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Review article

Environmental arsenic exposure: From genetic susceptibility to pathogenesis

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ABSTRACT

More than 200 million people in 70 countries are exposed to arsenic through drinking water. Chronic exposure to this metalloid has been associated with the onset of many diseases, including cancer. Epidemiological evidence supports its carcinogenic potential, however, detailed molecular mechanisms remain to be elucidated. Despite the global magnitude of this problem, not all individuals face the same risk. Susceptibility to the toxic effects of arsenic is influenced by alterations in genes involved in arsenic metabolism, as well as biological factors, such as age, gender and nutrition. Moreover, chronic arsenic exposure results in several genotoxic and epigenetic alterations tightly associated with the arsenic biotransformation process, resulting in an increased cancer risk. In this review, we: 1) review the roles of inter-individual DNA-level variations influencing the susceptibility to arsenic-induced carcinogenesis; 2) discuss the contribution of arsenic biotransformation to cancer initiation; 3) provide insights into emerging research areas and the challenges in the field; and 4) compile a resource of publicly available arsenic-related DNA-level variations, transcriptome and methylation data. Understanding the molecular mechanisms of arsenic exposure and its subsequent health effects will support efforts to reduce the worldwide health burden and encourage the development of strategies for managing arsenic-related diseases in the era of personalized medicine.

List of abbreviations

(IARC) International Agency of Research on Cancer
(iAs) Inorganic arsenic
(WHO) World Health Organization
(arsenate/As^{V}) Pentavalent arsenic
(arsenite/As^{III}) Trivalent arsenic
(MMA) Monomethylarsonic acid
(DMA) Dimethylarsinic acid
(ATP) Adenosine triphosphate
(NER) Nucleotide excision repair
(BER) Base excision repair
(OR) Odds ratio
(ATO) Arsenic trioxide
(APL) Acute promyelocytic leukemia
(*PML*) Promyelocytic protein
(*RARα*) Retinoic acid receptor α
(CML) Chronic myelogenous leukemia
(PNP) Purine nucleoside phosphorylase
(GSH) Glutathione
(AS3MT) Arsenic (III)-methyltransferase
(SAM) s-Adenosylmethionine
(ROS) Reactive oxygen species
(ATRA) All-*trans* retinoic acid
(lncRNAs) Long non-coding RNAs
(GEO) Gene Expression Omnibus
($NaAsO_2$) Sodium arsenite
(CIHR) Canadian Institutes for Health Research

1. Background

Exposure to arsenic has a major impact on human health across the world. In fact, this naturally occurring metalloid is considered a well-established "Class I" human carcinogen by the International Agency of Research on Cancer (IARC) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans). In the environment, arsenic is most commonly found in its inorganic form (inorganic arsenic, iAs) (Smedley and Kinniburgh, 2002). Despite the ubiquitous distribution of arsenic in soil, air and water, human industrial activities such as mining, combustion of fossil fuels and the use of arsenic-based pesticides potentiate the environmental accumulation of this toxic metalloid (Martinez et al., 2013b; Singh et al., 2015; Vimercati et al., 2016; Vimercati et al.,

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2017). Increasing concentrations of arsenic in the environment pose major threats to human health, as exposure through inhalation, ingestion and skin contact can result in a multitude of adverse health effects (Vimercati et al., 2017). A primary route of human exposure to arsenic is through the consumption of contaminated groundwater sources, however, the intake of contaminated food products, such as fish and grains, is also a growing issue (Huang et al., 2015). The greatest impact of arsenic exposure is observed to result from groundwater levels above the World Health Organization (WHO) safety standard of 10 μg/L (Huang et al., 2015; Naujokas et al., 2013). However, recent evidence has uncovered the potential toxicity of arsenic even at levels below this safety guideline (Health Canada, 2017).

Several studies indicate that arsenic toxicity is derived from its metabolism and excretion processes (Ebert et al., 2011; Styblo et al., 2002). After the uptake of arsenic into the body, it goes through a biotransformation process as part of its metabolism, wherein pentavalent arsenic (arsenate/As^{V}, the most prevalent oxidation state of iAs in the environment) is reduced to a trivalent form (arsenite/As^{III}), which is subsequently mono-, di-, and tri-methylated (Drobna et al., 2009). These by-products are toxic and can accumulate throughout the body, leading to several genetic and epigenetic disruptions and posing a great threat to many normal biological processes (Bustaffa et al., 2014; Hubaux et al., 2013; Sage et al., 2017). The accumulation of arsenic and its metabolic by-products leads to widespread health effects, ranging from disorders of the cardiovascular and nervous systems, to nephrotoxicity and skin lesions, and particularly cancer (Bhattacharyya et al., 2014; Feseke et al., 2015; Nong et al., 2016; Robles-Osorio et al., 2015; Sage et al., 2017; Tolins et al., 2014; Tsuji et al., 2015). Arsenic is known to be mainly associated with the development of skin, liver, lung, bladder and urinary tract cancers (Sankpal et al., 2012). However, susceptibility to the development of arsenic-associated diseases varies among individuals, and can be influenced by age, gender, and nutrition, as well as alterations in genes involved in arsenic biotransformation (Paul et al., 2015; Schlawicke Engstrom et al., 2009; Yu et al., 2014).

The inter-individual genetic susceptibility to arsenic-induced health effects has been related with variations in genes responsible for arsenic biotransformation, such as methyltransferases, and DNA damage repair genes (Paul et al., 2015). Some studies suggest that a higher capacity to methylate arsenic or the decreased activity of DNA repair enzymes are associated with decreased risk of arsenic-associated diseases (Banerjee et al., 2016; Ghosh et al., 2008; Pierce et al., 2013). However, the mechanisms underlying arsenic toxicity and susceptibility are not yet fully understood, particularly due to discrepancies in study design and a lack of animal models that can sufficiently replicate observed human health effects (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004). Here we review the magnitude of arsenic contamination, as well as the intertwined role of arsenic biotransformation and genetic/epigenetic factors that are associated with susceptibility to arsenic.

2. Worldwide burden of arsenic-exposure

Exposure to arsenic occurs largely through the contamination of groundwater sources; however, individuals can also come into contact with this metalloid through food, such as grains including rice, seafood, air sources, and even apple juice (Arslan et al., 2016; Health Canada, 2017; Hubaux et al., 2012; Quarato et al., 2017). It is estimated that over 200 million people are chronically exposed to concentrations at or above the WHO threshold across the world (Naujokas et al., 2013). The global magnitude of the issue of arsenic contamination may be larger than the data suggests, as it is marred by availability and accessibility issues. In fact, high levels of arsenic have been found in groundwater in > 70 countries across 5 continents, including Australia, India, Canada and the United States (Bhattacharjee et al., 2013a; Hubaux et al., 2012; Hubaux et al., 2013).

Much of the epidemiological data available are derived from areas where arsenic contamination is endemic, such as Taiwan, Bangladesh, Northern Chile and Argentina. In these areas, several studies have demonstrated associations between high arsenic exposure and the onset of adverse health effects, particularly cancer (Ahmed et al., 2017; Liang et al., 2017; Liang et al., 2016; Loewenberg, 2016; Yunus et al., 2011). For example, in Northern Chile the incidence of lung squamous cell carcinoma, a disease which is mainly the result of cigarette smoke, is not decreasing despite the dramatic drop in smoking rates. The rate of lung squamous cell carcinoma in never-smokers is unusually high in this region (Martinez et al., 2012). This is particularly interesting when considering that the molecular signature of lung squamous cell carcinoma is different between smoking-related and arsenic-related tumours, suggesting that the high concentrations of arsenic may be playing a much larger role in the incidence of lung cancer in this region (Martinez et al., 2010).

Bangladesh serves as one of the most prevalent cases of high concentrations of arsenic in groundwater, with about 20–45 million individuals exposed to well-above standard levels. It has been estimated that arsenic is the cause of over 19,000 deaths per year in the country (Flanagan et al., 2012). Due to the enormous impact on the health of its population, Bangladesh is one of the most well-studied areas of arsenic exposure, while data from many other countries around the world remains scarce.

Among North American countries, the United States has well-documented case reports of arsenic contamination, with particular high risk areas in the states of Utah, Oregon (West Oregon), Nevada, California, Florida, West Virginia, Kentucky, Maine, Vermont and New Hampshire (Banerjee et al., 2007; Hubaux et al., 2013). In Canada, less attention has been given to this issue, though the accumulation of arsenic in soil derived from mining activities has been noted over time (Bari and Kindzierski, 2016). Particularly, high levels of naturally occurring arsenic in private well water supplies have been documented in a number of provinces, including Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Québec, and Saskatchewan (Martinez et al., 2013b; Saint-Jacques et al., 2014). For example, in Nova Scotia, high levels of arsenic have been found throughout the province and measured concentrations have been shown to exceed the safety guidelines in natural drinking water (Dummer et al., 2015). Additionally, the mobilization of arsenic in soil due to the activities of the Giant Mine in Yellowknife, Northern Canada, represents an enormous risk for water contamination (Martinez et al., 2013b). While these examples shed light on the global magnitude of arsenic contamination, the true impact of arsenic exposure remains veiled by complex molecular mechanisms and data scarcity.

3. Health effects derived from arsenic exposure

While the effects of acute exposure to high concentrations of arsenic can have directly observable consequences, including vomiting, abdominal pain, and can even be fatal in extreme cases, exposure to levels near the WHO threshold can potentiate chronic health effects (World Health Organization, 2016). In fact, exposure to arsenic is known to be involved in the onset of nephrotoxicity, diabetes, cardiovascular and pulmonary diseases, as well as multiple diseases of the skin (Bhattacharyya et al., 2014; Feseke et al., 2015; Robles-Osorio et al., 2015; Sage et al., 2017; Tolins et al., 2014; Tsuji et al., 2015).

Cardiovascular disease is a highly prevalent, particularly in North American populations. Arsenic exposure has been associated with an increased risk of developing peripheral arterial and atherosclerotic cardiovascular diseases (Newman et al., 2016; Nong et al., 2016). Further effects of arsenic on the vascular system can be seen in its involvement in the onset of Blackfoot disease, which severely damages the vasculature in the feet and is mainly seen in the arsenic-endemic area of Southern Taiwan (Tseng, 2005).

However, the clearest association can be seen in skin diseases including hyperkeratosis, an abnormal thickening of the skin, which may