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Minireview:

ARSENIC, GSTO2 ASN142ASP POLYMORPHISM, HEALTH AND TREATMENT

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ABSTRACT

Arsenic is a natural metallic element found in low concentrations in virtually every part of the environment, including waters and foods. The ingestion of arsenic by humans can cause a variety of disorders. Glutathione S-transferase omega (*GSTO*) is a member of phase II xenobiotic metabolizing enzymes. GSTO2 (a member of GST omega) participates in detoxification of inorganic arsenic. In human, the A>G transition at nucleotide position 424 of *GSTO2* was reported. This variation causes an Asn142Asp substitution. The Asp142 allozyme was expressed at approximately 80 % of the level of Asn142 allozyme. It is hypothesized that the *GSTO2* polymorphism may alter the risk of several diseases which are related to chronic arsenic poisoning. On the other hand, because arsenic trioxide is used for treatment of acute promyelocytic leukemia; it is possible that Asn142 allozyme may decrease the therapeutic effect(s) of the drug.

Keywords: arsenic, GSTO2, health, polymorphism, treatment

Arsenic and health

Among the general public, the word “arsenic” has become almost synonymous with the word “poison”. Arsenic has a wide variety of industrial applications from computers to fireworks. It should be noted that there is some evidence of clinical manifestations resulting from arsenic deficiencies in certain animal species. However, currently there is no known beneficial biological function of arsenic in humans.

Groundwater with elevated concentrations of arsenic has been recognized as a problem of global concern. Arsenic contamination of groundwater is one of the principal pathways of human exposure to inorganic arsenic (Kapaj et al., 2006). Because arsenic is present in soil, water, air, plants and all living organisms, presence of arsenic in foods is not unexpected. Foods and drinking water together usually accounts for 99 % of the total human intake of arsenic (Jones, 2007; Navarro Silvera and Rohan, 2007).

Chronic arsenic poisoning is occurred due to consumption of contaminated drinking water. Health effects are occurred dependent on the duration and dose of exposure. The ingestion of arsenic can cause a variety of disorders, including skin lesions, respiratory problems, nervous system effects, several types of cancers, cardiovascular disease, and reproductive effects (Kapaj et al., 2006; Mazumder, 2007; Navas-Acien et al., 2005; Navarro Silvera and Rohan, 2007). Arsenic has been shown to induce carcinogenesis via a wide range of cellular changes including alterations in cell differentiation and proliferation (Hayes, 1997; Navarro Silvera and Rohan, 2007). Inorganic arsenic has been found to induce chromosomal aberrations and sister chromatid exchange (Hayes, 1997). It is reported that high numbers of chromosomal

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aberrations occurring in human lymphocytes was related to chronic arsenic exposure (Mahata et al., 2004).

Arsenic compounds were used in traditional medicine of India and China for treatment of some diseases. At present, arsenic trioxide is used for treatment of acute promyelocytic leukemia worldwide. In addition, arsenic trioxide induces apoptosis in numerous cancer cell lines, including esophageal carcinoma, neuroblastoma, and gastric cancer, in vitro (Akao et al., 1999; Gu et al., 2000; Shen et al., 1999; Wang, 2001).

Glutathione S-transferases (GSTs)

Most xenobiotics require metabolic activation by phase I enzymes and detoxification by phase II enzymes. The coordinated expression and regulation of phase I and II xenobiotic metabolizing enzymes and their metabolic balance may be an important host factor in determining susceptibility to several multi-factorial traits. Glutathione S-transferases (GST, EC 2.5.1.18) are ubiquitous multi-functional enzymes, which play a key role in cellular detoxification. They have important functions such as removal of reactive oxygen species, regeneration of S-thiolated proteins and conjugation of glutathione to endogenous and exogenous electrophile substrates (Sheehan et al., 2001). In addition to their role as detoxification enzymes, the GSTs have shown their involvement in many different biological signaling, such as the synthesis of various prostaglandins, the production of steroid hormones, transport of hydrophobic ligands, gene regulation and apoptosis (Wang et al., 2005).

In human GSTs were divided into several classes, including GST omega (GSTO) (Nebert and Vasiliou, 2004). The GSTO has been identified with novel structural and functional characteristics. The omega class GSTs has a unique N-terminal extension of 11-20 amino acid residues and an active site cysteine residue, while the serine or tyrosine residue is characteristic of other eukaryotic GSTs and conserved between classes (Neber and Vasiliou, 2004; Wang et al., 2005; Wilce and Parker, 1994).

There are two functional *GST* omega class genes in humans (named *GSTO1* and *GSTO2*). The full-length cDNA of human *GSTO2* is 1179 bp long and encodes a protein of 243 amino acid residues with 64 % identity to the 241 residues of GSTO1. The *GSTO2* gene has six exons spanning 24.5 kb and lies 7.5 kb downstream of GSTO1. The gene encoding *GSTO2* was localized on human chromosome 10q24.3 (Whitbread et al., 2003). Expression of GSTO2 mRNA was seen in a variety of tissues; including the liver, kidney, skeletal muscle, prostate, pancreas, small intestine, heart, thymus, and testis (Wang et al., 2005; Whitbread et al., 2003).

The physiological importance of GSTO2 has not been fully elucidated yet. It is reported that the GSTO2 participates in detoxification of inorganic arsenic, catalyzes the reduction of monomethylarsonic acid to monomethylarsonous acid, the rate limiting step in detoxification of inorganic arsenic (Wang et al., 2005; Zakharyan et al., 2001). Over expression of GSTO2 indicated apoptosis. Therefore, it is suggested that GSTO2 may play an important role in cellular signalling (Wang et al., 2005).

Genetic polymorphism of *GSTO2* in human

In human, the A>G transition at nucleotide position 424 in exon 4 of *GSTO2* was reported (dbSNP: rs 156697). This variation causes an Asn142Asp substitution (Mukherjee et al., 2006; Whitbread et al., 2003). Studies of a series of genetic polymorphisms and mutations have shown that the change of only one or two amino acids can alter the quantity of encoded proteins during expression in mammalian cells. It is reported that Asp142 allozyme was expressed at approximately 80 % of the level of the Asn142 allozyme (Mukherjee et al., 2006).

There were few studies which investigated the association of GSTO2 Asn142Asp polymorphism and risk of mul-

tifactorial diseases, such as Parkinson's disease, breast cancer, hepatocellular carcinoma, colorectal cancer, basal cell skin carcinoma, ovarian cancer, and gastric cancer (Leite et al., 2007; Marahatta et al., 2006; Masoudi et al., 2008; Morari et al., 2006; Pongstaporn et al., 2006; Wahner et al., 2007).

Hypothesis

It has been reported that about 30-40 % of populations that are using arsenic contaminated drinking water show no clinical symptom of chronic arsenic poisoning related diseases (Kapaj et al., 2006). Also levels of arsenic metabolites vary greatly in the urine of individuals drinking the same contaminated water (Marnell et al., 2003; Vahter, 2000). Genetic polymorphism in GSTO enzymes that catalyze the rate-limiting step in arsenic biotransformation in humans, might explain a portion of that variation. Therefore, it is hypothesized that the Asn142 allozyme may have protective effect against diseases which they are related to chronic arsenic poisoning. Alternatively, the Asp142 allozyme may increase the risk of diseases which have an inverse relation to arsenic. On the other hand, because arsenic trioxide is used for treatment of acute promyelocytic leukemia; it is possible that Asn142 allozyme may decrease the therapeutic effect(s) of the drug.

This hypothesis could be tested especially in areas polluted with arsenic, also in persons occupationally exposed to arsenic.

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