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Individual susceptibility to arsenic-induced diseases: the role of host genetics, nutritional status and the gut microbiome

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Abstract

Arsenic (As) contamination in water or food is a global issue affecting hundreds of millions of people. Although As is classified as a group 1 carcinogen and is associated with multiple diseases, the individual susceptibility to As-related diseases is highly variable, such that a proportion of people exposed to As have higher risks of developing related disorders. Many factors have been found to be associated with As susceptibility. One of the main sources of the variability found in As susceptibility is the variation in the host genome, namely, polymorphisms of many genes involved in As transportation, biotransformation, oxidative stress response and DNA repair affect the susceptibility of an individual to As toxicity and then influence the disease outcomes. In addition, lifestyles and many nutritional factors, such as folate, vitamin C, and fruit, have been found to be associated with individual susceptibility to As-related diseases. Recently, the interactions between As exposure and the gut microbiome have been of particular concern. As exposure has been shown to perturb gut microbiome composition, and the gut microbiota has been shown to also influence As metabolism, which raises the question of whether the highly diverse gut microbiota contributes to As susceptibility. Here, we review the literature and summarize the factors, such as host genetics and nutritional status, that influence As susceptibility, and we also present potential mechanisms of how the gut microbiome may influence As metabolism and its toxic effects on the host to induce variations in As susceptibility. Challenges and future directions are also discussed to emphasize the importance of characterizing the specific role of these factors in inter-individual susceptibility to As-related diseases.

Keywords

arsenic exposure; individual susceptibility; gut microbiome; genetics; nutrition

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Introduction

As a ubiquitous metalloid element in the earth, arsenic (As) is widely distributed in water and soil, and over 200 million people are affected by As contamination [1]. Chronic As exposure is associated with a series of diseases, such as cardiovascular diseases, neurological disorders, liver diseases, skin lesions, and diabetes mellitus, and multiorgan cancers, such as bladder cancer, skin cancer and lung cancer [1]. It is clear that As exposure can cause significant health hazards, and in particular, a proportion of exposed people have higher risks of developing As-related diseases [2, 3]. The marked interindividual variability in the susceptibility to As was also observed among an exposed population with similar exposure history, socioeconomic status and diet [4, 5]. Previous studies found that many factors, such as host genetics, nutrition status and lifestyle, could affect the susceptibility of an individual to As-related diseases [3, 6, 7]. The variants of host genes induce the variabilities in the metabolism and eliminating efficiency of As and cause different sensitivities and tolerances to As-induced damage [3]. In addition, certain nutritional factors affect As biotransformation, and its adverse health effects are also related to the individual susceptibility to As exposure [6]. In recent years, gut microbiota has been concerned for its crucial role in the biotransformation and disease outcomes of multiple xenobiotics, such as pesticides, drugs, and As [8, 9]. The gut microbiome has been shown to affect As biotransformation, but its composition and function can also be perturbed by As exposure [10, 11], both of which can influence the health of the host. However, the gut microbiome composition is highly variable between different individuals, which renders it a potential source of individual susceptibility to As-related diseases.

The specific aim of this report is to review the factors associated with As susceptibility and summarize the current knowledge of the interactions between the gut microbiome and As exposure to highlight the potential roles of the gut microbiome in As susceptibility.

As biotransformation in mammals and its pathogenic mechanisms

Inorganic arsenic (iAs) is the main form of As exposure and can be absorbed into our bodies by transporters located in the gastrointestinal tracts, such as the aquaporin 7/9 (AQP7/9), hexose permease and phosphate transporter [12–14]. The biotransformation of As in mammalian bodies is a very complex process, and the three different pathways that have been proposed [3, 15] are shown in Figure 1. Briefly, iAs^V is first reduced to iAs^{III} with the assistance of phosphorolytic enzymes such as purine nucleoside phosphorylase (PNP) [16, 17]. The first metabolic pathway, which is called the Challenger model, consists of a series of reduction and oxidative methylation reactions [18, 19]. iAs^{III} is methylated to MMA^V , which is then converted to MMA^{III} . MMA^{III} can be further methylated to DMA^V , which can also be reduced to DMA^{III} and then methylated to generate TMA^V . In the second pathway, iAs^{III} first reacts with glutathione (GSH) and forms $As^{III}(GS)_3$, which can be further methylated to $MMA^{III}(GS)_2$ and $DMA^{III}(GS)$ and finally methylated to generate MMA^V and DMA^V [19, 20]. The third pathway was a variant of the second pathway and was first found in rats; iAs^{III} binds to a protein to form AsS_3 -protein and is finally methylated to MMA^V and DMA^V [15, 21]. Arsenic (+3) methyltransferase (AS3MT) is the main enzyme conducting As methylation in the human body [22]. GSTOs can catalyze the transform from

As^V to As^{III}, but previous studies indicated that GSTOs conducted As reduction was relatively limited and some other genes played important role in this process [23, 24]. Most of the As is pumped out of cells by the multiple drug resistance proteins MRP1 (encoding by gene ABCC1) and MRP4 (encoding by gene ABCC4) and is finally excreted with urine [25]. As transport pathways and related genes has been summarized by a recent review [26].

Multiple pathogenic mechanisms of As have been proposed. For example, As exposure can increase the reactive oxygen species (ROS) level in cells to cause oxidative stress [27], which can further induce DNA damage and lipid peroxidation. In addition, As can inhibit the activities of certain key enzymes, such as pyruvate dehydrogenase and GSH reductase, by conjugating with thiol groups in those proteins [28]. As exposure can also alter DNA methylation, damage DNA repair and perturb cell proliferation signals [29]. Previous studies have also demonstrated the immunotoxic effects of As [30].

Host genetic variations affect As susceptibility

Host genetic variation is one of the main factors related to the variability in interindividual susceptibility to As toxicity. According to previous studies, three types of genes are mainly involved, including genes related to As transportation and biotransformation, genes involved in the oxidative stress response and DNA repair, and other genes including p53 and NALP2 [31].

Genes related to As transportation and biotransformation

As toxicity is known to be largely determined by its methylation state and valence state [32]. Generally, the trivalent species iAs^{III}, MMA^{III} and DMA^{III} are much more toxic than the pentavalent species iAs^V, MMA^V, and DMA^V [32–34]. Moreover, methylated pentavalent species MMA^V and DMA^V are less toxic than iAs^V [34]. Therefore, As metabolism, especially As methylation, is considered a detoxifying process, and the efficiency of As biotransformation partly determines the host tolerance to As exposure. In fact, individual As susceptibility has been shown to be associated with variations in genes involved in As metabolism, namely, PNP, AS3MT, GSTO1, GSTO2, MTHFR (encoding methylenetetrahydrofolate reductase), and *CBS* (encoding cystathionine β-synthase) [35–37]. The urinary As profile is a widely used indicator of As methylation efficiency, As metabolic status and As toxic effects in the host.

PNP was previously thought to be involved in reducing iAs^V to iAs^{III} [16, 17]. A previous study carried out in 428 subjects exposed to As in West Bengal (India) found that polymorphisms of PNP, including His20His, Gly51Ser, and Pro57Pro, were significantly associated with As-induced skin lesions in an Indian population [36]. Moreover, in another study with 384 cases and 479 controls in Taiwan, Gly51Ser and Pro57Pro of PNP were found related to the increased risk of carotid atherosclerosis in high As (>50 µg/L) exposed population [38]. However, previous studies indicated that catalyzing the reduction of As^V to As^{III} is only one of the functions of PNP, and it is not necessary for As reduction that some other enzymes are also involved in this process in mammals [39–41]. Therefore, the relationship between polymorphisms of PNP and As susceptibility need to be further verified. AS3MT is the key enzyme that catalyzes the methylation of trivalent species, and

its polymorphisms are highly associated with As methylation efficiency [36]. For example, AS3MT Met287Thr polymorphisms have been found to strongly correlate with AS3MT activity [42]. Further study indicated that AS3MT with Met287Thr has different As methylation efficiency compared with the wildtype, that it has significantly lower $V_{\max}$ and K_m values for iAs^{III} than the wildtype enzyme in the absence of GSH [43]. Met287Thr polymorphisms were associated with As-induced micronucleus frequency as well as with the risk of development of skin lesions and bladder cancer [44–46]. GSTOs also partly participate As metabolism and detoxification in mammals. A case-control study found that GSTO1 genotypes were associated with skin lesions [35]. In a study that analyzed urinary As speciation and single-nucleotide polymorphism of 247 subjects exposed to As in southwestern Taiwan, GSTO1 Ala140Asp was associated with lower levels of MMA in urine, which correlated with metabolic syndrome [47]. In addition, a hospital-based case-control study with 149 urothelial carcinoma (UC) cases and 251 healthy controls in Taiwan found that a homogenous variant polymorphism Asp142Asp of GSTO2 inversely associated with the risk of UC [48]. However, there are also many studies that did not find any association between GSTO polymorphisms and As-related diseases [3, 31, 41]. For example, a study with 415 subjects from Hungary, Romania, and Slovakia failed to detect a significant association between polymorphisms in GSTO1 and the alteration of urinary arsenic metabolite pattern [49].

In addition to genes directly involved in As biotransformation, polymorphisms of multiple genes involved in one-carbon metabolism also influence As susceptibility. As shown in Figure 1, MTHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate (5,10-methyl-THF) to 5-methyltetrahydrofolate (5-methyl-THF) to promote the formation of S-adenosylmethionine (SAM), which is the methyl donor of As methylation [50]. Interestingly, MTHFR C677T genotypes were found to be associated with lower blood folate concentrations according to a meta analysis study [51], and multiple studies also found MTHFR polymorphisms correlated with the urinary As profile [3, 31]. A case-control study carried out in 492 exposed people (219 bladder cancer cases and 273 controls) in Southeastern Michigan found that MTHFR 222Ala allele was associated with the lower risk of bladder cancer [44]. Moreover, the sensitivity of As embryotoxicity was enhanced in the MTHFR knockout mouse [52]. Another related gene is CBS, which catalyzes the conversion of homocysteine to cystathionine. Homocysteine can be used to generate SAM and cystathionine to participate in GSH production [53]. The activity of the CBS gene influences the balance of one-carbon metabolism and thus influences As methylation [37]. Furthermore, variant genotypes for CBS SNPs (rs234709 and rs4920037) have been found to be associated with the level of urinary MMA and As-induced lung cancer according to two studies in Argentina. One study had 45 lung cancer cases and 75 controls, and the other one had 58 lung cancer cases and 84 controls, respectively [37, 54].

In addition, the ability to eliminate As can also influence the toxic effects of As. In the human body, MRP4/ABCC4 is mainly responsible for the export of methylated As from hepatocytes to the blood and from renal proximal tubular cells to urine [25]. A recent study expressed multiple MRP4 variants (C171G-, G187W-, K304N-, Y556C-, and wildtype MRP4) in human embryonic kidney cell line and found the As transporting capacities of

them were highly variable; these variants were also related to interindividual differences in As susceptibility [55].

Additional As susceptibility related genes and studies involved in As transportation and biotransformation are summarized in Table 1.

Genes involved in oxidative stress

Genes that protect against As-induced adverse effects, especially oxidative stress response genes and DNA repair genes, also contribute to the variability in As susceptibility. For example, glutathione *S*-transferases (GSTs, including GSTM1, GSTT1, and GSTP1) conjugate the reduced GSH to xenobiotic substrates for the purpose of detoxification, and the polymorphisms of GST genes are related to the susceptibility to oxidative stress [3]. According to a study in Taiwan with 115 exposed subjects and a study in Argentina with 170 exposed subjects, people with the GSTM1 null genotype had a higher proportion of urinary MMA and iAs [58, 61]. Another study carried out in 422 As-exposed subjects in West Bengal (India) indicated that the risk of As-induced skin lesions among people with at least one functional allele of GSTM1 was significantly higher than that of people with the GSTM1 null genotype [4]. For GSTT1, a study which completed the genotyping of 1062 subjects in Bangladesh indicated that the homozygous wide-type genotypes were associated with a high risk of As-induced skin lesions [62], while this association was not detected in studies conducted in China (354 exposed subjects from 2 different clans) and India (422 exposed subjects) [4, 63]. A study in Taiwan with 70 cases and 209 controls suggested that the null genotype of GSTT1 was associated with skin cancer [64]. In addition, some studies suggested that polymorphisms of GSTP1 were associated with As-induced skin lesions [62, 65]. While the Ile105Val variant of GSTP1 was found to be associated with carotid atherosclerosis, a recent study didn't find an association between this variant and either the blood or urinary As levels of 95 Turkish male smelter workers with occupational As exposure [59, 66]. Data collected from different areas and from subjects with different backgrounds are not always consistent; as such, future studies are required to elucidate the association between GST polymorphisms and As-related diseases.

In addition, the influence of polymorphisms of some oxidative stress response genes, including myeloperoxidase (MPO) and catalase (CAT), on the risk of As-induced skin lesions were assessed by a case-control study in Bangladesh with 30 cases and 104 controls [67]. It found that G463A of MPO and C262T of CAT were associated with a higher risk of As-induced skin lesions. Likewise, heme oxygenase-1 (HO-1) is also an antioxidant enzyme that can be induced by oxidative stress [68], and multiple studies in Taiwan indicated that HO-1 GT-repeat polymorphisms significantly associated with As-related carotid atherosclerosis, cardiovascular mortality and skin cancer [69–71]. In addition, according to a study in Taiwan carried out in 65 cases and 189 controls, Tyr113His polymorphisms in another related gene, microsomal epoxide hydrolase 1 (EPHX1), also significantly correlated with As-induced skin cancer [64].

Genes related to DNA repair

Inducing genotoxic damage and inhibiting DNA repair pathways are two of main aspects of As toxicity [29]. Therefore, the association between DNA repair related genes and As susceptibility has been widely explored. The base excision repair pathway is one of the major DNA repair pathways in humans for repairing ROS-induced DNA damage [72–74]. Previous studies found that polymorphisms of multiple genes, including 8-oxoguanine DNA glycosylase (OGG1), apurinic/apyrimidinic endonuclease (APE1), and X-ray and repair and cross-complementing group 1 and group 3 (XRCC1 and XRCC3), were associated with individual susceptibility to As-induced diseases [3, 31]. For example, a study found that different variants of hOGG1 and APE1 in 100 As-exposed Vietnamese correlated with different concentrations of urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG), that Cys/Cys of hOGG1 Ser326Cys and Asp/Glu of APE1 Asp148Glu were correlated with highest 8-OHdG [75]. 8-OHdG is a biomarker for assessing the risk of oxidative stress-induced carcinogenesis [76]. A study carried out in 240 Taiwanese rural residents indicated that Cys/Cys of OGG1 Ser326Cys were associated with a higher risk of As-induced hypertension than Ser/Ser and Ser/Cys [77]. A case-control study with over 1500 subjects conducted in Bangladesh indicated that variants of APE1 and XRCC1 were associated with As-induced skin lesions; however, OGG1 variants were not associated with skin lesions [78]. A case-control study with 324 UC cases and 647 controls also found that XRCC1 polymorphisms (399 Gln/Gln and 194 Arg/Trp and Trp/Trp) were significantly associated with UC [79]. According to a case-control study in India, XRCC3 Thr241Met polymorphisms correlated with the low incidence of As-induced skin lesions and the low frequency of chromosomal aberrations [80]. The excision repair cross-complementing group 2 (ERCC2)/XPD gene is involved in nucleotide-excision repair, and the associations between polymorphisms of ERCC2/XPD and As-induced diseases have been explored by several studies [5, 81]. For example, in a study carried out in 165 exposed subjects with hyperkeratosis and 153 controls in India, Lys/Lys of ERCC2/XPD Lys/Glu was significantly associated with As-induced hyperkeratosis [5]. However, in a study with 592 cases and 597 controls in Bangladesh, polymorphisms of Asp312Asn and Lys751Gln of ERCC2/XPD were no significant association with As-related skin lesions [82]. Another study with 324 UC patients and 647 controls didn't find significant association between polymorphisms of Lys751Gln of ERCC2/XPD and UC [79].

Other genes

In addition to the genes we mentioned, several other genes were also found to strongly correlate with the individual susceptibility to As-induced diseases. First, the correlation between the tumor suppressor p53 gene and As susceptibility have been widely discussed. Multiple studies demonstrated that Arg72Pro polymorphisms of the p53 gene were associated with different As methylation capacity and the different risk of As-related keratosis [83, 84]. Interestingly, Arg/Arg of p53 Arg72Pro was suggested over represented in people with keratosis according to a study in India with 366 exposed subjects [83], but the other study in Taiwan indicated that people with Arg/Arg of p53 Arg72Pro had lower risk of As-induced renal cell carcinoma (RCC) than those with Arg/Pro and Pro/Pro [84]. Moreover, As is also known to profoundly affect the immune system and induce disorders. Several studies in India (West Bengal) indicated that variations in certain related genes were

associated with As susceptibility. For example, a case-control study found that polymorphisms of TNF- α (Tumor necrosis factor alpha) and IL-10 (Interleukin 10) were associated with the risks of As-induced skin lesions, ocular, and respiratory diseases and that the high TNF- α producing genotype (GA/AA of G308A) of TNF- α and the low IL-10 producing genotype (TA/AA of T3575A) of IL-10 were implicated in high disease risk [85]. Moreover, the Ala1052Glu polymorphism of the NALP2 (LRR and PYD domains-containing protein 2) gene was found associated with fewer chromosomal aberrations and low risk of As-related respiratory diseases and skin lesions according to a case-control study with 219 cases and 213 controls in West Bengal (India) [86].

A detailed list of host genes related to As susceptibility and related studies are found in Table 2.

Other factors related to individual susceptibility

In addition to host genetics, other factors, such as nutritional factors and lifestyles, are also play important role in As metabolism and its toxic effects, thus, are also related to As susceptibility [7, 90, 91].

Diet and nutrients

Multiple studies indicate that diet and nutrients can deeply affect the As metabolism and its toxic effects. Although the mechanisms are not fully understood, there are three potential mechanisms that diet and nutrients could influence As exposure. First, some nutritional factors, such as trace elements selenium (Se), iron (Fe) and Zinc (Zn), can alter the bioaccessibility of As [6]. For example, low concentration of Se can bind As and form As-Se compound $[(GS)_2AsSe]^-$, which can be excreted from body [15]. Likewise, Zn supplement co-administrated with Se can increase As excretion in cattle that decrease As in milk but increase As in hair and feces [92]. Fe can be used to precipitate As, and a recent study demonstrated that sulfates of Fe^{2+} and Fe^{3+} could efficiently decrease the solubility of iAs and DMA^V in aqueous solution in a static in vitro model of gastrointestinal digestion [93, 94]. Second, some diet and nutrients can directly participate the As metabolism in host body. A typical example is the B type vitamins, especially folic acid. Folic acid is a type of B vitamin and plays an important role in one-carbon metabolism, which is related to SAM synthesis (Figure 1) [95]. An increase in folate intake can reduce blood As and increase DMA in urine, while a decrease in folate intake is associated with a high risk of As-induced skin lesions [90, 96]. Likewise, administration of GSH, which is an important substrate in As metabolism, can decrease the level of MMA and total As in blood and brain of mice [97]. Thirdly, As toxic effects can profoundly modulate by some nutrients. Multiple studies demonstrated that the administration of antioxidants, such as vitamins C (ascorbic acid), vitamin E (α -tocopherol), GSH, and N-acetylcysteine (NAC), can protect organs from As toxicity [6, 98, 99]. For example, a previous study demonstrated that As could improve nitric oxide and ROS generation, and increase lipid peroxidation in brain cells, but those adverse effects can be relieved by vitamins C, E and chelator dimercaptosuccinic acid [100]. Tea, which contain tea polyphenols as antioxidants, can reduce As-induced oxidative stress and DNA damage according to previous animal studies [101–103]. Likewise, Zn administration

could decrease lipid peroxidase and increase the activities of superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase, which ameliorated As-induced oxidative stress and thus decrease As-induced hepatotoxicity [104]. Besides, according to McCarty *et al.*, fruit consumption is associated with a reduced risk of As-induced skin lesions, whereas bean and betel nut are associated with an increased risk of this disease [105]. Previous epidemiological studies in Taiwan found that serum carotene levels were associated with several As-related diseases, such that low serum carotene level was significantly associated with a high risk of As-induced skin cancer and blackfoot disease [106, 107]. On the other hand, some diets could enhance the As toxic effects. For example, high-fat diet can deteriorate As-induced oxidative stress in rat heart and liver and exaggerated hepatofibrogenesis in mice caused by chronic As exposure [108, 109]. A recent study indicated that high-fat diet increased the sensitivity of mice to iAs exposure to increase hepatotoxicity [110]. A recent review summarized the effects of diet and nutrition factors on As metabolism and toxicity [6].

Lifestyles

Lifestyle is another factor that can influence As toxicity and thus related to individual susceptibility to As-induced diseases. For example, according to previous studies, there are synergistic effects between As exposure and smoking on the risk of lung cancer as well as skin lesions [7, 111, 112]. On the other hand, exercise might be helpful to against the adverse effects of As exposure. An animal study indicated that swimming exercise could prevent As-induced impairment of long-term memory of object recognition in mice [113].

Gut microbiome and As susceptibility

Gut microbiome introduction

With trillions of microbes in the human gastrointestinal tract, there are 100 times more genes in the gut microbiome than those in the human genome. As such, the gut microbiome is considered the second genome of the human body [114–117]. The gut microbiota plays important roles in food digestion, host energy homeostasis, and immune system development and has complex interactions with the neural system [118, 119]. In addition, the large gene pool of the gut microbiome confers powerful xenobiotic biotransformation ability [8, 120]. Bacteria-conducted biotransformation can deeply alter the toxic effects of certain xenobiotics, including drugs and heavy metals [121]. For example, nitrazepam, a hypnotic drug used in the treatment of insomnia, can be transformed to 7-aminonitrazepam by gut microbiota and then be transported to be metabolized to 7-acetylaminoitrazepam, a compound with teratogenicity [122]. Chromium (Cr) is another typical example of bacteria-conducted biotransformation; gut bacteria have a powerful ability to reduce highly toxic Cr(VI) to the less toxic Cr(III), and this ability reduces the toxicity of Cr(VI) in drinking water [123]. However, multiple environmental factors can also perturb the normal compositions and functions of the gut microbiome and are associated with a series of diseases such as obesity, glucose intolerance and inflammation [124, 125].

The oral route is the main approach of As exposure for human, which renders the gut microbiota as the first batches of cells exposed to As. Accumulating evidence indicates that

As exposure can alter the gut bacteria composition and that gut bacteria also influence the As metabolism in mammals [10, 11]. Since the gut microbiota plays a critical role in host metabolism, the interactions between As and gut bacteria could also further affect the host health status. However, the gut microbiome is known to be a highly dynamic system and that there is a wide variation in the bacterial composition between different groups of people [126, 127]. Therefore, this raises the question of whether the variation in gut microbiota is another factor that contributes to the individual susceptibility to As-induced disorders.

The interactions between gut microbiota and As have been widely discussed, and two main aspects have been proposed. First, accumulating evidence indicates that gut microbiota activities influence the bioaccessibility and biotransformation of As, which could influence the toxic effects of As on the host body [128, 129]. Second, studies show that As exposure can perturb the normal composition and functional gene profile of the gut microbiome and thus could potentially affect host health [10, 130]. As such, both of these aspects could influence the individual susceptibility to As-induced diseases.

Gut microbiota conducts the presystemic As biotransformation and influences As bioaccessibility

As we mentioned earlier, gut microbiota-conducted biotransformation, known as presystemic metabolism, can largely modify the toxicity of xenobiotics and then influence the host tolerance. Previously, the As metabolic potency of mammalian gut microbiota has been investigated by Rowland and Davies, and the *in vitro* experiments indicated that rat gut bacteria could generate iAs^{III} and DMA from iAs^V [131]. Methylated and thiolated As species (MMA^V, TMAO, TMA^S, DMMTA, DMDTA^V, MMTTA) were previously detected in experiments performed by incubating iAs with mouse gut microbiota [132–135]. As metabolism by human gut microbiota was also explored. First, high-throughput sequencing data from the Human Microbiome Project (HMP) indicates that the genes related to As transportation and metabolism, such as Aqp, arsA, arsB, arsC and arsD, are widely distributed in the genomes of human gut bacteria [136]. Indeed, *in vitro* fermentation confirmed the As metabolizing ability of the human gut microbiota. For example, Van de Wiele *et al.* (2010) detected iAs^{III}, MMA^V, MMA^{III} and MMTA^V by incubating iAs^V or As-contaminated soil with *in vitro* cultured human colon microbiota, which suggested the existence of presystemic As metabolism in humans [128]. Another study proved that sulfate-reducing bacteria (SRB) in human fecal and colon microbiota could convert MMA^V to MMTA^V [129] and that MMA^V can be demethylated to iAs^{III} by human colon microbiota, which highlights the complexity and multiple directions of presystemic As biotransformation. Since As toxicity is highly determined by its species, the gut bacteria involved in biotransformation should be able to modify the original toxicity of As exposure and influence the effects of As on the host. For example, DMMTA is a more cytotoxic species than DMA^V in human epidermoid A431 cells [33]. Moreover, previous studies also indicated that human gut microbiota could increase the bioaccessibility of As in soil particles [137, 138]. As bioaccessibility is the fraction of As dissolved in the gastrointestinal environment, which equates to the total As that can be absorbed by the human body [139]. As an important parameter to evaluate the health risk of As, the increase of bioaccessibility may enhance the disease risk in humans.

However, there is a high variation in the gut microbiome composition observed between different individuals, and several factors could influence the composition profile of gut microbiota. The high variability in microbiota may suggest the diversity of the As metabolic potency among different people. A recent study confirmed that the degree of As methylation by gut bacteria from different healthy individuals was largely different [140]. Another *in vitro* study suggested that Fe^{3+} decreased the As bioaccessibility and increased As methylation by altering the gut microbiota composition [141]. Therefore, the variable potencies of presystemic As metabolism of different people might cause different healthy effects on the host body and might partially contribute to the observed variability in individual susceptibility to As-related diseases.

Gut microbiota influences host As metabolism and alters its toxic effects by supplying special metabolites

The gut microbiota is deeply involved in multiple physiological processes, and several necessary materials can be supplied by gut bacteria, such as short-chain fatty acids and multiple vitamins [118], thus making it possible for gut bacteria to influence the toxic effects of As by modulating the host metabolism. For example, the gut microbiota has been considered an endogenous source of many vitamins including folate, riboflavin, cobalamin and vitamin K [142–144]. Multiple species in *Bifidobacterium*, such as *Bifidobacterium adolescentis* and *Bifidobacterium pseudocatenulatum*, can produce folate [142], whereas *Bacillus subtilis* and *Escherichia coli* can produce synthetic riboflavin [143, 145]. These vitamins facilitate the processes of As methylation, DNA repair, and antioxidative stress [143, 146–148]. As we mentioned previously, previous studies indicated that increasing the intake of folate, riboflavin and cobalamin could protect people from As-induced diseases, which is related to As susceptibility [90, 91]. Our recent study found that in the low As-exposed gut microbiome, vitamin synthetic genes were largely enriched, suggesting a potential protective response to As exposure [130]. Likewise, choline is an essential nutrient and can be transformed into betaine to remethylate homocysteine in the one-carbon metabolism pathway [149]. A previous study found that the use of a low dietary choline supplement decreased the methylation of As in rabbit [150], whereas an increase in choline supplement was shown to promote As methylation in pregnant women, especially in women with low folate intake [151]. Moreover, choline can also be derived from the gut microbiome [118, 152]. The microbial synthesized vitamins and other metabolites may promote As metabolism and confer As resistance to the host. Therefore, besides directly conducting As biotransformation, gut microbiota also can influence As metabolism in host bodies, which suggests that different gut microbiota composition may cause different effects. Indeed, our previous studies also indicated that the difference of gut microbiome caused by host genetics and pathogen infection affected As metabolism [153, 154]. Taken together, the high variations in the gut microbiome might differently affect host As biotransformation and its toxic effects, and thus influence host tolerance to As exposure, which could be another reason for As susceptibility.

As-induced gut microbiome dysbiosis influences host health

Since it has important roles in host metabolism, the gut microbiome is considered the second genome and an extra organ of the human body [117, 155]. However, the variability in the gut

microbiome is much larger than the variability in the host genome and organs [156, 157]. This variation in the gut microbiome contributes to the interindividual susceptibility to certain diseases. For example, the difference in the gender susceptibility to type 1 diabetes (T1D) in non-obese diabetic mice was directly caused by their differential commensal microbial community [158]. Previous studies also found that different microbial populations also dramatically affect the susceptibility to rheumatoid arthritis [159, 160]. Moreover, the normal development and homeostasis of the gut microbiome are critical for human health, and xenobiotic-induced dysbiosis of gut microbiome could modulate host susceptibility to certain diseases. For example, antibiotic-induced dysbiosis of gut microbiome in mouse increased the susceptibility to *Clostridium difficile* infection [161]. As exposure has been shown to perturb the normal composition and functional pathways of the mouse gut microbiome and to alter the fecal metabolome [10], which might also influence host susceptibility to related diseases. In addition, as we mentioned previously, this perturbation is not consistent between different groups of people, such that different gut microbiota profiles may have different levels of tolerance to As toxicity or induce different responses to As exposure [162]. Likewise, our previous study found that gut bacteria and their functional pathways in male and female mice were differently altered by As exposure, thus suggesting the different response to As exposure of gut bacteria in different hosts [162]. Although the specific effects of As-induced gut microbiome dysbiosis on host health are still unclear, it is likely that different degrees of dysbiosis and perturbations of the gut microbiota will differently affect host health and could cause different disease outcomes.

Challenges and perspectives

Inter-individual susceptibility to As exposure is linked to and influenced by multiple factors of the host and gut microbiome, as illustrated in Figure 2. Although great progress has been made in the last decades, there are still several challenges to fully understand and intervene inter-individual susceptibility to As exposure. First, inter-individual susceptibility to As exposure is highly related to As metabolism and its mechanisms of action, which are not fully understood yet. Studies aimed to better decipher the fate of As species and the specific mechanisms involved in As-induced diseases will aid in further understanding the variability in As susceptibility. In addition, the association between host genes and As susceptibility needs to be further examined using both animal models and well characterized human cohorts. Findings are not consistent for studies conducted in different geographic areas with different subjects, disease endpoints, and sample sizes, again highlighting the complex interactions of multiple potential environmental contributors. Moreover, although accumulating evidence indicates that the gut microbiome plays an important role in As metabolism and its health effects, the specific and systemic effects of the gut microbiome on As and how these effects cause human disease outcomes are still underexplored. The underlining mechanisms of As, host, and gut microbiota interactions need to be further investigated. Although *in vitro* experiments are informative to study As biotransformation catalyzed by gut bacteria, future studies on the role of the gut microbiota in As metabolism *in vivo* are particularly important. In addition, the gut microbiome is known to be a highly dynamic system and to have complex interactions with other factors such as diet, drug, sex and host genetics. Therefore, individual As susceptibility and disease outcomes should be a

result of the cross-talk of a series of factors including host genetics, diet nutrition, and gut microbiota. However, how multiple host and microbiome factors interact and influence As-induced disease outcomes is still unclear. Exploring the interactions between these factors and building animal models to examine these interactions would lead to a better understanding of the variability in As susceptibility, which could work in concert with studies using large human cohorts, with the goal to better understand and ultimately mediate As toxicity in susceptible populations. On the other hand, while it is challenging to understand the specific role of gut microbiome in As exposure, the highly dynamic nature of gut microbiome and its interactions with other factors make gut microbiome manipulation as a promising approach to intervene As-induced diseases in people with different susceptibility. For example, modulating gut microbiota by special diet to increase some probiotics may help decrease As bioaccessibility, promote As detoxification, and/or reduce As toxic effects. Continuous revealing the factors contributing to As susceptibility would facilitate a better understanding of the effects of As on human health and provide clues for conducting specific interventions for people with different susceptibility.

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Figure 1.

Three proposed As biotransformation pathways and the one-carbon metabolism pathway in mammalian cells. (AS3MT: arsenic (+3) methyltransferase; GSTO: glutathione-s-transferase omega; DHF: dihydrofolate; THF: tetrahydrofolate; 5,10-methyl-THF: 5,10-methylenetetrahydrofolate; 5-methyl-THF: 5-methyltetrahydrofolate; DHFR: dihydrofolate reductase; SHMT: serine hydroxymethyltransferase; MTHFR: methylenetetrahydrofolate reductase; MS: methionine synthase; SAM: *S*-adenosylmethionine; SAH: *S*-adenosylhomocysteine; MAT: methionine adenytransferase; CHDH: choline dehydrogenase; BHMT: betaine-homocysteine *S*-methyltransferase; SAHH: *S*-adenosylhomocysteine hydrolase; CBS: cystathionine β-synthase.)

Figure 2.

An array of host, microbiome and environmental factors influence As biotransformation and As-induced diseases, which contribute to inter-individual susceptibility to As exposure.

Table 1.

Summary of studies investigating the influence of genes involved in arsenic transportation and biotransformation on susceptibility to arsenic exposure.

Gene and study	Region and sample size	Polymorphism	Association
PNP			
[36] [*]	West Bengal, India; 428	His20His, Gly51Ser, Pro57Pro	Variants of PNP are associated with skin lesions.
[38]	Taiwan; 863	Gly51Ser, Pro57Pro,	No association with carotid atherosclerosis; However, for high exposure level (>50 µg/L), the A-T haplotype is associated with a high risk of carotid atherosclerosis.
[56]	Mexico; 135	8 polymorphism sites: -1626, 567, -1545, 2934, 3746, 5837, 6760, 7821	No association with the urinary As profile (DMA:MMA ratio).
AS3MT			
[36]	West Bengal, India; 428	Met287Thr	No association with skin lesions.
[38]	Taiwan; 863	Met287Thr	No association with carotid atherosclerosis; However, for high exposure level (>50 µg/L), the T-C haplotype is associated with a high risk of carotid atherosclerosis.
[56]	Mexico; 135	10 polymorphism sites: -400, 49, -262, 2393, 5207, 7388, 7588, 8597, 20984, 30585	Polymorphisms G2393A, G7388C, T30583C are associated with urinary As profile (DMA:MMA ratio).
[42]	Chile; 50	Met287Thr, promoter-114(G/C), exon 1-UTR 5'(GC/AT), intron 1-114(T/G)	Met287Thr, promoter-114(G/C), exon 1 UTR 5'(GC/AT) are associated with the urinary As profile (MMA%).
[44]	Southeastern Michigan; 492	Met287Thr	Polymorphisms of Met287Thr are associated with a high risk of bladder cancer for people exposed to high levels of As.
[45]	Chile; 207	Met287Thr	Polymorphisms of Met287Thr is associated with cytogenetic damage.
[46]	West Bengal, India; 315	G9527A	An allele in G9527A is associated with high risk of skin lesions and cytogenetic damage.
[57]	Argentina; 147	G12390C, C14215T, and G35991A	G12390C, C14215T, and G35991A are associated with low MMA% and high DMA % in urine.
GSTO1			
[35]	Bangladesh; 1635	Ala140Asp, Glu208Lys	Diplotype is associated skin lesions.
[36]	West Bengal, India; 428	Ala140Asp, -/AGG, Glu208Lys	No association with skin lesions.
[38]	Taiwan; 863	Ala140Asp,	No association with carotid atherosclerosis; However, for high exposure level (>50 µg/L), haplotypes are associated with a high risk of carotid atherosclerosis.
[56]	Mexico; 135	5 polymorphism sites: 1859, 8102, -1242, 5711, 8147	No association with the urinary As profile (DMA:MMA ratio).
[47]	Taiwan; 247	Ala140Asp	Asp allele is associated with low urinary MMA% and a slightly high risk of metabolic syndrome.
[48]	Taiwan; 400	Ala140Asp, Glu208Lys	Wild-type Ala140Asp is associated high MMA% in urine.
GSTO2			
[36]	West Bengal, India; 428	Asn142Asp	No association with skin lesions.
[38]	Taiwan; 863	Asn142Asp, A-183G	No association with carotid atherosclerosis; However, for high exposure level (>50 µg/L),

Gene and study	Region and sample size	Polymorphism	Association
			haplotypes are associated with a high risk of carotid atherosclerosis.
[48]	Taiwan; 500	Asp142Asp	Polymorphisms of Asp142Asp are associated with urothelial carcinoma risk.
MTHFR			
[44]	Southeastern Michigan; 492	A1476413G	An allele in A1476413G is associated with low bladder cancer risk.
[52]	-	MTHFR knockout	As embryotoxicity is enhanced in MTHFR knockout mice.
[35]	Bangladesh; 1635	Ala222Val, C1298A	Diplotype is associated skin lesions.
[58]	Argentina; 170	Ala222Val, A1298C	TT/AA variant is associated with high urinary iAs% and low urinary DMA%.
[54]	Argentina; 142	Ala222Val, Glu429Ala	No association with the urinary As profile.
[57]	Argentina; 147	Ala222Val	Polymorphism of Ala222Val in pregnant women is potentially associated with the urinary As profile.
MTR			
[54]	Argentina; 142	Asp919Gly	No association with the urinary As profile.
[57]	Argentina; 147	Asp919Gly	Polymorphism of Asp919Gly in pregnant women is potentially associated with the urinary As profile.
CBS			
[37]	Argentina; 120	C234709T and G4920037A	Variants of C234709T and G4920037A are possibly associated with urinary MMA% and lung cancer.
[54]	Argentina; 142	C234709T and G4920037A	Variants of C234709T and G4920037A are associated with urinary MMA%.
MRP1/ABCC1			
[59]	Turkey; 95	G1666A	Polymorphisms of G1666A are associated with urinary As levels but not with blood As levels.
[60]	Mexico; 102	Expression level in bronchoalveolar lavage cells	For high As-exposed (>50 µg/L) people with lung cancer, the MRP1/ABCC1 expression is significant low.
MRP4/ABCC4			
[55]	SV40-transformed human embryonic kidney cell line	C171G, G187W, K304N, G487E, Y556C, E757K, V776I and C956S	Different polymorphisms have different DMA ^V transport efficiency.

*. All numbers in parentheses are reference number.

Table 2.

Summary of studies investigating the influence of genes involved in As-induced adverse health effects on susceptibility to As exposure.

Gene and study	Region and sample size	Polymorphism	Association
GSTM1			
[61] [*]	Taiwan; 115	null genotype of GSTM1	Null genotype of GSTM1 is associated with high urinary iAs%.
[58]	Argentina; 170	null genotype of GSTM1	Null genotype of GSTM1 is associated with high urinary MMA%.
[4]	West Bengal, India; 422	null genotype of GSTM1	GSTM1-positive genotypes are associated with a high risk of skin lesions.
[62]	Bangladesh; 1200	null genotype of GSTM1	No association with skin lesions.
[63]	Guizhou, China; 354	null genotype of GSTM1	No association with skin lesions.
[66]	Taiwan; 605	null genotype of GSTM1	No association with carotid atherosclerosis.
[64]	Taiwan; 280	null genotype of GSTM1	No association with skin cancer.
[57]	Argentina; 147	null genotype of GSTM1	Null genotype of GSTM1 is weakly associated with MMA in urine.
[87]	Vietnam; 100	null genotype of GSTM1	Null genotype of GSTM1 is associated with low DMA%.
GSTT1			
[61]	Taiwan; 115	null genotype of GSTT1	Null genotype of GSTT1 is associated with high urinary DMA%.
[58]	Argentina	null genotype of GSTT1	No association with urinary As profile.
[4]	West Bengal, India; 422	null genotype of GSTT1	No association with skin lesions.
[62]	Bangladesh; 1200	null genotype of GSTT1	Wild-type GSTT1 is associated with a higher risk of skin lesions risk than null genotype.
[63]	Guizhou, China; 2402	null genotype of GSTT1	No association with skin lesions.
[66]	Taiwan; 605	null genotype of GSTT1	No association with carotid atherosclerosis.
[64]	Taiwan; 280	null genotype of GSTT1	Null genotype of GSTT1 is associated with skin cancer.
[57]	Argentina; 147	null genotype of GSTT1	Null genotype of GSTT1 is weakly associated with MMA and DMA in urine.
[87]	Vietnam; 100	null genotype of GSTT1	No association with the urinary As profile.
GSTP1			
[4]	West Bengal, India; 422	Ile105Val, Ala114Val	No association with skin lesions.
[62]	Bangladesh; 1200	Ile105Val	GG polymorphism is associated with a high risk of skin lesions.
[65]	Guizhou, China; 323	Ile105Val	Polymorphisms of Ile105Val are associated with skin lesions.
[59]	Turkey	Ile105Val	No association with the blood or urinary As levels.
[66]	Taiwan; 605	Ile105Val	For the high As-exposed (>50 µg/L) group, GSTP1 polymorphisms of Ile/Val and Val/Val are associated with carotid atherosclerosis.
[64]	Taiwan; 280	Ile105Val	No association with skin cancer.
[87]	Vietnam; 100	Ile105Val	Ile105Val polymorphisms are associated with the urinary As profile.
MPO			
[67]	Bangladesh; 134	G463A	GG genotype of MPO is associated with a high risk of hyperkeratosis.
CAT			
[67]	Bangladesh; 134	C262T	CT/TT genotype is associated with a high risk of hyperkeratosis.
[88]	Taiwan; 292	C262T	No association with hypertension.
HO-1			

Gene and study	Region and sample size	Polymorphism	Association
[70]	Taiwan; 894	Short GT-repeat	HO-1 short allele is associated with a low risk of cardiovascular mortality in people with hypertension.
[71]	Taiwan; 787	Short GT-repeat	HO-1 short allele is associated with a low risk of carotid atherosclerosis.
[64]	Taiwan; 280	Short GT-repeat	No association with skin cancer.
EPHX1			
[64]	Taiwan; 280	Tyr113His, His139Arg	Polymorphisms of Tyr113His are associated with skin cancer.
[2]	Taiwan; 302	Polymorphisms in exon 3	Polymorphisms in exon 3 are associated with a high risk of skin cancer.
MnSOD			
[77]	Taiwan; 240	Ala9Val	For individuals with high urinary As level, 9Val/Ala and 9Ala/Ala polymorphisms are associated with a high risk of hypertension.
[88]	Taiwan; 292	T24C	Polymorphisms of T24C is associated with hypertension.
OGG1			
[77]	Taiwan; 240	Ser326Cys	For individuals with high urinary As level, 326Cys/Cys polymorphism is associated with a high risk of hypertension.
[78]	Bangladesh; 1584	Ser326Cys	No association with skin lesions.
[64]	Taiwan; 280	Ser326Cys	No association with skin cancer.
[75]	Vietnam; 100	Ser326Cys	326Cys/Cys polymorphism is associated with a high urinary 8-OHdG.
APE1			
[78]	Bangladesh; 1584	Asp148Glu	148Glu/Glu polymorphism is associated with a high risk of skin lesions.
[75]	Vietnam; 100	Asp148Glu	148Asp/Glu polymorphism is associated with high urinary 8-OHdG.
XRCC1			
[78]	Bangladesh; 1584	Arg399Gln, Arg399Gln	For individuals with high toenail As, 194Arg/Arg polymorphism is associated with a high risk of skin lesions.
[79]	Taiwan; 981	Arg194Trp, Arg399Gln	3999Gln/Gln and 194Arg/Trp and 194Trp/Trp are associated with urothelial carcinoma.
[64]	Taiwan; 280	Arg280His, Arg399Gln	No association with skin cancer.
XRCC3			
[79]	Taiwan; 981	Thr241Met	No association with urothelial carcinoma.
[80]	West Bengal, India; 421	Thr241Met	Met allele is associated with a low risk of skin lesions, peripheral neuropathy, and conjunctivitis.
ERCC2/XPD			
[64]	Taiwan; 280	C156A	Polymorphisms of C156A are associated with skin cancer.
[81]	Guizhou, China; 486	G23591A, A35931C	Polymorphisms of A35931C are potentially associated with skin lesions.
[82]	Bangladesh; 1189	Asp312Asn, Lys751Gln	No significant association with skin lesions.
[79]	Taiwan; 981	Lys751Gln	No association with UC and urinary As profiles.
[5]	West Bengal, India; 318	Lys751Glu	Polymorphisms of Lys751Glu are associated with hyperkeratosis.
p53			
[66]	Taiwan; 605	Arg72Pro	For the high As-exposed (>50 µg/L) group, p53 variant polymorphisms of Arg72Pro and Pro72Pro are associated with carotid atherosclerosis.
[83]	West Bengal, India; 366	Arg72Pro	Polymorphisms of Arg72Pro are associated with keratosis.

Gene and study	Region and sample size	Polymorphism	Association
[84]	Taiwan; 381	Arg72Pro	Arg/Pro + Pro/Pro polymorphism is associated with a high risk of renal cell carcinoma.
MDM2			
[84]	Taiwan; 381	T309G	TG+GG genotype is associated with a high risk of renal cell carcinoma.
TNF-α			
[85]	West Bengal, India; 397	G308A	GA/AA genotype is associated with high risks of skin lesions, ocular, and respiratory diseases.
[89]	Taiwan; 894	G308A	Variant of G308A is associated with urothelial carcinoma.
IL-8			
[89]	Taiwan; 894	T251A	Variant of T251A is associated with urothelial carcinoma.
IL-10			
[85]	West Bengal, India; 397	T3575A	TA/AA genotype is associated with high risks of skin lesions, ocular, and respiratory diseases.
NALP2			
[86]	West Bengal, India; 432	Ala1052Glu	Ala1052Glu polymorphism is associated with low risks of skin lesions, respiratory diseases, chromosomal aberrations.

*. All numbers in parentheses are reference number.