu et al., 2021; Wang et al., 2017). These pathways are interconnected but are largely related to cell survival and escape from cell death and transformation.

The EGFR pathway has been closely linked with alterations of DNA repair and cell proliferation after arsenic exposure. Tong et al., 2015 found DNA mismatch repair was inhibited after arsenic exposure by promoting EGFR expression. Another study found EGFR and HB-EGF were activated in arsenic-transformed cells to promote cell proliferation (Wang et al., 2020). Recently a study in lung epithelial cells found EGFR expression was enhanced

after acute and chronic arsenic exposure, but the mechanism responsible for these changes was different depending on the exposure time (Kim et al., 2020).

The balance of cell survival and cell death pathways are shifted after arsenic exposure (Dreval et al., 2018; Watcharasit et al., 2012). The Nrf2-Keap1 signaling pathway is a cellular mechanism implicated in promoting cell survival and when dysregulated is considered to have cancer-promoting functions. Specifically, constitutively active Nrf2 leads to a variety of downstream implications including altered expression of growth factors, antioxidant proteins, transcription factors, and protein processing due to its activity in binding antioxidant response elements (AREs) in the promoter of genes (Hayes et al., 2010). Studies show arsenic constitutively activates Nrf2 is closely tied to the alteration of the autophagy pathway (Lau et al., 2013; Zhou et al., 2020b). Indeed, studies show arsenic increases autophagy activity (Bolt et al., 2010; Pucer et al., 2010).

Many studies have investigated the PI3K AKT, and mTOR pathways in arsenic cellular transformation and malignancy (Chen and Costa, 2018). When these pathways are unregulated normal cell growth becomes aberrant. Chronic arsenic exposure alters the PI3K/AKT pathway and is associated with anchorage-independent growth and cell migration (Carpenter and Jiang, 2013). Other studies have found autophagy dysfunction is tied to PI3K and mTOR signaling (Liang et al., 2020). Evidence shows in arsenic-transformed cells the AKT pathway is implicated in enhancing invasiveness (Wang et al., 2012) while being regulated upstream by JNK to promote alterations in phosphorylation of proteins involved in altering expression of tumor suppressors and oncogenes (Chen et al., 2013).

SECTION 3: CHEMICAL FORMS OF ARSENIC AND CARCINOGENESIS

Inorganic and Organic Arsenic Forms, Exposure, and Metabolism

Arsenic exists in several different oxidation states and various chemical forms (Carlin at al., 2016; Bolt and Henglestler, 2018). There are two major oxidation states of arsenicals, trivalent and pentavalent. Both oxidation states exist naturally (Carlin at al., 2016; Zhu et al., 2014). Arsenic occurs naturally in many minerals, usually in combination with sulfur and metals. Humans can be exposed to arsenic through different forms and oxidation states, and metabolism of arsenic also converts one form or oxidation state to another (Watanabe and Hirano, 2013). Each form/oxidation state may have different exposure routes, organ/tissue distribution, toxicity, and carcinogenic effects (Watanabe and Hirano, 2013; Sattar et al., 2016). There are two major forms of arsenicals, inorganic and organic. Inorganic arsenicals are the major form of arsenic exposure, occupationally and environmentally. Organic arsenicals are mainly acknowledged as metabolites of arsenic, specifically, in methylated forms (Negro Silva et al., 2017; Cohen et al. 2006).

Trivalent arsenicals are found in the form of sodium/potassium arsenite and arsenic trioxide (Dopp et al., 2005). Pentavalent arsenicals are mainly found as sodium arsenate. The environmental existence of inorganic arsenicals is in two major phases, solid and a liquid. Inorganic arsenicals in ground water can be found in both trivalent and pentavalent forms (Zheng et al., 2017). The trivalent and pentavalent forms mainly exist in oxic and anoxic

waters, respectively, due to their chemical properties. Drinking water is a major source of environmental exposure of inorganic arsenicals (Carlin at al., 2016; Zhu et al., 2014; Mantha et al., 2017). As mentioned in Section 1 arsenicals may also be accumulated in plants through irrigation (Zhu et al., 2014; Mantha et al., 2017; Dominguez-Gonzales et al., 2020), such as rice and vegetables, which also serve as a significant source of inorganic arsenic exposures. Trivalent and pentavalent arsenicals also exist in soil which leads to inhalation exposure from dust (Liu et al., 2016, Alamdar et al., 2016). Occupational exposure of arsenic can occur in facilities that manufacture pesticides, herbicides, and other agricultural products (Baker et al., 2018). Mine smelters and woodworking facilities are also major sources of occupational inorganic arsenic exposures.

Organic arsenicals are not commonly found naturally in the environment. Organic arsenicals include arsanilic acid, arsenosugars, and methylated arsenicals. Methylated arsenicals are produced as a consequence of inorganic arsenic biotransformation in various organisms. Humans may be exposed to methylated arsenicals from ingestion of seafood and meat (Yoshinaga and Narukawa, 2021; Naess et al., 2020).

Trivalent arsenic uptake into eukaryotes is mediated mainly by proteins in the aquaporin superfamily (AQPs) (Agre et al., 2002). Mammalian AQPs were first identified to transport trivalent arsenic in rat and mice as AQP9 and AQP7, respectively (Liu et al., 2002). Meanwhile, trivalent arsenic has also been shown to be taken up by glucose transporters such as GLUT1 (Liu et al., 2006) and hexose permeases (Liu et al., 2004). Both aquaglyceroporins and glucose permeases are bidirectional routes of trivalent arsenic into and out of cells.

Organic arsenic forms contribute to arsenic toxicity mainly through metabolic pathways. The metabolism of arsenic after absorption consists of two major types of reactions; oxidative methylation and reduction (Li et al., 2017; Hughes et al., 2011) (Figure 4). First, arsenite is oxidatively methylated into monomethylarsonic acid (MMA^V). MMA^V is thus reduced into monomethylarsonous acid (MMA^{III}). Second, MMA^{III} is oxidatively methylated into dimethylarsonic acid (DMA^V), then reduced into dimethylarsonous acid (DMA^{III}). The metabolism of arsenic plays a critical role in toxicity and carcinogenesis. The exact mechanisms of action of different arsenic forms is still unclear, but various hypotheses have been proposed.

Under drinking water exposure, an animal study of organ distribution of arsenicals suggested that kidney, lung and liver contain highest levels of arsenic (Li et al., 2013). In lung, the major form is DMA^{III} at almost all time points (Kenyon et al., 2005). At early stages of exposure, liver and kidney contain all forms of arsenicals, such as MMA^{III}, MMA^V, DMA^{III}, DMA^V, and inorganic arsenic. At later stages, both liver and kidney show an increase in the percentage of DMA^{III} in arsenicals (Kenyon et al., 2005). In contrast, blood and brain contains the lowest level of all arsenic forms compared to other organs across all time points. Inorganic and organic arsenicals were also reported to be strongly accumulated in reproductive organs (Pant et al., 2004).

The subcellular distribution of arsenicals largely depends on the cell type. According to the characteristics of arsenic metabolism, there are two different types of cells, methylating (such as hepatocytes) and non-methylating (such as urothelial cells) (Dopp et al., 2010). The membrane permeability and the efficacy of arsenic uptake depend upon both the arsenic species and the cell type (Dopp et al., 2005). Uptake rates of MMA^{III} and DMA^{III} were highest and exceeded those of their pentavalent counterparts by several orders of magnitude. Non-methylating cells accumulate higher amounts of arsenic within the cell than the methylating cells, and cellular uptake and efflux seem to be faster in methylating cells. Elevated concentrations of arsenic are present in the ribosomal fraction of non-methylating cells and in nucleic and mitochondrial fractions of methylating cells. However, cytotoxic and genotoxic effects are more pronounced in methylating cells (Dopp et al. 2008), which also suggests that methylated forms of arsenic may have greater cytotoxic effects than inorganic arsenic forms.

Carcinogenesis of Arsenic Forms

Arsenic exposure is mainly in the form of trivalent inorganic arsenic through gastrointestinal absorption. Different forms and oxidation state of arsenicals play various roles in carcinogenesis (Wadgaonkar and Chen, 2021). Some research indicates that organic arsenic forms such as MMA and DMA are most relevant to skin and bladder cancers (Gamboa-Loira et al., 2017). MMA and DMA are both positively related to almost all types of cancers (Gamboa-Loira et al., 2017; Di Giovanni et al., 2020; Kuo et al., 2017; Jomova et al., 2011). However, DMA level was found to be negatively correlated to lung cancer only (Gamboa-Loira et al., 2017).

MMA^{III} induces malignant transformation in a human bladder urothelial cell line (Bredfeldt et al., 2006), and this kind of transformation is irreversible (Wnek et al., 2010). Acute and chronic MMA^{III} exposure induces MAPK and COX-2, which may be a mechanism of bladder carcinogenesis (Eblin et al., 2007). Also, MMA^{III} alters histone modification patterns in human bladder cells (Ge et al., 2018). There are still gaps in research progress on organic arsenic forms and liver and lung cancers.

The molecular mechanisms of arsenic induction of various cancers can be summarized into two major categories: a) the trivalent arsenicals activate or inhibit signaling proteins or alter protein structure by reacting with proteinaceous thiol groups and b) inorganic or organic arsenicals activate ROS signaling or ROS-related signaling pathways. Carcinogenesis of inorganic arsenicals is related to both mechanisms. However, organic arsenicals are predominantly reported to correspond to ROS-dependent mechanisms at present (Huang et al., 2017). Current literature suggests that both inorganic and organic arsenicals contribute to arsenic carcinogenesis. It remains to be determined which specific form of arsenic is the most carcinogenic, although the answer may likely depend on the chemical properties of arsenical and the target organ.

Forms of Arsenic and Reactive Oxygen Species

Almost all forms and oxidation states of arsenicals can induce ROS and relevant signaling pathways (Lee et al., 2016). For example, for arsenic trioxide, superoxide induction occurs

through HO-1, hydrogen peroxide and also RNS such as nitric oxide and peroxynitrite (Zhou et al., 2019; Chen et al., 2008; Gurr et al., 2003). In murine embryonic maxillary mesenchymal cells, pentavalent arsenic leads to oxidative injury initiating cell death cascade, triggering cytotoxicity, mitochondrial dysfunction, and activation of caspase-9 (Singh et al., 2010). Specifically, the antioxidant N-acetylcysteine attenuates the effect of pentavalent arsenic, suggesting that ROS production may contribute to the mechanism of pentavalent arsenic cytotoxicity.

In human bladder urothelial cells, MMA^{III} is known to produce ROS (Wnek et al., 2011). In smooth muscle cells, MMA^{III} has been reported as a mitochondria toxicant that elevates ROS through mitochondrial and non-mitochondrial pathways (Pace et al., 2016). In rat liver cells, MMA^{III} has the highest potential of ROS generation, followed by DMA^{III}, then arsenic trioxide (Naranmandura et al., 2011). In human bladder urothelial cells, MMA^{III} was also observed to generate higher ROS than the same concentration of arsenic trioxide (Eblin et al., 2006). In human myeloid leukemic HL-60 cells, MMA^{III} and DMA^{III} cause apoptosis through inhibition to mitochondrial membrane potential and oxidative stress (Rehman et al., 2014). Caspase-9 and caspase-3 were significantly activated by MMA^{III} and DMA^{III} exposure. Similarly, antioxidant N-acetylcysteine is also able to reverse these effects (Rehman et al., 2014).

In HepG2 cells, MMA^{V}, DMA^{V}, or trimethylarsine (TMA^{V}) significantly induced CYP1A1 and NQO1 through an Hsp90 pathway (Anwar-Mohamed et al., 2014). ROS production by MMA^{V} exposure is also significantly higher than arsenic trioxide. Overall, MMA^{V} and DMA^{V} have moderate effect when compared to MMA^{III} and DMA^{III}, but the effects become stronger in a reductive environment, for example when there is a low ROS/GSH ratio (Sakurai et al., 2005).

In total, inorganic and organic arsenicals both contribute to ROS generation and ROS-dependent signaling pathways. However, there are still debates on which arsenic form generates higher ROS *in vivo*. It is still largely unclear whether metabolism of arsenic could enhance or reduce the strength of ROS effect. In addition, there is still limited knowledge on the differences of ROS type generated from different arsenicals, which should be of importance to ROS-related mechanisms.

Forms of Arsenic and DNA Damage/Repair

As mentioned in Section 2, trivalent arsenic inhibits DNA repair through direct interaction with zinc finger DNA repair proteins such as PARP-1 and XPA. For pentavalent arsenicals, there is no evidence currently demonstrating direct interaction with zinc fingers. However, pentavalent arsenicals are able to generate ROS which are not only able to induce DNA damage but also impair DNA repair pathways (Flora, 2011; Schwerdtle et al., 2003). Therefore, in contrast to trivalent arsenicals, which inhibit DNA repair through both direct and ROS pathways, pentavalent arsenicals inhibit DNA repair only through ROS-dependent signaling pathways.

In natural killer cells, at low concentration, MMA^{III} induces oxidative stress, DNA damage, and inhibits cell growth. DNA damage positively correlates with oxidative stress, indicating

that at environmentally relevant concentrations, MMA^{III} has a genotoxic effect (Xu and Wang, 2018). In human bladder urothelial cells, low-level chronic exposure to MMA^{III} elevates DNA damage, which remains at a high level after removal of MMA^{III}, and elevated levels of ROS also play a role in MMA^{III} induced-DNA damage (Wnek et al., 2009). While pentavalent arsenicals only act through ROS-dependent pathways, MMA^{III} has two potential interdependent mechanisms for human bladder urothelial cell transformation; elevated levels of MMA^{III}-induced DNA damage through the production of ROS and the direct MMA^{III}-induced inhibition of PARP-1 (Wnek et al., 2011), which has been confirmed *in vitro* (Zhou et al., 2014).

In T cells, MMA^{III} induces strong genotoxicity in the early developing T cells in the thymus. In terms of MMA^{III} induced genotoxicity and apoptosis, double negative ($CD4^{-}$ $CD8^{-}$) T cells were much more sensitive than double positive cells (Xu et al., 2017). ROS-dependent mechanisms are particularly important. For example, superoxide is involved either directly or indirectly in producing DNA damage in cells exposed to trivalent methylated arsenicals. DMA^{III} and MMA^{III} produced significantly more DNA damage in the homozygous knockout mouse splenocytes than in the splenocytes from the wild-type or heterozygous mice (Tennant and Kligerman, 2011).

Overall, the DNA damage effect and DNA repair inhibition capabilities of various arsenic forms and oxidative states largely depend on the tissue or cell type. Intriguingly, in bladder or human urothelial cells, DMA^{III} and MMA^{III} are the most hazardous arsenicals when considering cytotoxicity and genotoxicity (Bailey et al., 2012; Wang et al., 2007). However, in lung and skin cells, trivalent arsenicals show higher potency for DNA damage (Bolt and Hengstler, 2018; Sattar et al., 2016). This may be because of a difference in metabolism or cellular arsenic uptake.

Conclusion

There is extensive and strong epidemiological evidence that links arsenic exposure with increased risk of developing various types of cancer. Arsenic is ranked number one by the Agency for Toxic Substances and Disease Registry (ATSDR) on their priority list of substances that are determined to pose the most significant potential threat to human health. The most effective and efficient strategy to decrease arsenic-induced cancer risk is to reduce arsenic exposure. Based on convincing research findings, in 2001, U.S. EPA adopted a new standard for arsenic in drinking water of 0.01 mg/l or 10 parts per billion (ppb), replacing the old standard of 50 ppb. The same standard has since been used by most countries around the world. However, it is estimated that over 200 million people world-wide remain exposed to arsenic above this level (Li and Costa 2022).

Over the last several decades, extensive research has been carried out to investigate and identify various molecular and cellular changes caused by arsenic that are associated with known carcinogenic processes. Despite tremendous progress to date, we still do not fully understand exactly how arsenic causes cancer development, and what are the key cancer-driving events that play critical roles in arsenic-induced cancer. One of the significant barriers in research is the lack of relevant and appropriate animal models that mimic the

development of arsenic-induced cancer in humans, probably due to differences in genetics and arsenic metabolism between rodents and humans. Recent development in humanized mice could potentially provide an important tool to help resolve these critical questions (Koller et al., 2020).

Another major issue is that while current research has identified many individual molecular targets of arsenic involved in carcinogenic processes, it is difficult to assess which of these altered processes are predominantly responsible for arsenic-induced cancer in humans. The recent advances in whole genome sequencing and the associated informatics technology could help identify, using unbiased approaches, target molecules and processes that drive the mutation and tumorigenesis at the whole genome level.

Abbreviations

8-OHdG	8-hydroxy-2’-deoxyguanosine
AQP	aquaporin
AS3MT	arsenic methyltransferase
ATSDR	Agency for Toxic Substances and Disease Registry
BER	base excision repair
CPD	cyclobutene pyrimidine dimer
DMA	Dimethylated arsenic
DMA^{III}	dimethylarsonous acid
DMA^{V}	dimethylarsonic acid
EPA	US Environmental Protection Agency
GSH	glutathione
HR	homologous recombination
IARC	International Agency for Research on Cancer
MMA	Monomethylated arsenic
MMA^{III}	monomethylarsonous acid
MMA^{V}	monomethylarsonic acid
NER	nucleotide excision repair
NHEJ	non-homologous end joining
NOX	NADPH oxidase
PAH	polyaromatic hydrocarbons

RNS	Reactive nitrogen species
ROS	Reactive oxygen species
TMA(V)	trimethylarsine
UVR	ultraviolet radiation
WHO	World Health Organization

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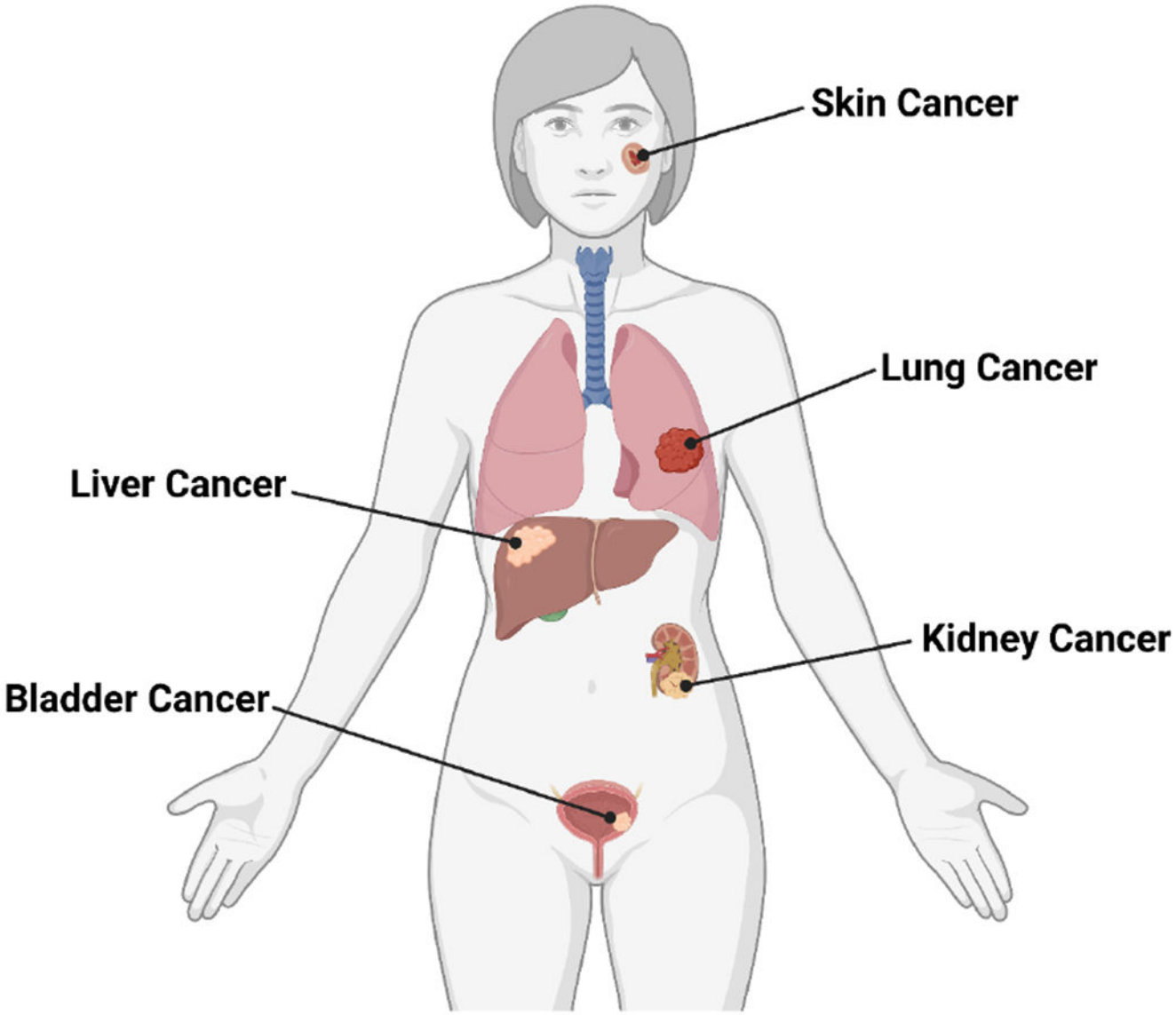

Figure 1.

Cancers associated with arsenic exposure. Epidemiology studies support the association of arsenic exposure through drinking water with increased risk of developing skin, lung, bladder, kidney, and liver cancers.

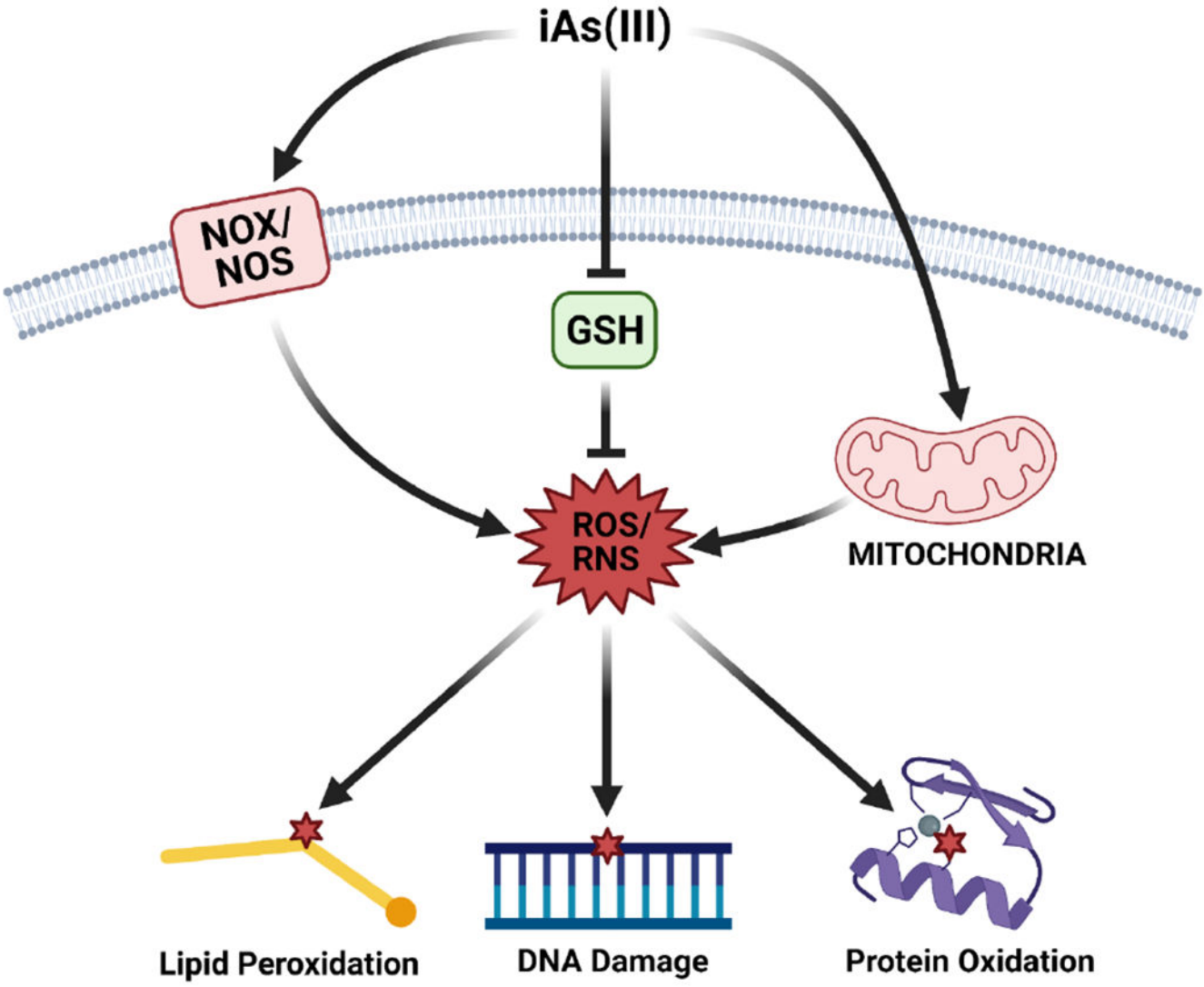

Figure 2. Mechanism of arsenic-induced ROS and oxidative damage to macromolecules.

Arsenic exposure stimulates the production of ROS and RNS through mechanisms such as the dysregulation of the electron transport chain and stimulation of enzymes such as NADPH oxidase and nitric oxide synthase. The depletion of GSH through the metabolism of arsenic further promotes redox imbalance. Consequently, macromolecules such as DNA, protein, and lipids are damaged by arsenic-induced ROS and RNS.

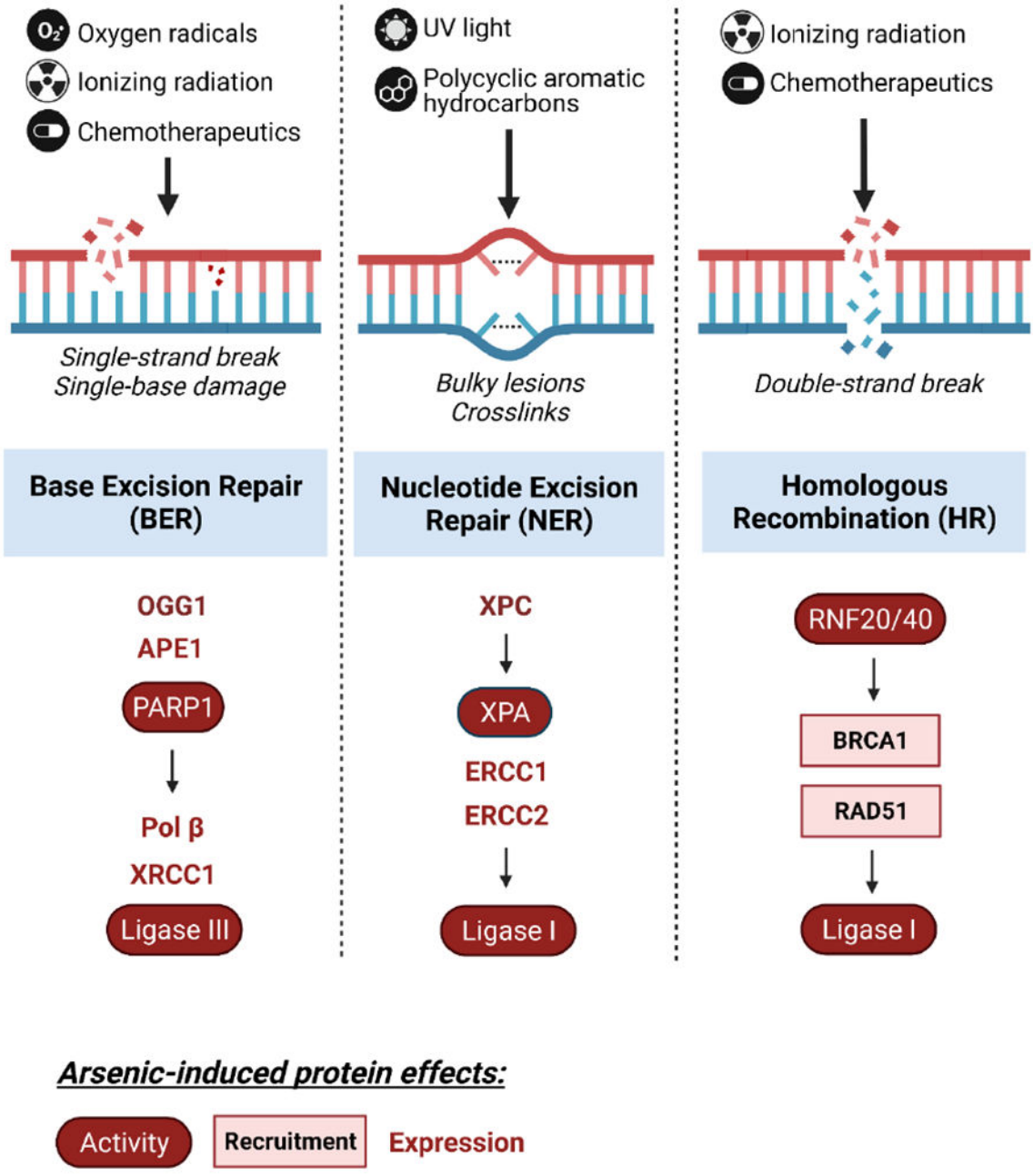

Figure 3. Arsenic inhibits DNA repair.

Exposure to DNA damaging agents such as ROS, UV light, and ionizing radiation can generate single-base damage, bulky lesions, and double-strand breaks, respectively. These types of damage are remediated by repair pathways which contain critical DNA repair proteins that facilitate the recruitment of repair proteins, removal of damage, and the synthesis and sealing of undamaged DNA. Arsenic alters the function of key DNA repair proteins through several means: zinc finger domain inhibition leading to loss of activity,

disruption in recruitment to DNA damage, and the suppression of expression by altering transcription and protein turnover.

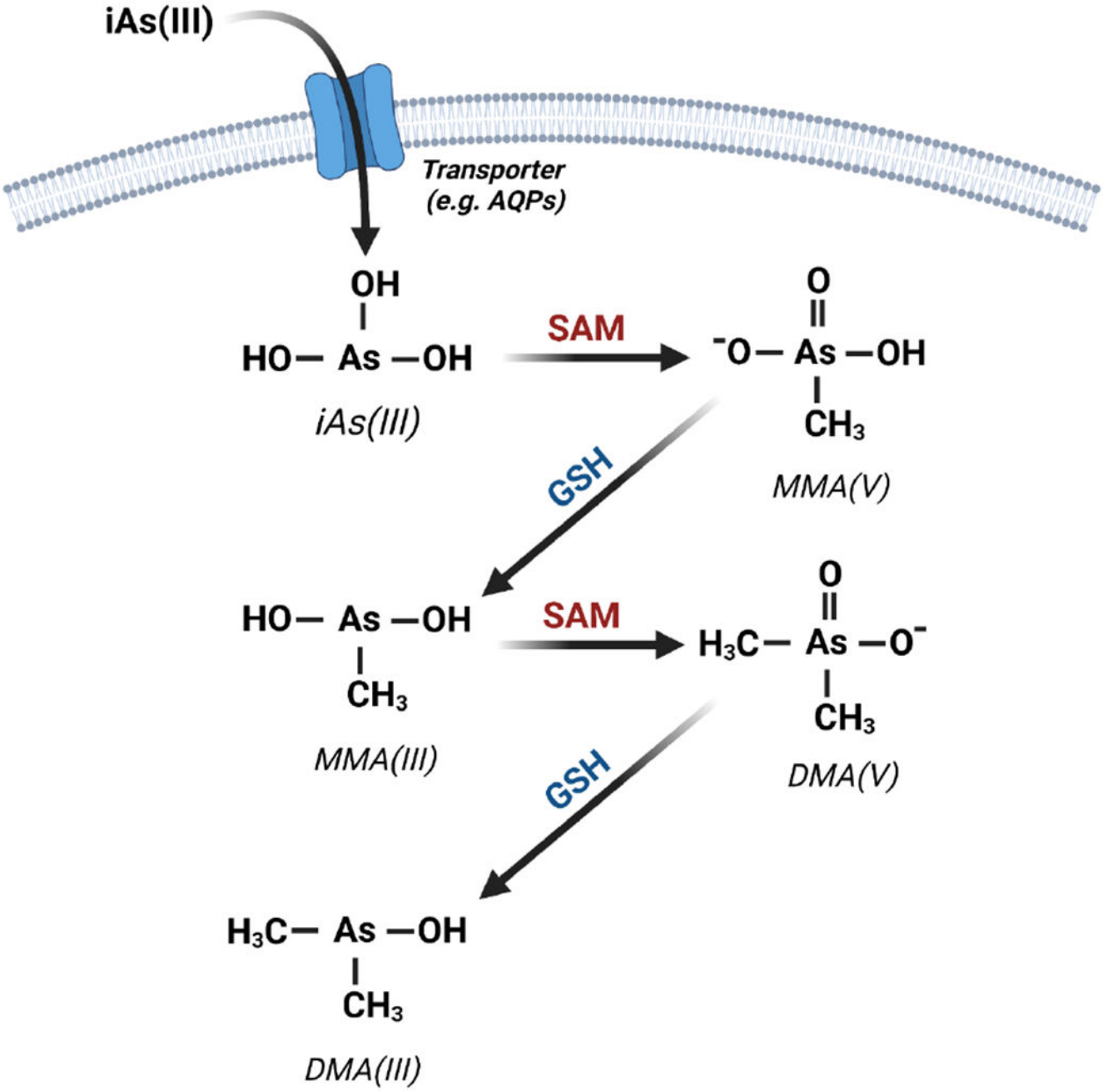

Figure 4.

The metabolism of arsenic. The uptake of trivalent arsenic into eukaryotes is mediated through several transporters such as AQPs. Trivalent arsenic is metabolized by successive oxidative methylation and reduction reactions. First, iAs(III) is oxidatively methylated into MMA(V) by S-adenosyl methionine (SAM), then reduced into MMA(III) by GSH. Second, MMA(III) is oxidatively methylated into DMA(V), then reduced into DMA(III)