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Impact of Prenatal Arsenic Exposure on Chronic Adult Diseases

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Abstract

Exposure to environmental stressors during susceptible windows of development can result in negative health outcomes later in life, a concept known as the Developmental Origins of Health and Disease (DOHaD). There is a growing body of evidence that exposures to metals early in life (*in utero* and postnatal) increase the risk of developing adult diseases such as cancer, cardiovascular disease, non-alcoholic fatty liver disease, and diabetes. Of particular concern is exposure to the metalloid arsenic, a drinking water contaminant and worldwide health concern. Epidemiological studies of areas with high levels of arsenic in the drinking water, such as some regions in Chile and Bangladesh, indicate an association between *in utero* arsenic exposure and the development of adult diseases. Therefore the need for experimental models to address the mechanism underlining early onset of adult diseases have emerged including the *in utero* and whole-life exposure models. This review will highlight the epidemiological events and subsequent novel experimental models implemented to study the impact of early life exposure to arsenic on the development of adult diseases. In addition, current research using these models will be discussed as well as possible underlying mechanism for the early onset of disease.

Keywords

Arsenic; prenatal exposure; chronic adult disease; cancer; cardiovascular disease

Introduction

The focus of developmental toxicology has shifted from studying the effects of toxicant-induced malformations to understanding how non-overtly toxic exposures, *in utero*, result in

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increased susceptibility to diseases in adulthood. A variety of terms have been used to describe this novel area of research including “fetal origins of disease”, “fetal beginnings of adult disease”, “fetal basis of adult disease” and the “developmental origins of adult disease”. However, although not established as official terminology, the term Developmental Origins of Health and Disease (DOHaD) is most commonly used (Barker 2007; Heindel et al. 2015; Heindel et al. 2017). Originating in the 1990s, the DOHaD hypothesis suggests that during sensitive windows of development, environmental stressors can alter tissue development and function, influencing health later in life (Gluckman et al. 2010; Barouki et al. 2012).

The Dutch famine is one of the earliest documented examples of prenatal environmental factors being associated with disease development in adulthood (Painter et al. 2005). Toward the end of WWII, during the winter of 1944–1945, the Dutch government implemented a railway strike with the intent of halting transport of German troops and reinforcements, thereby aiding the Allied Forces. In retaliation, the German government cut off food and fuel shipments to the German-occupied areas of the western Netherlands. As a result, the daily rations for the general adult population dropped from 1800 calories to < 1000 calories/day. From this unfortunate event came the Dutch famine birth cohort study (Painter et al. 2005). Although the offspring of women who were pregnant during the famine were small for gestational age, in adulthood this cohort had an increased incidence of obesity (Ravelli et al. 1999), diabetes (de Rooij et al. 2006; van Abeelen et al. 2012), and cardiovascular disease (Roseboom et al. 2000).

In the decades following the Dutch famine there have been numerous studies, performed in both humans and animals, that suggest that *in utero* exposures to environmental stressors, such as poor nutrition or exposure to environmental chemicals, contribute to the initiation, and/or exacerbation of chronic adult diseases such as cardiovascular disease (CVD) (Barker and Osmond 1986; Barker et al. 1989; Barker et al. 1993) and cancer (Newman et al. 1971; Newbold and McLachlan 1996; Waalkes et al. 2003). In 1986, Barker and Osmond observed that the same regions in England with high rates of low-birthweight induced infant mortality had the highest rates of death associated with coronary heart disease decades later (Barker and Osmond 1986). It is this observation that initiated the “fetal basis for adult disease” hypothesis, also known as the “Barker Hypothesis”.

Although many of the supporting studies that followed Barker’s observation were focused on the effects of altered nutrition *in utero*, there has been growing evidence that environmental exposures to metals early in life also increase susceptibility to the development of chronic adult diseases (Heindel et al. 2017). Prenatal exposure to metals has become of great concern due to widespread occurrence, and their ability to cross the placenta, be passed through breast milk, and have adverse effects on multiple organs, as well as mediate persistent epigenetic changes that have long-term adverse health implications (Sikorski et al. 1986; Foldspang and Hansen 1990; Chen et al. 2014). Arsenic, number 1 on the Agency for Toxic Substances and Disease Registry (ATSDR) list of hazardous environmental chemicals, is a major metal of concern as prenatal exposure to arsenic has been implicated in the development of disease late in life. However, two studies indicate that very little arsenic is excreted into breast milk, regardless of the extent of maternal arsenic

exposure (Fängström et al. 2008; Islam et al. 2014). Therefore, it is unlikely that the small amount of arsenic transferred through the breast milk will extend the exposure window beyond the in utero timeframe.

Arsenic: The Foundations for the Current Exposure Paradigm

Early life exposure to environmental stressors have been linked to the development of adult disease in both humans and rodents (Newman et al. 1971; Newbold and McLachlan 1996; Waalkes et al. 2003). The connection between *in utero* exposures to inorganic arsenic and increased risk of developing adult disease is evident in human epidemiological studies, thus creating the need for the development of novel experimental models to address the mechanism underlining the early onset of adult diseases.

Epidemiological Data

The effects of *in utero* arsenic exposures are best illustrated by studies from the northern Chilean city of Antofagasta, also known as Region II. In 1958, the development of a new drinking water supply resulted in an abrupt increase in the concentration of inorganic arsenic from 90 ppb to over 800 ppb, both concentrations well above the current U.S. Environmental Protection Agency (EPA) and World Health Organization maximum contaminant level of 10 ppb (Smith et al. 1998; Smith et al. 2006; Thomas 2013). After twelve years of remarkably high arsenic exposure, a new water filtration system implemented in 1970 lowered the inorganic arsenic levels to approximately 110 ppb, but still above the maximum contaminant level. This exposure scenario led to the identification of two cohorts: individuals born directly before the rise in arsenic concentrations (1940–1957) and those born during the elevated exposures (1958–1970) (Thomas 2013). This unique event has provided opportunities to study the impact of early life high arsenic exposure on the development of adult disease and mortality in humans.

Cardiovascular disease

During and immediately after the high exposure periods, acute myocardial infarction (AMI) was the leading cause of excess deaths in Antofagasta (Yuan et al. 2007), providing some of the first evidence that consumption of arsenic-contaminated drinking water is associated with CVDs. Subsequent studies from other parts of the world with high levels of arsenic in groundwater, such as Taiwan and Bangladesh, have also associated arsenic exposure with increased risk for CVD outcomes (Wu et al. 1989; Argos et al. 2010; Chen et al. 2011). Of note is that many of the excess AMI-induced deaths in Chile were individuals less than 40 years of age (Zaldivar 1980; Yuan et al. 2007). In addition, it was reported that *in utero* arsenic exposure caused AMI in infants whose mothers were exposed to the high levels of arsenic in the Region II drinking water (Rosenberg 1973; Rosenberg 1974). The observations by Rosenberg were the first to connect *in utero* arsenic exposure to the development of an “adult” disease in childhood.

Later epidemiology studies from other highly-exposed cohorts also associate *in utero* and early life arsenic exposures with increased risk of childhood cardiovascular disease, cancer and death. For example, Osorio-Yáñez and colleagues (2015) did a cross-sectional study of

161 children between ages of 3 and 8 from Zimapan, a region in Central Mexico that has historically high concentrations of inorganic arsenic in the drinking water supply (3–398 ppb) (Armienta et al. 1997). In this cohort, early-life inorganic arsenic exposure was associated with high blood pressure, greater left ventricular mass (indicative of hypertrophy), and a lower ejection fraction (indicative of impaired contraction) (Osorio-Yáñez et al. 2015). In a large population-based prospective study of children in Matlab, Bangladesh, *in utero* and early life arsenic exposure via contaminated well water was associated with increased risk of all-cause, cardiovascular disease, and cancer mortalities, with girls being at a higher risk compared to boys (Rahman et al. 2013).

Cancer

By the 1980's AMI mortalities in Antofagasta, Chile decreased; however, excess deaths from lung and bladder cancer increased (Yuan et al. 2007). Smith and colleagues (2006) reported that the mortality among young adults ages 30–49 from both malignant and nonmalignant lung diseases was significantly greater in the Region II cohort compared to age-matched controls, suggesting early onset of disease as a result of *in utero* and early life exposures to arsenic. By 2012, arsenic exposure in Antofagasta was correlated with increased mortality from bladder, laryngeal, liver, and lung cancer as well as chronic renal disease, resulting in the greatest escalation of mortality rates associated with early life environmental exposure in adults less than 50 years old (Smith et al. 2012). In a comparison of cancer mortality rates of Region II residents under the age of 20 born between 1950 and 2000, with those of unexposed Region V residents, it was found that although there was not an increase in overall childhood cancer mortality, the rates of liver cancer mortality were substantially higher in children between 10 to 19 years old (Liaw et al. 2008). This was the first study to connect childhood liver cancer mortality with high concentrations of arsenic in drinking water.

Overall, very early observations from the Region II study indicated that *in utero* and early life arsenic exposures are associated with the development of “adult” diseases in children (Rosenberg 1973; Rosenberg 1974; Liaw et al. 2008). However, later observations also suggest that the high arsenic exposure resulted in early onset of diseases in adulthood (Smith et al. 2006, Yuan et al. 2007). There is strong epidemiological evidence that *in utero* and early life arsenic exposures result in adverse health outcomes >20 years after exposure, supporting the DOHaD hypothesis. This hypothesis suggests that exposure to environmental stressors during susceptible windows of development can result in negative health outcomes later in life (Gluckman et al. 2010).

Early In Utero Exposure Models

Exposure to arsenic-contaminated drinking water is a worldwide health concern that has been linked to the development of adverse health outcomes (e.g. cancer) since the 1800's. However, it was not until the early 1980's that animal models were developed to study the underlying mechanisms of pathogenesis (Rudnai et al. 1980). Furthermore, it was not until the after 2000 that models addressing only *in utero*, transplacental exposures were studied (Waalkes et al. 2003; Srivastava et al. 2007).

The first *in utero* exposure model that established inorganic arsenic as a complete transplacental carcinogen in mice was published in 2003 by Dr. Michael P. Waalkes and colleagues (Waalkes et al. 2003). In this study, pregnant cancer-prone C3H mice were exposed to 0, 42.5, and 85 ppm arsenite *ad libitum* in drinking water from gestation day 8 to 18. After birth, the offspring received no additional arsenic treatment, therefore making the exposure to the offspring solely *in utero*. The arsenic exposures were not overtly toxic, indicated by unaltered body weight and water consumption in the dams. In addition, litter size, newborn weight, and weanling weight were not adversely impacted by the arsenic exposure. The offspring were followed for up to 90 weeks postpartum and tumor formation was assessed. Interestingly, the offspring developed dose-related, gender-dependent increases in tumor formation. As a result of *in utero* arsenic exposure, male offspring had an increased incidence of hepatocellular carcinomas, liver adenomas, and adrenal tumors whereas female offspring had a higher incidence of ovarian tumors and lung carcinomas as well as preneoplastic lesions of the uterus and oviduct (Waalkes et al. 2003). These findings were further confirmed by Dr. Keiko Nohara and colleagues in 2012 (Nohara et al. 2012). Overall, the Waalkes study was the first to establish a connection between *in utero* arsenic exposures and the development of cancer, thus creating the experimental framework to investigate non-cancer endpoints, such as atherosclerosis, associated with *in utero* exposures.

As mentioned above, chronic consumption of arsenic contaminated drinking water is implicated in the development of childhood and early onset cardiovascular disease in humans (Rosenberg 1973; Rosenberg 1974). However, the underlying pathogenic mechanisms were not addressed until 2007, over 30 years after the end of the highest exposure period in Chile. Directly mirroring the Waalkes cancer model, Srivastava et al (2007) exposed pregnant atherosclerosis prone apolipoprotein E knock-out (ApoE^{-/-}) mice to 85 mg/L sodium arsenite (49 ppm arsenic) *ad libitum* in drinking water from gestation day 8 to 20. Evidence of early disease was examined in the male offspring at 10 and 16 weeks after conception. The *in utero* exposure more than doubled the number of atherosclerotic plaques at both 10 and 16 weeks as well as altered vascular tone and endothelial cell signaling, indicating the early onset of atherosclerosis. This study, along with a postnatal follow-up experiment (Srivastava et al. 2009) showed that arsenic exposure alone, independent of a high-fat diet, could induce atherosclerosis (Srivastava et al. 2007). This model, as well as the preceding Waalkes cancer model, established an *in vivo* exposure paradigm that has paved the way for a myriad of studies that have since linked *in utero* exposures to environmental toxicants to a variety of adverse health outcomes (States et al. 2012; Ngilame et al. 2013; Ramsey et al. 2013). These more recent studies will be addressed later in this review.

The “Whole-life” Exposure Model

The development and implementation of the *in utero* exposure model provided a novel tool for studying mechanisms involved in progression of diseases resulting from transplacental exposures. It also provided a platform for discussion about relevance of the models to human environmental exposures such that exposures to many environmental toxicants are not limited to *in utero* or postnatal exposures, but are actually life-long. Therefore, the “whole-life” exposure model was created to more realistically duplicate human exposure.

In support of the “whole-life” exposure model Huff et al (2008) wrote a commentary that highlighted the need for regulatory agencies (i.e. government, drug companies, and the chemical industry) to revise their testing guidelines, established over 30 years ago, such that experiments were better designed to pinpoint adverse health outcomes throughout the entire increasing life span of humans. More specifically, many rodent-based carcinogenesis bioassays were initiated after birth and are terminated after less than 2 years of exposure, which is 6 months to a year short of a typical rodents’ full lifespan (Huff et al. 2008). However, there have been studies of certain chemicals that indicate the need to expose experimental animals starting pre-conception and continuing through until their natural death in order to validate and increase the sensitivity of the bioassays, as well as avoid false-negative results. For example, Wistar rats exposed to cadmium for 2 years did not have an increased incidence of tumor formation (Loser 1980) whereas after 31 months, there was an increase in lung tumor formation (Takenaka et al. 1983). Although it is important to point out that the two studies exposed their rats by different routes (oral and inhalation), and Loser (1980) actually exposed his rats for the full 24 months whereas Takenaka et al. (1983) exposed the rats for only 18 months, but followed them for 13 months (total of 31 months). Thus, there is still a need to address the length of not only time of exposure, but also time of observation after the exposure.

An excellent example of an environmental exposure known to occur throughout the entire life span is inorganic arsenic in drinking water. Therefore, Tokar et al. (2011) implemented a protocol in which mice were subjected to “whole-life” chronic arsenic exposure. In this model, cancer-prone CD1 (Chandra and Frith 1992) male and female breeder mice were exposed to arsenic in drinking water for two weeks before breeding (pre-conception exposure). The exposure continued through pregnancy and lactation as well as after weaning and through adulthood. Tumor formation was assessed in the offspring for 24 months. Compared to prior *in utero* studies, concentrations of arsenic used in this “whole-life” study (6, 12, and 24 ppm) were much lower to allow for prolonged treatment time. Although CD1 mice have a higher background incidence of lung and liver tumors, exposure-related increases were still seen in lung adenocarcinomas and hepatocellular carcinomas in both sexes, as well as increases in gallbladder tumors in males and uterine and ovarian carcinomas in females (Tokar et al. 2011). These target sites of tumor formation were remarkably similar to *in utero* only exposure studies (Waalkes et al. 2003). However, the tumors were induced at lower exposures and tended to be more aggressive and with greater frequency. These results suggest exposure *in utero* may dictate the site of tumor formation while exposure postnatally and throughout life may exacerbate the frequency and progression.

In a follow-up study, Tokar et al. (2012) employed the “whole-life” exposure model to study the ability of *in utero* arsenic initiated carcinogenesis to be exacerbated by postnatal, chronic exposure to pentavalent dimethylarsinate (DMA^(V)), an arsenic metabolite known to promote non-arsenical induced tumors (Tokar et al. 2010; IARC 2012). *In utero* exposure to 85 ppm arsenic alone resulted in 3 times more hepatocellular carcinomas compared to controls and this rate of tumor formation was again doubled with the addition of chronic postnatal DMA^(V) exposure for up to 2 years. DMA^(V) alone was not associated with enhanced hepatocellular carcinomas, which is consistent with previous studies (Yamamoto

et al. 1995). These results provide valuable insight into possible mechanism of arsenic carcinogenesis. In particular, it is possible that arsenic exposure *in utero* may initiate events in the liver that result in adulthood cancer promoted by products of hepatic arsenic metabolism, such as DMA (Tokar et al. 2012). It is important to point out that there are multiple competing theories of how arsenic exposure contributes to tumorigenesis including aneuploidogenesis, arsenic-induced oxidative stress, epigenetic alterations, histone modifications and DNA methylation (Martinez et al 2011; States 2015). However, although these proposed modes of action all have data to support them, there is no consensus on “a” mechanism of arsenic-induced carcinogenesis.

In order to better recapitulate human exposures, Waalkes et al. (2014) performed an experiment using the “whole-life” exposure model, but at much lower exposures than previously reported because human cancers associated with arsenic exposure typically occur in the parts per billion range (IARC 2004; IARC 2012). “Whole-life” exposure of CD1 mice to 50 and 500 ppb arsenic was associated with the development of lung tumors, a known target site of *in utero* and early life arsenic-induced tumors in humans (Smith et al. 2006).

The “whole-life” exposure model has provided a novel tool for studying how exposures to environmental toxicants throughout an individual’s life span may lead to adverse health outcomes later in life. However, there have been very few additional studies that have implemented this model. Those who claim to be doing a “whole-life” exposure tend to expose their animals *in utero*, but for less than 6 months postnatally, not fully mimicking “whole-life” (Ditzel et al. 2016). The limited use of this model may, in part, be due to the fact that these studies take a much longer time to complete and as such are considerably more costly. Human exposures to environmental toxicants may be life-long events and as seen in both epidemiological and rodent studies, time of exposure during the life-span may determine outcome later in life. It is important to note that there are different life stage windows of exposure that are defined by alterations in metabolism, anatomy and physiology (Cohen Hubal et al. 2014). These changes during specific time frames of development can modify the risk of exposure. Therefore, it is important that this model be used to investigate the effects of reproductive toxicants, such as metals, that humans may be exposed to throughout their life.

***In Utero* Exposures and the Development of Non-cancer Adult Disease**

The *in utero* exposure model, originally developed to look at cancer, has more recently been used to explore the effects of prenatal metal exposures on the development of non-cancer adult diseases. Of particular interest is the association of *in utero* metal exposure with metabolic syndrome (MetS). MetS is a multifactorial condition that affects over 47 million people in the United States (Wang et al. 2007). As defined by the World Health Organization, MetS diagnosis requires the manifestation of any of the three following clinical conditions: hyperglycemia resulting from insulin resistance, hypertension, central obesity, and dyslipoproteinemia as a result of high triglyceride levels or low levels of high-density lipoprotein (HDL) (von Bibra et al. 2016). Diagnosis of MetS is directly correlated with increased risk of the development of diabetes, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD). Many of the epidemiological studies that associate

metal exposure with the development of MetS pathologies have been in adults (Wang et al. 2007; Padilla et al. 2010; Stranges et al. 2010; Kuo et al. 2013; Moon et al. 2013). However, these pathologies have become increasing more prevalent in children, supporting the DOHaD hypothesis (Boney et al. 2005; Wang et al. 2014).

Non-Alcoholic Fatty Liver Disease (NAFLD)

The liver is major site of arsenic metabolism and toxicity (Santra et al. 1999). Arsenic exposure is associated with the development of fatty liver disease and is an example of toxicant associated steatohepatitis (TASH), liver diseases resulting from environmental toxicant exposures (Santra et al. 1999; Cave et al. 2010). However, until recently, the association between arsenic and NAFLD was based on chronic exposures from drinking arsenic-contaminated water without consideration of *in utero* exposures.

Using the *in utero* exposure model, Sanchez-Soria et al. (2014) reported that 36 week old Swiss-Webster male and female offspring of dams exposed to 100 ppb arsenic from embryonic day 6 until birth developed NAFLD (prominent micro- and macrovesicular steatosis). Furthermore, the offspring exhibited increased blood sugar levels and elevated low density lipoprotein (LDL) and total cholesterol, potentially placing the mice at a higher risk for developing metabolic syndrome (Sanchez-Soria et al. 2014). In another study, States et al. (2012) exposed atherosclerosis prone ApoE^{-/-} mice to 49 ppm arsenic *in utero* (gestation day 8 to term). Although there were no macroscopic histological changes in the liver after 10 weeks (PND 70) (determined by hematoxylin and eosin stained liver tissue), *in utero* arsenic exposure increased both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in the plasma, indicative of liver damage (States et al. 2012). Hepatic microarray analysis revealed elevated inflammatory cytokines in newborn pups followed by an activated stress response and pro-inflammatory state after 10 weeks. These results suggest subtle liver damage caused by *in utero* arsenic exposure may prime the liver for an enhanced inflammatory response, thereby increasing vulnerability to a second agent, or a 'second hit'.

The 'second hit' hypothesis has been well demonstrated in models of fatty liver disease (Day and James 1998). For example, Tan et al. (2011) exposed male C57BL/6 to subhepatotoxic concentrations of arsenic (4.9 ppm) and fed them either a low-fat or high-fat diet. Mice fed low-fat diet did not have increased liver damage. However, arsenic exposure exacerbated high-fat diet induced liver damage and inflammation. To test how diet might affect the development of metabolic disease pathologies in mice exposed *in utero* to arsenic Ditzel et al. (2016) used male Swiss Webster mice to look at the effects of *in utero*, postnatal, and continual exposures (*in utero* + postnatal) to 100 ppb arsenic combined with a high fat diet. NAFLD was present in both groups exposed to arsenic *in utero*, and the severity of the pathology was greater when exposure to arsenic was continued postnatally (Ditzel et al. 2016).

Cardiovascular Disease

As already discussed, *in utero* exposure to arsenic is associated with increased risk of CVD both in experimental models (Srivastava et al. 2007) and in human populations (Rosenberg

1973, 1974; Smith et al. 2012). Continued utilization of the *in utero* exposure models has been imperative in furthering the understanding disease development mechanisms as well as the contributions of one disease to another. Disease pathologies are commonly multifactorial such that one disease increases the risk of developing another. For example, in humans, NAFLD has been shown to increase the risk of developing atherosclerosis (Brea et al. 2005), independent of other MetS pathologies (Schindhelm et al. 2007; Sookoian et al. 2010), possibly due to alterations in the programming of the fetal liver.

Studies have suggested that *in utero* arsenic exposure results in epigenetic reprogramming of the developing liver, leading to a hyper-responsiveness to inflammatory stimuli (Ngalame et al. 2012; States et al. 2012). For example, States et al (2012) conducted a hepatic transcriptome study of ApoE^{-/-} mice exposed to 49 ppm arsenic *in utero* (gestation day 8 to term). Microarray analysis of both mRNA and microRNA were evaluated at postnatal day (PND) 1 and 70. Gene ontology analysis showed that at PND 1 gluconeogenesis and glycolysis pathways were suppressed and by PND 70 processes related to inflammation, stress, and lipid synthesis were upregulated, all of which may contribute to early onset of atherosclerosis (States et al. 2012). A similar delay in hepatic stress response was reported by Ngalame et al. (2012), who showed a temporal delay of upregulated inducible Hsp70 (a stress response molecular chaperone) in the livers of prenatally arsenic exposed ApoE^{-/-} mice. These studies provide mechanistic evidence for how liver disease, which results in dysregulation of stress and inflammatory responses, may be initiated by an *in utero* toxicant exposure and contribute to atherosclerosis.

Diabetes

In 2011, the National Toxicology Program reported that there was sufficient human data to link high inorganic arsenic exposures (150 µg As/L drinking water) to diabetes (Maull et al. 2012). This association was first reported in a study of 891 adults who lived in the southern region of Taiwan stricken by an arsenicosis endemic (Lai et al. 1994). Since this original study, reports from many other countries have been published on the correlation between environmental arsenic exposure and increased risk of developing diabetes (Afridi et al. 2008; Del Razo et al. 2011; Gribble et al. 2012; Jovanovic et al. 2012; Makris et al. 2012). However, very few studies have investigated the impact of *in utero* or early life arsenic exposures on the development of diabetes.

A recent population-based study evaluated the association of arsenic exposure with type 1 and type 2 diabetes in youth under the age of 22 (Grau-Perez et al. 2017). Arsenic species [inorganic arsenic (iAs), monomethylarsonate (MMA), and DMA] were measured in the plasma of six hundred and eighty-eight participants (429 with type 1 diabetes; 85 with type 2 diabetes, and 174 control) from South Carolina, Ohio, Colorado, California, and Washington. There was no correlation between the sum of the arsenic metabolites (%iAs, %MMA, %DMA) and either type of diabetes. However, low %iAs and high MMA% and DMA% were associated with higher odds of type 1 diabetes (Grau-Perez et al. 2017). Unfortunately, plasma measurements of total arsenic nor its metabolites are established biomarkers. Therefore, the association between arsenic exposure and early onset of diabetes could be highly understated in this study.

Although limited, there is evidence that *in utero* and early life exposure are linked to the development of diabetes. For example, in a combined pre- and post-natal exposure to 3 ppm arsenic (as arsenite) rat offspring had impaired glucose tolerance and showed increases in insulin resistance measured by HOMA-IR (Dávila-Esqueda et al. 2011). Sanchez-Soria et al. (2014) reported increased blood sugar in 36 week old Swiss-Webster rats that had been exposed *in utero* to 100 ppb arsenic. In addition, *in utero* arsenic exposure was associated with increases in miR-107 and miR-126, both involved in diabetes-related signaling pathways (Guay et al. 2011; Rager et al. 2014; Bodin et al. 2015). It is clear that there is a pronounced need for further investigation of the relationship between diabetes and early life arsenic exposure.

Respiratory Disease and Pulmonary Function

Early life exposure to arsenic impacts respiratory health in both animals (Lantz et al. 2009; Petrick et al. 2009; Ramsey et al. 2013) and humans (Smith et al. 2006; Dauphiné et al. 2011; Steinmaus et al. 2016; Ahmed et al. 2017). In addition to increased lung cancer mortality in young adults (30–49), Smith and colleagues (2006) reported that individuals from Antofagasta, Chile who were exposed to high levels of arsenic *in utero* and in early childhood had elevated bronchiectasis mortality rates. Furthermore, Dauphiné et al. (2011) found that early life arsenic exposure was associated with reduced lung function in adulthood. For example, compared to individuals from the less exposed city of Arica, those from Antofagasta with high early life exposure reported more breathlessness, had a 12.2% lower forced vital capacity and 11.5% lower forced expiratory volume in one second. Impaired lung function has also been associated with arsenic exposure in other areas of the world such as West Bengal (De et al. 2004) and Bangladesh (Milton and Rahman 2002).

There are several *in vivo* experiments that support the epidemiological data that suggest early life arsenic exposure impacts pulmonary function, and subsequent lung disease. For example, gene and protein expression analysis of embryonic lungs from Sprague-Dawley rats exposed *in utero* to 500 ppb arsenic identified 34 proteins and 59 genes that were differentially expressed as direct results of arsenic exposure (Petrick et al. 2009). Many of the differentially expressed proteins were related to the β -catenin/Wnt signaling pathway and c-Myc, both important in lung development and known to play a role in chronic lung disease. In addition, expression of extracellular matrix proteins and cell motility genes were largely suppressed, suggesting arsenic-induced lung remodeling (Petrick et al. 2009). Lantz et al. (2009) showed that lower *in utero* arsenic exposures (5, 10, 50, 100 ppb NaAsO₂) also altered extra cellular matrix protein expression. More specifically, arsenic exposure increased expression of collagen (COL3A1 and COL1A2) and elastin. However, histological analysis showed decreased total collagen around airways and increased actin smooth muscle (Lantz et al. 2009). In this same study, arsenic increased airway reactivity in 28 day old mice in a non-reversible manner (Lantz et al. 2009). In the lung, smooth muscle actin increased in a concentration-dependent manner, indicative of increased airway smooth muscle mass, a common histopathological hallmark of chronic obstructive pulmonary disease and asthma (Lantz et al. 2009).

Microarray analysis of fixed lung tissue from *in utero*, arsenic-exposed (100 ppb) C57BL/6 mice indicate that alterations in mucociliary clearance and immune cell response are possible mechanisms by which arsenic impacts respiratory health (Ramsey et al. 2013). Specifically, expression of genes involved in mucus production (*Clca3*, *Muc5b*, *Scgb3a1*), innate immunity (*Reg3γ*, *Tff2*, *Dynlrb2*, *Lplunc1*), and lung morphogenesis (*Sox2*) was induced after arsenic exposure. Furthermore, the arsenic exposed mice had smaller lungs and impaired lung function compared to controls (Ramsey et al. 2013). Arsenic-induced impairment of infection clearance and immune response may result in a greater susceptibility to infections and potentially increase the risk for developing bronchiectasis (Farzan et al. 2013).

Overall, there is both epidemiological and animal model based evidence that *in utero* arsenic exposures are associated with increased risks of developing adult pulmonary diseases. However, it is clear that the evidence is limited and the need for further investigation is imperative.

***In Utero*, Arsenic-induced Epigenetic Reprogramming**

The term “epigenetics”, which means “above genetics”, was coined by Conrad Waddington in the 1940’s to describe mechanisms of inheritance above and beyond regular genetics (Noble 2015). Today, epigenetics is defined as changes in gene expression, not directed by changes in the DNA sequence, that are heritable across generations (Feinberg and Tycko 2004). To date, there are three defined epigenetic mechanisms involved in the regulation of gene expression: DNA methylation, histone modifications, and gene silencing mediated by non-coding RNAs (Paul and Bhattacharjee 2016). Dysregulation of epigenetic mechanisms by environmental stressors, such as arsenic exposure, may cause persistent alterations in gene expression that increase the risk of adverse health effects and are most often the mechanism underlying transgenerational effects.

Incorporation of epigenomic studies has been essential in advancing our knowledge of the underlying molecular mechanisms responsible for arsenic toxicity. Arsenic alters DNA methylation, modifies histones, and changes mRNA expression patterns (Gonzalez-Cortes et al. 2017). Furthermore, several studies have indicated that the etiology of some arsenic-induced diseases result from exposure during sensitive windows of development (i.e. *in utero*) and that these exposures alter the genome via epigenetic processes.

Arsenic metabolism depletes one of the major components of the DNA methylation pool, *S*-adenosylmethionine (SAM). SAM is a methyl-donor involved in transmethylation of the DNA double helix, a modification that primarily takes place in cysteine-guanine rich regions of the genome. These regions, also known as “CpG islands”, are highly prevalent in promoter regions of genes (Becker et al. 1985; Paul and Bhattacharjee 2016). Biotransformation of inorganic arsenic to its mono- and dimethylated metabolites (MMA and DMA) requires SAM (Thomas 2016); therefore chronic arsenic exposure can lead to depletion of SAM and subsequent global hypomethylation of the genome (Paul and Bhattacharjee 2016). For example, in a hepatocyte cell line from 10 week old rats (TRL1215), chronic arsenic exposure reduced levels of SAM and induced genomic DNA

hypomethylation in a time- and concentration-dependent manner (Zhao et al. 1997). *In utero* exposures to 85 ppm arsenic, a concentration known to induce liver cancer, significantly reduced methylation of G-C rich regions throughout the genome of newborn mice and induced aberrant expression of genes involved in liver carcinogenesis (Xie et al. 2007).

As discussed in the previous section, *in utero* and early life exposures to arsenic cause dysregulation of stress and immune system responses that may in turn increase the risk of developing adult diseases (Fry et al. 2007; Ngalame et al. 2012; States et al. 2012; Farzan et al. 2013; Ramsey et al. 2013). Epigenetic reprogramming of such responses are a possible mechanism by which arsenic modifies disease susceptibility. Fry et al. (2007) reported increased expression of stress and inflammatory responses genes in the cord blood of infants born in Thailand whose mothers were exposed to arsenic. Network analysis of the 447 arsenic responsive genes in the cord blood indicated activation of the NF- κ B signaling pathway, which is involved in inflammation and tumorigenesis (Luo et al. 2004; Fry et al. 2007). In Bangladesh, total urinary arsenic was correlated with several pro-inflammatory cytokines in the cord blood of newborns including tumor necrosis factor (TNF), interleukin 1 beta (IL-1 β), and interleukin 8 (IL-8) (Ahmed et al. 2011). Additionally, genome-wide expression analysis of newborn cord blood samples from Gomez Palacio, Mexico (maternal drinking water arsenic ranging from 1–236 ppb) associated expression of 12 miRNAs and 334 mRNAs with total maternal urinary arsenic (Rager et al. 2014). Pathway analysis indicated that arsenic exposure was associated with decreased expression of genes involved in the innate and adaptive immune systems, possibly increasing the risk of developing chronic diseases, such as cancer.

Early life arsenic exposures are associated with a higher risk of developing childhood liver cancer (Liaw et al. 2008). In the *in utero* arsenic exposure model, development of hepatocellular cancer is a frequent outcome (Waalkes et al. 2003, Waalkes, Liu, et al. 2004). Hepatic microarray analysis of male mice with *in utero* arsenic-induced hepatocellular carcinoma revealed changes in expression of genes involved in estrogen receptor alpha (ER- α) signaling (Liu et al. 2006). Interestingly, these changes in gene expression occurred in parallel with DNA hypomethylation patterns in the promoter regions of ER- α (Waalkes, Liu, Chen, et al. 2004). These parallel results suggest that arsenic exposure, *in utero*, alters gene expression in the liver via epigenetic mechanisms. Arsenic's ability to reprogram the fetal liver was further demonstrated by States et al. (2012) in ApoE $^{-/-}$ mice exposed *in utero* to 49 ppm arsenic. Compared to control, arsenic exposure changed the transcriptional profiles of the liver of mice at PND1 and PND70. Importantly, the mRNA and miRNA profiles at PND1 were different than at PND70, indicating altered programming of the fetal liver (States et al. 2012). The hepatic gene expression profiles of these mice showed induction of immune, inflammatory and stress response pathway that are also the top pathways activated in human cord blood lymphocytes of newborns born to mothers exposed to high levels of arsenic (States et al. 2012; Fry et al. 2007). Therefore the weight of evidence clearly indicates that there are corresponding changes in gene expression profiles resulting in an increased inflammatory response, which underlies many chronic diseases including diabetes, CVD, NAFLD, and cancer (States et al. 2008).

Dysregulation of epigenetics have also been implicated in the development of *in utero*, arsenic-induced lung cancer and other respiratory diseases. Matrix metalloproteinase-9 (MMP-9), tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), and soluble receptor for advanced glycation end-products (sRAGE) are involved in extracellular matrix remodeling of lung tissue. In adults, these biomarkers are inversely correlated with arsenic exposure (Josyula et al. 2006; Lantz et al. 2007). However, it was not until recently that these biomarkers were associated with early life arsenic exposures. Olivas-Calderón and colleagues (2015) did across-sectional study of 275 male and female children (6–12 years old) from 4 rural communities in Comarca-Lagunera, Mexico with high arsenic concentrations in their drinking water (104 – 360 ppb). Urinary arsenic was inversely correlated with lung function and sRAGE levels and positively correlated with MMP-9 and TIMP-1. In the same cohort, urinary and toenail arsenic were positively associated with DNA methylation patterns in the promoter regions of sRAGE, MMP-9, and TIMP-1 (Gonzalez-Cortes et al. 2017). These results suggest that the etiology of *in utero* arsenic-induced lung disease is in part due to aberrant epigenetic mechanisms.

Exposure to arsenic during susceptible windows of development is associated with adverse health outcomes. Dysregulation of the epigenome is one mechanism by which *in utero* arsenic exposure can cause early onset of adult disease. However further studies are needed to elucidate the specific mechanism of altered gene expression and how it contributes to the development of adverse pathologies.

Animal models of arsenic-induced human pathogenesis

Mice have long been used as a model of human biology and pathogenesis. Mice are physiologically similar to humans, sharing the same organ systems and systemic physiology (Demetrius 2005; Perlman 2016). These similarities combined with the significant genetic homology (Waterston et al. 2002) between the two species and the experimental accessibility are among the many reasons why mouse models are used to study human disease. Indeed, there are vast similarities in pathogenesis. For example, Balmain & Harris (2000) showed that both mice and humans acquire a comparable spectrum of mutations in tumor suppressor and proto-oncogenes which may contribute to the fact that both species develop histologically similar tumors. However, mice can respond much differently to exposures, stress, drugs and experimental interventions. For example, there are many substances that do not cause cancer in mice, but are carcinogenic in humans, and vice versa (Anisimov et al. 2005). In other instances, it has proven difficult to replicate the same disease endpoints in mice as observed in humans in the context of toxicological exposures.

This challenge in replicating human pathologies in mice is exemplified by arsenic exposures. Since the early 1800s, arsenicals have been linked to development of human skin cancer. Although the International Agency for Research on Cancer (IARC) linked arsenic exposure to human cancer in 1973, there was an absence of solid evidence implicating arsenic as an animal carcinogen (IARC 1973). Animal-based arsenic studies slowly progressed from *inadequate evidence* for carcinogenicity of arsenic compounds in 1980 to *limited evidence* for inorganic arsenicals (IARC 1980) and continued *inadequate evidence* for organic arsenicals in 1987 (IARC 1987). Even by 2004, there was *limited evidence* that inorganic

arsenic caused cancer in rodents (IARC 2004). More specifically, it was indicated that DMA^v (biomethylated product of inorganic arsenic) produced urinary bladder tumors in rats and lung tumors in mice, both of which are human targets of arsenic carcinogenesis (IARC 2004). By 2012, IARC found that there was sufficient evidence for arsenic to be considered a human skin, lung, and urinary bladder carcinogen and some evidence implicating kidney and liver as possible target tissues for arsenic carcinogenesis (IARC 2012). Interestingly, there are still no whole animal models for arsenic-induced prostate cancer, a known arsenical target site in humans (Waalkes 2008; Benbrahim-Tallaa and Tokar et al. 2016).

Animals and humans can have the same exposure; however the same exposure can result in a very different dose based on a number of factors including size, metabolic rate, and life history. Therefore, these differences must be taken into account when extrapolating results from mouse models to human disease. Humans are over 2500 times larger than mice (Perlman 2016). This obvious size difference directly correlates with metabolic rate, which is seven times greater in mice than in humans (Demetrius 2005). The high metabolic rate of mice results in greater nutrient demand and therefore an increased density of mitochondria (Hulbert and Else 2005). Mice also have more docosahexaenoic acid (a polyunsaturated fatty acid) in their cellular membrane (Hulbert 2008) as well as higher rates of oxidative damage compared to humans (Perlman 2016). There are also numerous difference in life history strategies, which are collections of traits that a species has evolved to adapt to environmental variability (Griskevicius et al. 2011). Examples include length of gestation (mice = 19–20 days, humans = 280 days) and age of reproductive maturity (female mice = 6–8 weeks old, humans = 15–17 years old) (Perlman et al. 2016).

In terms of toxicological studies, these differences are of particular concern as they alter pharmacokinetics. For example, methylation of inorganic arsenic is one possible route of detoxification (Vahter and Concha 2001). However, there are considerable differences in the rate of methylation not only between species but also among individuals (Vahter et al. 2009). In rats, although the arsenic is sufficiently methylated, much of the trivalent DMA metabolite accumulates in the red blood cells, binding with high affinity to rat hemoglobin (Lu et al. 2004), that contains a reactive cysteine residue (Cys13) that humans do not have (Shen et al. 2013). As a result, the rat shows a low rate of excretion of arsenic. Taken together, there is an undeniable need to account for the immense differences between humans and rodents in order to understand the correlation between human epidemiological studies and data derived from rodent models.

The extrapolation of animal doses to human equivalent doses is a highly discussed topic in both the scientific community and the general public. Best exemplified by recent studies of the ability of resveratrol, an antioxidant found in red wine, to protect against aging, calculating human equivalent dose solely based on bodyweight results in invalid calculations and misinformation (Reagan-Shaw et al. 2008). In the example of resveratrol, the doses used in the mice translated to 672 bottles of red wine. According to the United States Food and Drug Administration (USFDA), the most appropriate way to extrapolate animal dose to human dose is by using the Body Surface Area (BSA) normalization method (Center for Drug Evaluation and Research 2002). The method accounts for the obvious difference in BSA between humans and mice. According to the USFDA, the BSA for a human is more

than 200 times greater than a mouse. Importantly, this normalization method includes a number of biological parameters that may vary across mammalian species such as oxygen utilization, basal metabolism, blood volume, and caloric expenditure (Reagan-Shaw et al. 2008). Although this method is most commonly talked about in the context of drug development, it should be considered when determining the doses used in animal models as it pertains to basic toxicological studies and research of disease initiation and progression.

Although important, the conversion between mice and human exposures is not exact. In addition, the conversions do not take into account difference in species-specific metabolism, making extrapolation of data between species complicated. Therefore, implementation of means, other than BSA, to translate the experimental murine data to human pathology is imperative. One approach has been “phenotypic anchoring”, in which alterations in gene expression as a result of environmental stressors are correlated to pathological changes (Cunningham et al. 2003; Paules 2003). For example, in a hepatic gene expression analysis, *in utero* exposure of 10 week old ApoE^{-/-} mice exposed to 49 ppm arsenic induced immune, inflammatory, and stress response pathways (States et al. 2012). These same pathways are also induced in human cord blood lymphocytes as a result of high arsenic exposure (Fry et al. 2007). These parallel results suggest that there is a correlation in gene expression, a phenotypic anchor, between the mouse exposures and high arsenic exposures in humans (States et al. 2011).

Another possible phenotypic anchor is target tissue dosimetry, a means of calculating the absorbed dose in specific tissues as the result of an exposure (States et al. 2011). However, this approach is complicated by the human data. First of all, human studies often only include the exposure, and not the doses. Therefore, even with the ability to conduct tissue dosimetry studies in mice, the comparative human data is highly imprecise. Secondly, as previously mentioned, there is much variation within species, such as body weight and individual exposure times that are not accounted for in the human population-based studies. The calculations of dose with individual precision that can be obtained in animal models is not replicated in the collection of human data, indicating a need for human data collection to be less population-based in order to better translate findings between mice and humans (States et al. 2011).

Regardless of the vast differences between humans and mice and the obstacles involved in extrapolating results, mice have led, and continue to lead to the improved understanding of the initiation, progression, and exacerbation of human diseases. With improved methods of extrapolation combined with the collection of individual-based epidemiological data, *Mus musculus*, will continue to be a powerful research tool.

Conclusion

Epidemiology and animal model studies both indicate that *in utero* exposure to arsenic is associated with increased risk of developing adult diseases such as CVD, NAFLD, chronic pulmonary disease and cancer. The development of new technologies and novel animal models has undoubtedly contributed to advancing our knowledge. Based on the current research, it is likely that there are multiple mechanisms, such as epigenetic and

inflammatory dysregulation, involved in the development of adult disease associated with *in utero* arsenic exposure. However, the underlying mechanisms are still not well understood indicating a need for further research.

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