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*Review paper*

# THE INFLUENCE OF HIGH AND LOW LEVELS OF ARSENIC IN THE HUMAN BODY ON THE PROCESS OF CARCINOGENESIS, BASED ON FUNCTION, EXPRESSION AND GENETIC POLYMORPHISMS IN THE GENES ENCODING THE TWO ARSENIC TRANSPORTERS - WATER CHANNELS *AQP* AND GLUCOSE TRANSPORTERS GLUT (*SLC2A)*

Jakub KUBIŚ[1*], Marek KMIEĆ[2], Jan BIŃKOWSKI[3], Marta SRÓŻYŃSKA[4]

[1]West Pomeranian University of Technology Szczecin, Department of Polymer and Biomaterials Science, Szczecin, Poland
[2]Pomerania Medical Univeristy in Szczecin,Department of Genetics and Pathology, Szczecin, Poland
[3]West Pomeranian University of Technology Szczecin, Faculty of Biotechnology and Animal Husbandry, Department of Genetics and General Animal Breeding, Szczecin, Poland
[4]University of Medical Sciences, Department of Dermatology, Poznań, Poland

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Arsenic is a metallic element commonly found in soil, water and plants, and thereby can easily enter the food chain. When arsenic enters the body through food consumption, it subsequently passes into the cells through water channels (AQP) and glucose transporters (GLUT), where it may exert a various metabolic alterations including genotoxicity, which may finally promote carcinogenesis. However, there are human populations showing a reduced adverse effects of arsenic. This is mainly due to a natural selection caused by a long-term environmental exposure to a large doses of arsenic. Aquaporins *AQP3, AQP7, AQP9, AQP10* and glucose transporters *SLC2A1* (GLUT1), *SLC2A4* (GLUT4) are considered as the candidate genes associated with resistance to arsenic in the carcinogenesis process as they are closely related to the occurrence of a various types of cancers, while their products are associated with arsenic transport.

*Keywords:* cancer, arsenic, AQP, GLUT, tumor

Corresponding authors*:* Jakub Kubiś, West Pomeranian University of Technology Szczecin, Department of Polymer and Biomaterials Science, Aleja Piastów 45, 70-311, Szczecin, Poland. E-mail: jakub.kubis1996@gmail.com, Phone: +48 695 092 013

## INTRODUCTION

*Arsenic*

Arsenic is a metal belonging to the nitrite group that is widely distributed in nature. It belongs to the toxic compounds to which most people from highly developed and/or developing countries, where economies are based largely on metallurgy, mining and agriculture, are exposed to (BIZOŃ *et al*., 2013; KULIK-KUPKA *et al*., 2016; STOJSAVLJEVIĆ *et al*., 2019). This is due to the fact that arsenic in minerals gets into the water, and the development of industry intensifies this process. In many countries this has resulted in a high concentrations of arsenic in groundwater exceeding the standards (10 μg / l) up to a hundred times (TSENG, 2009; BIZOŃ *et al*., 2013; KULIK-KUPKA *et al*., 2016; SOZA-RIED *et al*., 2019). Among the high risk countries of arsenic groundwater contamination are Canada, India, Bangladesh, United States, China, Taiwan, Mexico, Poland, Japan, Nepal, Iran and Serbia (GOERING *et al*., 1999; KULSHRESTHA *et al*., 2014; SOZA-RIED *et al*., 2019; STOJSAVLJEVIĆ *et al*., 2019).

Groundwater pollution is closely related to the penetration of arsenic compounds into food, which must be subject to strict control. Its highest concentrations are recorded in wheat, vegetable and confectionery products, with the average arsenic content in a cereal and soy products ranging from 0.017 mg/kg to 0.058 mg/kg (GOERING *et al*., 1999; WOJCIECHOWSKA-MAZUREK *et al*., 2008; KULIK-KUPKA *et al*., 2016). In Iranian rice, the content of inorganic arsenic is 82 μg/kg, and the total arsenic forms is at the level of 120 μg/kg. This content, however, falls within the reference standards of the Chinese and FAO UN/WHO and amounts to 150 μg/kg and 200 μg/kg, respectively (CANO-LAMADRID *et al*., 2015; KULIK-KUPKA *et al*., 2016).

Arsenic is a toxic heavy metal that can be found at four degrees of oxidation i.e. -III, 0, +III, +V (KULSHRESTHA *et al*., 2014). The trivalent and pentavalent forms are the most common oxidation states of As, with compounds at +III oxidation being characterized by a higher toxicity than +V valencies. On the other hand, methylated compounds with the oxidation state +III are more harmful than inorganic compounds (LIS *et al*., 2010; TSENG, 2009; KULIK-KUPKA *et al*., 2016; GAMBOA-LOIRA *et al*., 2017; SOZA-RIED *et al*., 2019).

***P**athogenesis associated with arsenic compounds*

The occurrence of arsenic in groundwater and food is associated with an increased risk of skin, liver, kidney and lung cancers as well as other diseases such as atherosclerosis and cardiovascular diseases, diabetes, hypertension and neurological diseases (Alzheimer, Parkinson). Moreover, the International Agency for Research on Cancer has put arsenic and its compounds in the group of the first carcinogenic compounds whose action has been proven epidemiologically (KULSHRESTHA *et al*. 2014; GAMBO-LOIRA *et al*., 2017; LUO *et al*., 2018). Initially, the daily intake of arsenic was 15 μg/kg of body weight, but studies have shown that even lower doses can contribute to the development of lung, bladder and skin cancers. It was shown that the consumption of 3 μg/kg per day increases the risk of lung cancer by 0.5% (KULIK-KUPKA *et al*., 2016; SOZA-RIED *et al*., 2019). Other studies have shown that the occurrence of arsenic in waters at the level below 10 μg/l already may have a significant impact on the skin cancer development (MAYER and GOLDMAN, 2016).

In order to exert its harmful effects, arsenic needs to be first transported into the cells of human body, where it is metabolized to the compounds that can be expelled, causing many changes such as disturbance of metabolic pathways, blockage of the cellular respiration process, but also neurotoxicity and genotoxicity. This can be mediated by the protein channels such as aquaporins (AQP3, AQP7, AQP9, AQP10) and glucose transporters (GLUT1, GLUT4), which are capable of transporting arsenic to and out of a human cells (LIS *et al*., 2010).

*Arsenic, medicine or poison? - dualism of arsenic influence on the body*

It should be emphasized that arsenic was and still isused for medicinal purposes. Previously, it was used as a salt of meta arsenic acid ($KAsO_4$) for the treatment of asthma, diabetes, tuberculosis, rheumatoid fever and anemia (BIZNOŃ *et al*., 2013; KULIK-KUPKA *et al*., 2016). It also has found its application in cancer therapy. It was used as the first chemotherapeutic agent in patients with chronic myeloid leukemia in the form of arsenic trioxide. In the 1970s, it was used in the treatment of skin cancer in the form of an arsenic ointment, however oral test have proven to be too toxic for general use (LITIWN *et al*., 2009; LALLEMAND-BREITENBACH *et al*., 2012; BIZNOŃ *et al*., 2013; KULIK-KUPKA *et al*., 2016). Arsenic trioxide ($As_2O_3$) has toxic properties that result from the ability to react with a sulfhydrol groups of proteins. This leads to disturbances in the Krebs cycle and cellular respiration. It also contributes to the formation of free radicals in the form of $H_2O_2$ and reduces the concentration of glutathione in the cell by inhibiting the action of glutathione reductase. The safe dose of arsenic for an adult human is approximately from 10μg to 15μg per day, and the toxic dose is between 5 mg and 50 mg (HOFFMAN and MIELECKI, 2013; KULIK-KUPKA *et al*., 2016).

The therapeutic effect of arsenic trioxide in the fight against cancer is aimed at limiting proliferation and inducing apoptosis of tumor cells. The process of apoptosis can be triggered by various ways. Among them we can distinguish an activation of arsenic compounds by JNK kinase, inhibition of NF-kappaB, telomerase activity, disturbance of membrane mitochondrial potentials, as well as activation of proapoptotic kinases. Mitochondrial damage can cause an increase in reactive oxygen species, disruption of electrolyte transport and DNA damage, thus activating the apoptosis pathway associated with the TP53 protein (LITWIN *et al*., 2009; LALLEMAND-BREITENBACH *et al*., 2012; BIZOŃ *et al*., 2013; KULIK-KUPKA *et al*., 2016; SOZA-RIED *et al*., 2019)

Arsenic trioxide ($As_2O_3$) is used as the first line of defense in acute promyelocytic leukemia (APL), as its effects have been demonstrated both *in vitro* and *in vivo*. APL is characterized by an excess of immature leukocytes in the bone marrow. As a medicine, arsenic trioxide may also be effective in the treatment of chronic myelogenous leukemia (CML). At low doses (about 0.5μmol/l), $As_2O_3$ induces differentiation of mature cells, and at a higher concentrations leads to their apoptosis (LITWIN *et al*., 2009; LALLEMAND-BREITENBACH *et al*., 2012; HOFFMAN and MIELECKI, 2012; KULIK-KUPKA *et al*., 2016).

Despite the therapeutic effects of arsenic, it is still on the list of substances with a strong carcinogenic effect. It has been shown that exposure to arsenic causes an increased risk of skin cancer and internal organ cancers (bladder, respiratory tract, liver, kidneys) (MUKHOPADHYAY and BEITZ, 2010). Arsenic trioxide ($As_2O_3$) has been approved by the Food and Drug

Administration for the treatment of acute form and recurrent promyelocytic leukemia (KULIK-KUPKA *et al*., 2016; SOZA-RIED *et al*., 2019).

It is interesting that the susceptibility to diseases associated with arsenic poisoning may vary in people of different ages, sexes or genetically adapted (LINBERG *et al*., 2007; ENGSTROM *et al*., 2007; TSENG *et al*., 2009; TORRES- SANCHEZ *et al*., 2016; LUO *et al*., 2018; STOJSAVLJEVIĆ *et al*., 2019; SOZA-RIED *et al*., 2019). For instance, in children an increased methylation of inorganic forms of arsenic and its urinary excretion were observed. However, these findings were not supported by other studies (TSENG *et al*., 2009; TORRES-SANCHEZ *et al*., 2016). On the other hand, it was also shown that the first stage of methylation was much more pronounced in adults, and only the subsequent stages were more intense in children (TORRES- SANCHEZ *et al*., 2016).

A large number of researches have also been carried out aimed at analyzing the influence of gender on the difference in arsenic metabolism. Most studies in adults have suggested that women exerted better methylated ability when compared to men. This findings clearly indicate that women exhibit higher arsenic methylation efficiency, manifested by a lower percentage of inorganic arsenic and methylarsonatecontent, with a concomitant higher urinary excretion of dimethylarsinate. The above was partially explained by the stimulating effects of estrogen, which promotes choline synthesis and in turn remethylate homocysteine to methionine (LINDBERG *et al*., 2007; ENGSTROM *et al*., 2007; TSENG *et al*., 2009; TORRES- SANCHEZ *et al*., 2016; LUO *et al*., 2018; STOJSAVLJEVIĆ *et al*., 2019; SOZA-RIED *et al*., 2019).

Furthermore, many prior researches also indicate differences in the occurrence of cancers caused by arsenic poisoning in different ethnic groups, probably resulting from a genetic variation existing between them (TSENG, 2009; LUO *et al*., 2018). This phenomenon may be due to thousands of years of exposure to high doses of arsenic in water of populations of people living in more or less As-polluted areas. Constant exposure to arsenic resulted in the selection of resistant genotypes to high doses of arsenic through natural selection, as in the case of populations living in the Andes mountain regions who appear to be resistant to the effects of arsenic compounds (SMITH *et al*., 2000).

*Aquaporine (AQP)*

Water is the substance found in all living cells and is essential for their life, therefore it is vital to ensure its continuous flow through the lipid layer both outside and inside. Water transport can occur through the lipid bilayer through a simple diffusion, but it is a very energetic process which makes it unprofitable. However, there exist integral membrane proteins from a larger family of aquaporins (AQPs) that enable free water movement with low energy expenditure (HACHEZ and CHAUMONT, 2010). AQPs belong to the MIP (major intrinsic protein) protein family that can be found in organisms of all kingdoms from vertebrates, through insects, plants, bacteria and even viruses. MIPs form protein channels through the cell membranes allowing for water and other small solutes movement (LIS *et al*., 2010; HACHEZ and CHAUMONT, 2010). A different number of homologues are found in different species (from 3 to 5 in insects and 13 in mammals) (HACHEZ and CHAUMONT, 2010; MAGOULIOTIS *et al*., 2019). Apart from water transport, AQPs also indicate transepithelial fluid transport during urine concentration or secretion of glandular fluid. They are also involved in many other physiological processes such

as cell migration, corneal and brain edema, skin hydration, adipocyte fat accumulation, nerve signals and apoptosis transmission (HACHEZ and CHAUMONT, 2010).

The growing number of studies indicate that AQPs are multi-functional channels. Although each type of AQP has a permeability to water, the number of substrates that are transported is greater. It has also been proven that various AQP subfamilies have different distribution in a different tissues and subcellular components . Some AQP isoforms, in addition to water, transport dissolved substances thatplay a significant physiological roles. Some of them may transport non-polar substances such as carbon oxides, nitrogen dioxide, hydrogen peroxide and metals like arsenic (As), boron (B) or silicon (Si). This proves their key role in many physiological processes. It has also been shown that glycerol may be transported by the aquaglyceroporin family, which allows for skin hydration, and fat cell metabolism (HACHEZ and CHAUMONT, 2010; ROSEN and TAMAS, 2010; MAGOULIOTIS *et al*., 2019).

Aquaporins and aquaglyceroporins help to transport substances such as water, glycerol and other dissolved substances. They are also responsible for the metal diffusion such as arsenic or antimony. At neutral pH, on (+III) oxidation state forms of these metals take the form similar to the glycerol, which allows them to penetrate into the cell (ROSEN and TAMAS, 2010).

AQP7 and AQP9 have been shown to have the greatest impact on arsenic uptake, whereas AQP3 showed limited transport of this compound (ROSEN, 2002; GOURBAL *et al*., 2004; ISHIBASHI *et al*., 2009; LIS *et al*., 2009; SHINKAI *et al*., 2009; LIU, 2010). AQP10 is also associated with arsenic transfer (ROSEN, 2002; LIS *et al*., 2009; LIU, 2010).

*Glucose transporters (GLUT)*

Human metabolism is closely related to the collection and processing of energy compounds supplied along with food. All living cells need glucose as a fuel to maintain the basic physiological processes. Glucose is not capable to exceed the lipid bilayer of the cell membrane by a diffusion and therefore needs a specific transporters for this purpose. Such transporters include GLUT transporters encoded by the *SLC2A* genes. In total, there are 14 transmembrane proteins from this family that regulate the sugar homeostasis of the human body (MAGIER and JARZYNA, 2013).

Tumor cells show an increased metabolism and thus increased demands for the metabolic substrates. This is the result of the growth of a tumor that is unable to provide itself with the right amount of oxygen, as it can diffuse only 150 micrometers deep into the tissue. Even the process of angiogenesis and the formation of new blood connections to the tumor is not able to provide an adequate dose of oxygen, therefore it uses an anaerobic glucose metabolism to produce ATP. Anaerobic processes, due to their poor energy production efficiency, cause that the cancer demand on sugar substrates increases, which consequently results in increased expression of GLUT transporters. The anaerobic digestion of glucose by the tumor cells leads to the increased production of lactate and thus strong acidification of the environment (MUECKLER *et al*., 2014).

GLUT proteins are divided into three subclasses, all of which share a certain similarity: i.e. 12 trans membrane domains, N- and C-terminal polypeptides inside the cell, hydrophobic stem, common evolutionary fragments that are specific to the GLUT family. Despite such significant structural similarities, various isoforms not only have different tissue specificity, but

also represent different mRNA assembly methods, intracellular localization, and the degree of affinity for both the substrates and inhibitors (MAGIER and JARZYNA, 2013).

There exists a large body of evidence demonstrating that not only aquaporins are capable of transporting arsenic in the body, but also glucose transporters such as GLUT1 and GLUT4 can contribute to this process. It has been shown that they are involved in the transport of arsenic acid (III) and its methylated derivatives (WALTON *et al*., 2004; ROSEN and LIU, 2009; LIS *et al*., 2009; KULSHRESTHA *et al*., 2014).

*The penetration and metabolism of arsenic compounds in the body*

Arsenic compounds can enter the body via the alimentary and respiratory tracts. The initial effect of poisoning with arsenic compounds is the inhibition of enzymes such as lactate dehydrogenase, alpha-ketoglutarate dehydrogenase, leading to the lactate and pyruvate accumulation with subsequent neurological disorders and finally death (LIS *et al*., 2009). As the arsenic crosses the placenta in the early stages of pregnancy and accumulates in the epithelial tissue of the fetus it can be very dangerous (VAHTER, 2009). It can also cause cancers, vascular diseases, nervous system disorders, pharyngitis, bronchitis, larynx and the damage to the liver, heart, mucous membranes and the skin (GOERING *et al*., 1999; KUO *et al*., 2013; KULSHRESTHA *et al*., 2014; MAYER and GOLDMAN, 2016; SAGE *et al*., 2017).

Metabolism of arsenic occurs in the liver, and a methylation that comprises its first stage takes place under the influence of S-adenosylmethionine as a donor of methyl groups and sulfhydryl glutathione as a cofactor of the reaction. Methylated forms of arsenic take on the forms of a many organic compounds. The occurrence of methylation of arsenic compounds is evidenced by the presence of monomethylarsonic acid (MMA(V)) and dimethylarsinic acid (DMA(V)) in the urine and the bile. However, it turns out that intermediate metabolites, such as monomethylarsonic acid and dimethylarsinic acid, are more toxic than arsenic itself (GOERING *et al*., 1999; VAHTER, 2009; KULSHRESTHA *et al*., 2014). Arsenic enters the body in the form of salts and esters of arsenic acid and is metabolized to the corresponding metabolites. DMA is excreted in the urine and DMMTA(V) is present in the urine as well as in the tissues and organs, from which it appears to be simply absorbed by the tissues and is more toxic than the form initially absorbed (KULSHRESTHA *et al*., 2014).

One of the toxic effects of arsenic relies on oxidative stress triggering via blocking an antioxidant enzymes. The main place of production of reactive oxygen species in the body are the mitochondria, whose abnormal functioning is manifested by an increased production and release of reactive oxygen species. This is caused by an abnormal electron transmission through the respiratory chain, which results in the formation of $H_2O_2$ hydrogen peroxide, superoxide anion $O^{2-}$ and $OH^-$ hydroxyl radicals. Free radicals are also formed during the oxidation of As(II) to As(V), at the time of transition metabolites such as dimethylarseno [(CH3) 2As*] and dimethyl arsenic peroxyl [(CH3) 2AsOO*] radicals. Arsenic causes an increase in the oxygen consumption resulting in increased production of reactive oxygen species (GOERING *et al*., 1999; LIS *et al*., 2009; KULSHRESTHA *et al*., 2014).

Physiologically produced in the cell, free radicals are responsible for the regulation of cell function through a various processes such as autophagy, gene expression, glucose homeostasis, inflammation etc. (GOERING *et al*., 1999; LIS *et al*., 2009; KULSHRESTHA *et al*., 2014). The ROS

effect results in stimulating or suppressing many cellular signals by oxidizing the sulfhydryl groups and altering the redox potential of the cell. The above induces many signaling pathways leading to the changes in the gene expression, cell reproduction and death. Arsenic cause dysfunction of signal molecules like tyrosine kinases, phosphatases, serine-threonine kinases, G protein, signal lipids, $Ca^{2+}$ mediated signaling and transcription factors (KULSHRESTHA *et al*., 2014).

Low concentrations of MMA(II) and DMA(III) are cytotoxic to human skin, lungs, bladder and hepatocytes. MMA(II), DMA(II) and trimethylarsenic oxide (TMAO) may cause genotoxicity effect, i.e. carcinogenic effect on the cell genetic material.

As(V) shows a similarity to phosphorus (P) and therefore it can replace it in many biochemical reactions in the body. This results in the substitution of arsenic instead of phosphorus in the products of the glycolysis process, e.g. the formation of glucose-6-arsenic instead of glucose-6-phosphate, thereby affecting the inhibition of ATP formation in this process. Arsenic causes disruption of phosphate that binds to ATP, resulting in the formation of ADP-arsenic. Moreover, it inhibits insulin stimulation by taking glucose through the cells. It binds to the sulfhydryl groups of enzymes such as pyruvate and alpha-ketoglutarate dehydrogenase and competes with phosphorus binding sites on the glycolytic enzymes, impairing glucose metabolism and blocking ATP synthesis, leading to cell death (LIS *et al*., 2009; KULSHRESTHA *et al*., 2014).

Cell glucose uptake is regulated upon insulin receptors activation. The binding of insulin to the alpha-subunit of the insulin receptor activates the tyrosine kinase residues and autophosphorylates the beta-subunit of the insulin receptor, This initiates the phosphorylation of further protein kinases and consequently results in the PKB / AKT signal pathway phosphorylation, what finally allows for the transport of GLUT4 from the nuclear area to the cell membrane. GLUT4 is a transport channel for glucose which allows for its influx into the cells. Arsenic(III) and its methyl derivatives influence the inhibition of the PKB / AKT pathway, which results in the glucose uptake inhibition via GLUT4. However, it has been shown that this effect occurs only at low doses of arsenic, and its high doses cause an insulin-independent glucose uptake (WALTON *et al*., 2004; KULSHRESTHA *et al*., 2014).

Another example is the replacement of the phosphate groups in a sodium-potassium pump and an anion exchange system which can interfere with the exchange of ions between the cell and the environment (KULSHRESTHA *et al*., 2014).

*Mutations and changes in the expression of AQP and SLC2A genes, and the process of carcinogenesis*

Aquaporins move water and other small molecules dissolved in it, including arsenic, and therefore they play a key role in maintaining the cellular homeostasis and the appropriate cell environment. AQPs in mammals consists of thirteen unique members marked from AQP0 to AQP12. In many types of tumors, correlations between AQP expression and tumor advancement and prognosis have been demonstrated, what make AQPs a real therapeutic goal and biomarker of cancer prognosis. In breast cancer, there is a significant expression of AQP1, AQP3 and AQP5, with AQP1 inducing the development of angiogenesis, which is a very dangerous metastatic factor. On the other hand, overexpression of AQP3 and AQP5 has been shown to

regulate the migration of breast cancer cells, which can be used as prognostic markers. In other types of cancers such as gastrointestinal neoplasms, neurological and lung cancers, an increased expression of the AQP family was also noted. A good demonstration of the role in AQP carcinogenesis is the fact that in normal epithelial tissue, AQP expression is negligible, but epithelial tumors are characterized by an increased expression of AQP1, AQP4, AQP6, AQP8 and AQP9. Studies show that AQP1, AQP2, AQP3, AQP4, AQP5, AQP8 and AQP9 are closely related to the regulation of the cancer cell volumes, angiogenesis, cell dissociation, migration, invasion and metastasis (DAJANI *et al*., 2018; MAGOULIOTIS *et al*., 2019).

Reactive oxygen species play a significant role in the destruction of proteins, lipids and DNA structure and thus promotes carcinogenesis. In addition to destruction, they also participate in a cell signaling pathways, which can significantly support the occurrence of a various types of cancer. AQPs play an important role in regulating the permeability of free oxygen radicals, what can be closely related to the fact that arsenic, which is also transported through AQPs, has a strong effect on the formation of reactive oxygen species. The combination of these two factors may be closely associated with the cancerogenesis. It has been shown that the regulation of a free radicals by the AQP3 plays an important role as the $H_2O_2$ controls the epidermal growth factor receptor (EGF) and influences the progression of the breast cancer. It has also been shown that the *AQP3* geneknockout is associated with a less viable breast cancer cells (DAJANI *et al*., 2018; MAGOULIOTIS *et al*., 2019).

The results of many studies have shown that arsenic can be taken through the aquaporin channels and then transported to the cell interior. Aquaporins are found mainly in the kidneys, testis, liver, spleen and the brain tissue (LIU *et al*., 2006; HACHEZ and CHAUMONT, 2010). It should be pointed out that despite the fact, that in some of the tissues there are no aquaporins, the transport of arsenic into the cells still occurs. It seems that in these cases glucose transporters (GLUT) are mainly responsible for this process. A study by LIU *et al*. (2006) has shown that GLUT1 is able to capture and transport certain forms of arsenic, thereby contributing to unwanted changes in the cell (LIU *et al*., 2006). ROSEN and LIU, 2009 have also suggest that GLUT4 may contribute to the transport of arsenic in humans because they have shown heterologous activity in yeast and frog oocytes (ROSEN and LIU, 2009).

Also mutations in the GLUT glucose transporter genes (*SLC2A*) can lead to a serious genetic diseases and also expose the patient to the risk of metabolic syndrome, obesity or diabetes. It is also known that a certain types of tumors, due to increased glycolytic needs, show an increased expression of genes encoding individual transporters (PIZZI *et al*. 2009; BARRON *et al*., 2012; MUECKLER *et al*., 2014).

The glucose transporters are found in the cells such as erythrocytes, endothelial cells of the blood-brain and blood-nerve barrier and also in the liver cells. An increased expression of GLUT family proteins is closely related to the cancer cells that have an increased need for glucose metabolism, which allows them to increase the expression of *SLC2A*. The increase in *SLC2A1* (GLUT1) protein expression has also been demonstrated in some types of cancers. Studies show that *SLC2A1* overexpression is a negative prognostic factor in the bladder cancer, lung tumors, gastric cancer, breast cancer, cervical cancer, ovarian cancer and others, as shown by the correlation between *SLC2A1* (GLUT1) overexpression and the incidence and survival of these tumors (PIZZI *et al*. 2009; BARRON *et al*., 2012; MUECKLER *et al*., 2014).

Lymphoma cells exhibit a reduced expression of GLUT1, which may indicate an increased expression of another specific tumor transporter. Melanocytic tumors such as melanoma and lymphomas show an increased expression of the *SLC2A3* (GLUT3) transporter. Prostate adenomas also show a specific pattern of *SLC2A2* (GLUT2) transporter expression characteristic of this type of cancer. In the stomach cells, however, *SLC2A2* (GLUT2) and *SLC2A4* (GLUT4) were overexpressed, whose increased expression was also detected in the breast cancer as well (LIS *et al*., 2009; BARRON *et al*., 2012; MUECKLER *et al*., 2014). It is also interesting that immunoassay analysis have demonstrated the presence of GLUT5 in the breast cancer tissue, while its absence was shown in a normal breast tissue. The above-mentioned studies clearly show that the level of expression of individual GLUT carriers may be considered as a molecular markers and also targets for modern therapies (MUECKLER *et al*., 2014; ZHOU *et al*., 2017).

It is known that the cancer cells show a greater uptake of glucose, which is associated with their increased metabolism. Glucose transport is closely related to the GLUT family protein transporters. In the human cells, up to 14 isoforms of these proteins have been discovered, of which GLUT 1, 3, 4 and 12 have been extensively examined for its presence in the tumors. Studies have shown an increased expression at both mRNA and protein levels in GLUT 1, 3, 4 and 12 proteins in cancer cells (BARRON *et al*., 2012). An abnormal expression pattern of these proteins was also shown in comparison with the healthy cells. Such a turn of events shows that the genes encoding these proteins can serve as an attractive target for a prognosis in lung, breast and prostate cancer (BARRON *et al*., 2012; ZHOU *et al*., 2017).

Page *et al*., 2005 analysed the genotype frequency for SNP T>A (rs710218) mutations within the *SLC2A1* (GLUT1) gene promoter at the position -2841T in the case of renal cell carcinoma. The results showed a significantly smaller number of homozygous AA genotypes among patients and an increase in the heterozygous AT genotypes compared to the controls, suggesting a protective effect of the AA genotype in this type of cancer (PAGE *et al*., 2005). In turn, AMANN *et al*. (2011) did not show any effect of SNP T>A (rs710218) mutations on hepatocellular carcinoma, but the authors have noticed its effect on an increased *SLC2A1* expression and cancer progression in this type of cancer (AMANN *et al*., 2011).

The relationship between the SNP T>A mutation (rs710218) and the lung cancer was also tested. FENG *et al*. (2017) showed that there is a higher risk of lung cancer for the TT and AT genotype compared to the AA genotype. An association with the T allele and an increased *SLC2A1* (GLUT1) expression has also been demonstrated (FENG *et al*., 2017).

## DISCUSSION

Arsenic is a trace element commonly found in nature that causes water and finally food pollution, which is strongly associated with the industrialized areas. Consumption of arsenic is associated with the occurrence of many complications and ailments, of which cancer seems to be the most dangerous.

From survey reviews by LINBERG *et al*. (2007), ENGSTROM *et al*. (2007), TSENG *et al*. (2009), TORRES-SANCHEZ *et al*. (2016), LUO *et al*. (2018), STOJSAVLJEVIĆ *et al*. (2019), SOZA-RIED *et al*. (2019) results that age, gender and genetic background have a great impact on the detoxification and the occurrence of disease symptoms related to arsenic consumption.

The studies by TSENG (2009) and LUO *et al*. (2018) shows that while water with a high content of arsenic is consumed in many countries and regions, only some of the exposed people develop skin lesions or other diseases caused by arsenic. The development of both bladder cancer and the lung cancer differ among various ethnic groups. This is probably due to the high genetic diversity that has developed over the years among individual populations exposed to lower or higher doses of arsenic.

Research conducted by SMITH *et al*. (2000) showed that some populations display better tolerance to high doses of arsenic in food without showing major disease symptoms. This is probably related to the appropriate genetic profile shaped by a natural selection associated with the exposure to high doses of arsenic of subsequent generations over thousands of years.

The results of the other studies by ROSEN (2002), GOURBAL *et al*. (2004), ISHIBASHI *et al*. (2009), LIS *et al*. (2009), SHINKAI *et al*. (2009), LIU (2010), have demonstrated that proteins from the aquaglyceroporin family, namely AQP3, AQP7, AQP9 and AQP10 play an important role in the transport and detoxification of arsenic. As reviewed by WALTON *et al*. (2004), LIU *et al*. (2006), ROSEN and LIU (2009), LIS *et al*. (2009), KULSHRESTHA *et al*. (2014) also the proteins belonging to the glucose transporter family such as GLUT1 and GLUT4, are considered to play the same role as the AQPs, as they show the possibility to transport a certain forms of arsenic.

Studies on both GLUT and AQP family proteins indicate higher expression of their genes in many types of cancer. DAJANI *et al*. (2018) and MAGOULIOTIS *et al*. (2019) demonstrated that both *AQP3* and *AQP10* overexpression occurs in the breast cancer, *AQP3* in the lung cancer, *AQP9* in the epithelial tumours, *AQP3* and *AQP9* in the gastrointestinal cancer and hepatic cancer, *AQP7* displays in thyroid cancer. For the GLUT glucose transporters, a reviews by PIZZI *et al*. (2009), BARRON *et al*. (2012), MUECKLER *et al*. (2014) indicate that overexpression of *SLC2A1* (GLUT1) in the bladder cancer, lung tumours, gastric cancer, breast cancer, cervical cancer, ovarian cancer and others. PAGE *et al*. (2005), AMANN *et al*. (2011) and FENG *et al*. (2017) over the years, have conducted a number of studies on the SNP T>A (rs710218) mutation in the *SLC2A1* (GLUT1) gene to determine sensitive genotypes. Their results showed that a mutation in the promoter region of this gene affects the occurrence of the tumours and an increased expression of *SLC2A1*.

Taking above it may be hypothesised that both AQP and GLUT proteins can have a significant impact on the occurrence of cancers related to the toxic effects of arsenic on the body. Their participation in the transport and detoxification of arsenic and the relationship with the occurrence in many types of cancers means that their genes can be considered as a potential prognostic biomarkers and motives for therapies targeted in the fight against cancers caused by the arsenic pollution.

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# UTICAJ VISOKIH I NISKIH NIVOA ARSENA U LJUDSKOM TELU NA PROCES KARCINOGENEZE ZASNOVAN NA FUNKCIJI, EKSPRESIJI I GENETIČKOM POLIMORFIZMU GENA KOJI KODIRAJU DVA TRANSPORTERA ARSENA – VODENIH KANALA (*AQP*) I TRANSPORTERA GLUKOZE (*SLC2A*)

Jakub KUBIŚ[1*], Marek KMIEĆ[2], Jan BIŃKOWSKI[3], Marta SRÓŻYŃSKA[4]

[1]Zapadnopomorski Univerzitet tehnologije, Departman za polimere i biomaterijale, Ščećin, Poljska.
[2]Pomorski Medicinski Univerzitet, Departman za genetiku i patologiju, Ščećin, Poljska.
[3]Zapadnopomorski Univerzitet tehnologije, Fakultet za biotehnologiju i stočarstvo, Departman za genetiku i oplemenjivanje životinja, Ščećin, Poljska.
[4]Univerzitet za medicinske nauke, Departman za dermatologiju, Poznanj, Poljska.

Izvod

Arsen je metal koji se obično nalazi u zemlji, vodi i biljkama i na taj način lako ulazi u prehrambeni lanac.Konzumiranjem hrane sa visokim nivoom arsena, ona ulazi u ćelije preko vodenih kanala (AQP) i transportera glukoze (GLUT) u ćelije, gde može da izvrši različite metaboličke promene, uključujući genotoksičnost, što konačno može da dovede do karcinogeneze. Međutim, postoje ljudske populacije koje pokazuju smanjene štetne efekte arsena na organizam. To se uglavnom dešava zbog prirodne selekcije uzrokovane dugotrajnim izlaganjem okoline velikim dozama arsena. Akvaporini *AQP3, AQP7, AQP9, AQP10* i transporteri glukoze *SLC2A1* (GLUT1), *SLC2A4* (GLUT4) smatraju se genima kandidatima povezanim sa rezistencijom na arsen u procesu karcinogeneze, jer su usko povezani sa pojavom različitih vrsta karcinoma, dok su njihovi proizvodi povezani sa transportom arsena.

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