Critical Reviews in Oncology / Hematology 139 (2019) 128–133

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Oncogenic role of arsenic exposure in lung cancer: A forgotten risk factor

Cristian Soza-Ried[b,f], Eva Bustamante[a,*], Christian Caglevic[c,a], Christian Rolfo[d], Rafael Sirera[e], Hugo Marsiglia[a]

[a] Instituto Oncológico Fundación Arturo López, Santiago, Chile
[b] Escuela de Bioquímica, Facultad de Ciencia, Universidad San Sebastián, Santiago, Chile
[c] Departamento Oncología Médica, Clínica Alemana, Santiago, Chile
[d] Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, USA
[e] Departamento de Biotecnología, Universitat Politenica de Valencia, España
[f] Fundación Oncoloop, Santiago, Chile

ABSTRACT

Several drinkable water sources worldwide have been highly contaminated with arsenic, which means that an estimated 160 million people have been exposed to this chemical agent. If we analyse exposure by region, we will find a high correlation between arsenic contamination and the incidence of lung cancer (among other malignancies). In order to determine what the risks of these exposures are, we need to understand how this chemical is processed in our body and how it is linked to cancer. In this article we reviewed how biotransformation of ingested arsenic may lead to cancer by modulating the activation of several essential signalling pathways such as EGFR, PI3K/AKT, RTK/Ras/PI3K, JNK/STAT3 and Nrf2-KEAP1; by producing epigenetics modifications and by disrupting normal expression of miRNAs. In order to design effective health policies, educational strategies, decontaminations plans and effective medical treatments are necessary to understand the impact of arsenic pollution and the relevance of the environment in our health.

1. Introduction

The principal risk factor for lung cancer is tobacco consumption. This habit promotes genetics and epigenetics aberrations leading to tumour progression and metastasis (Sun et al., 2007). Yet never smokers - which represent approximately 25% of the total numbers of patients - are also at risk. One of the main extra contributing factors for this is environmental pollution (Hecht, 1999). Nonetheless, it appears, that tumourigenesis between smokers and non-smokers is driven by different genetic pathways (Sun et al., 2007). Hence, high-income countries have designed strategies and policies to reduce tobacco consumption and to address pollution and contaminant exposure (World Health Organization, 2015).

The effect of environment on different pathologies has been under exhaustive examination over the past years, and as a result, it has become clear that chronic exposure to chemicals lead to genetic and epigenetic alterations, affecting important signalling pathways and even may change the bacterial community composition in the lung, contributing to cancer development (Hosgood et al., 2014; Hubaux et al., 2012). Arsenic-exposure, for example, produces dramatic cellular changes that may explain the rise of lung cancer cases in certain geographical regions.

If we want to diminish the actual cancer burden we need to understand how populated regions interact with their environments. Thus, we will be able to control and reduce arsenic exposure, contributing to health policies and preventive plans in the future. The challenge, however, is also to define precisely how different signalling pathways respond to arsenic exposure and what other molecular factors contribute to the cancer process. In this article, we focus on the relationship arsenic-lung cancer and the molecular mechanism underlying this relationship

2. Arsenic: an important risk factor

The correlation between lung cancer incidence and geographic and temporal distribution of smokers is remarkable. Over the past years, several studies have demonstrated this strong association (IARC Working Group, 2012), however, learning this lesson took us several years, partly due to the time that it takes for an active smoker to develop cancer. Later the epidemiology evidence gave us insight into another important issue: non-smokers have a 20–25% risk of developing lung cancer (IARC Working Group, 2012).

Since 1950 it has become clear that lung cancer risk is higher among workers exposed to several industrial by-products (occupational exposures). Chemicals such as asbestos (1950) and later arsenic (1960) have been considered as occupational carcinogens (Pass et al., 2014).

* Corresponding author.
E-mail address: bustamantee@falp.org (E. Bustamante).

https://doi.org/10.1016/j.critrevonc.2019.01.012
Received 25 June 2018; Received in revised form 11 January 2019; Accepted 17 January 2019

Workers employed in hot smelting or mining activities were at risk and also cities that were supplied with drinkable water highly contaminated with arsenic. Mining minerals with high concentrations of arsenic such as copper, gold and mercury (used for mineral precipitation) (IARC, 2004) contaminate the air, the soil and the water of surrounding areas, affecting nearby cities and agricultural fields (Ferreccio and Sancha, 2006; Queirolo et al., 2000). However, volcanic zones, hot springs and geysers also contribute to arsenic pollution (Ferreccio and Sancha, 2006; Queirolo et al., 2000; Martinez et al., 2012; Vahter, 2008). In several countries, arsenic levels in soils and drinking water have exceeded the maximum levels allowed (10 μg/L), becoming the main arsenic-related risk factor for different diseases (Ferreccio and Sancha, 2006). A remarkable example is the Bangladesh mass poisoning, where it was estimated that 77 million people were chronically exposed to ground-waters with high levels of arsenic (well above the 10 μg/L permitted levels according to the World Health Organisation guidelines) through drinking water (Martinez et al., 2012; Argos et al., 2010).

In South-East Asia, several deltas environment have accumulated sediments with arsenic concentration contaminating soils and rivers. Arsenic exposure cases in China, Taiwan, Viet-Nam and Thailand have been well documented (Vahter, 2008). In Viet-Nam the Red River has been a major contributor to arsenic pollution, affecting rural and urban districts. The insufficient treatment of the drinkable water in these areas constitutes a permanent risk for the population.

In India, dug wells, hand pumps and spring waters of different areas (villages of the Punjab or Chandigarh) are the sources of arsenic contamination. For example, arsenic levels in samples obtained from a hand pump were up to 55 times higher than the permitted level. Likewise, West-Bengal has serious problems with groundwater contamination, which is used as a source of drinkable water (Vahter, 2008). Several countries of Central and South America, such as Mexico, Argentina and Chile also show regions contaminated with arsenic. In these countries, copper, gold and silver mining contaminate soils and water sources. In addition, particular geochemical characteristics related to the “Ring of fire” in the Pacific activate volcanoes, geysers and thermal waters contributing to arsenic pollution, this is the case of Chile. In the north of this country lies the Atacama desert and the few water sources available for the northern cities were exposed for more than 10 years to high levels of arsenic (Steinmaus et al., 2014). Most of the people lived in cities distributed between the Andes mountains and the Pacific Ocean coast. The Loa river was the water source of drinking water and for their agriculture activities – mainly crops and potatoes. Saltpetre mining was the first big mining business. Later the saltpetre mining decreased and was replaced by other minerals mining activities such as gold and copper. As consequence, the need for water increased enormously. To face this problem in 1958 was built the Toconce adduction system. Unfortunately, this solution only brought water with high levels of As (860 mg/L in average) to the population, it was estimated that 130,000 inhabitant consumed this water between 1958 and 1970 (Ferreccio et al., 2000). To improve the situation the government built in 1970 the first As treatment plant called Salar del Carmen. Later other As treatment plant followed, Calama 1978 and Antofagasta 1989, which reduced the arsenic levels to about 100 μg/L (Marshall et al., 2007; Roh et al., 2018). Currently levels of As in Antofagasta are less than 10 μg/L, however, cancers such as lung and bladder are higher in Antofagasta than in unexposed regions such as Valparaiso (Marshall et al., 2007). Likewise, Roh and colleges found that lung, bladder and laryngeal cancer standardized mortality ratios (SMR) are higher compared with the rest of Chile; even when these ratios were analysed 30–40 years after arsenic exposure cessation. Roh et al, study suggests a strong relationship between age and exposure, being the highest SMR when the exposition to arsenic was at birth. For example, bladder cancer showed a SMR of 16.0 (95% CI: 10.3–23.8), laryngeal cancer a SMR of 6.8 (95% CI: 2.2–15.8) and lung cancer a SMR of 3.8 (95% CI: 2,9–4,9) (Roh et al., 2018). The long-time from exposure to developing cancer is an obstacle for prospective studies. Therefore, most of the data that relate to arsenic exposure to cancer correspond to retrospective studies (Argos et al., 2010). Argos et al., prospective cohort study estimated hazard ratios of mortality (all-cause mortality) at different doses of arsenic exposure in a Bangladeshi population. After adjusting for potential confounders, this study found that mortality rates were associated with chronic arsenic exposure through drinking water (Argos et al., 2010). Recently Rahman et al., analysed the association between chronic arsenic exposure through drinkable water and risk of young-adult mortality in Bangladesh. This prospective cohort study also found that regardless of the gender, arsenic exposure is related to an increase in mortality among young adults (Rahman et al., 2018). On the other hand, a prospective study of a Danish cohort revealed that exposure to low doses of arsenic in drinking water might be associated with a protective effect against skin cancer (Baastrup et al., 2008).

Arsenic contamination cases in other regions in the world such as Japan (southern region of the Fukuoka Prefecture), Spain (Madrid), Finland, Romania, Ghana, Egypt, Iran and Australia have been also reported (Martinez et al., 2012).

If we consider that approximately 2% of the human population lives in regions highly contaminated with arsenic, understanding precisely how arsenic factor disturb human health is essential. Especially considering that early-life exposure may have a great impact on long-term mortality.

3. Arsenic derivatives generated during inorganic Arsenic cell processing leads to genomic aberrations

Health problems related to inorganic arsenic exposure emerge with a delay of up to 40 years after exposure has ceased (Steinmaus et al., 2013). In fact, several studies suggest that arsenic exposure at an early age or even during gestation produce lung and bladder cancer in adulthood (Steinmaus et al., 2014; Dauphine et al., 2011). But, how does arsenic lead to cancer? The background of this problem has been reported (Hubaux et al., 2012, 2013; Bustaffa et al., 2014), and will be briefly presented here. Arsenic can induce tumour formation by altering genomic integrity, disrupting the DNA repair mechanisms and affecting the expression of several important molecular pathway genes.

When Arsenic is absorbed in the gastrointestinal tract, it is reduced from arsenate (As^{V}) to arsenite (As^{III}) by the action of the antioxidant glutathione. In the cells, As^{V} interferes with phosphorylation reactions and As^{III} reacts with proteins sulfhydryl groups, interrupting different molecular pathways (Hubaux et al., 2012). The oxidative methylation of arsenite drove by S-Adenosyl methionine- (SAM)-dependent arsenic methyltransferase (AS3MT) produces several methylated species: monomethylarsonous acid (MMA^{III}), methylarsonate (MMA^{V}) and dimethylarsenate (DMAV) (Hubaux et al., 2012), a process already present in lower vertebrates and so evolutionarily conserved (Hamdi et al., 2012). MMA^{III} by-product has the ability to inhibit the mitochondrial complexes I and III by producing electron leaks from the electron transport chain. Through this process reactive oxygen (which can also be generated by cycling forms of arsenic), reactive nitrogen (RNS) and several free radical species are produced. These elements not only affect genomic integrity and produce DNA mutations but also disrupt the expression of genes associated with both nucleotide excision mechanism (NER) and base-exchange repair systems (Hubaux et al., 2013) (Fig. 1). Likewise, the expression of Xerodermapigmentosum complementation group and PARP1 proteins are down-regulated, contributing to the survival of cells with genomic aberrations (Qin et al., 2012). Examples of the arsenic-effect over genomic stability are deletions at chromosomal locus 1q21 and DNA amplifications at 19q13.31 and 19q13.33 loci. These mutations are usually observed in lung tumours from never smokers that have been chronically exposed to arsenic (Hubaux et al., 2012).

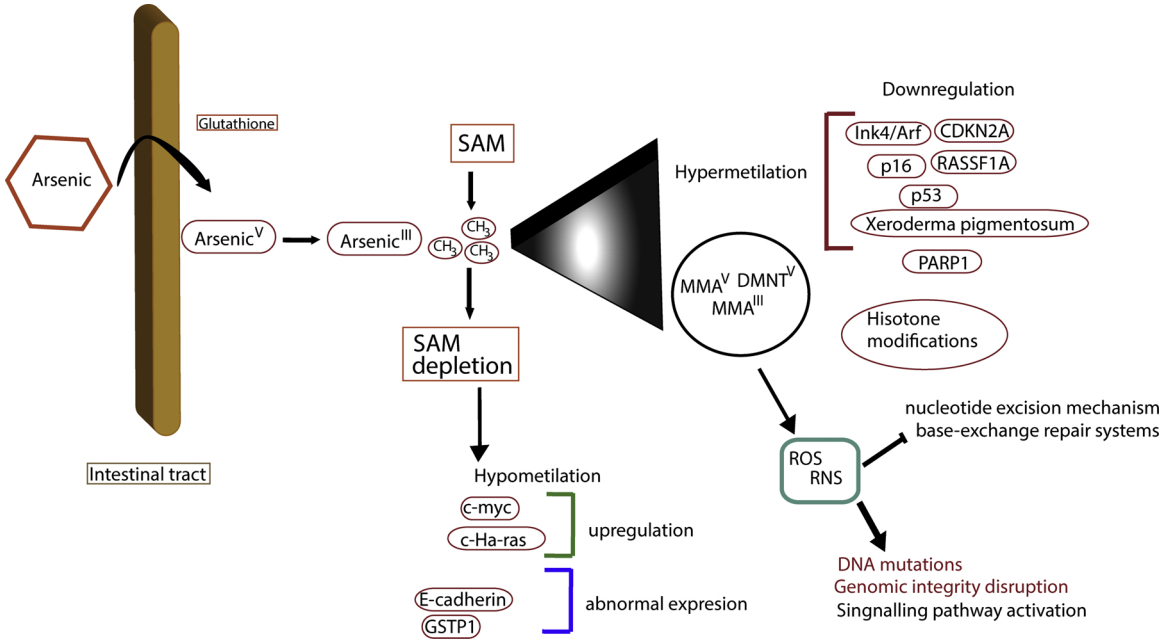

Fig. 1. Arsenic is absorbed in the intestinal tract and transformed into several arsenic derivatives. Arsenic is reduced from arsenate (As^{V}) to arsenite (As^{III}) by the action of the antioxidant glutathione. In the cells SAM is use to methylate As^{III} and as a consequence MNA^{V}, MNA^{III} and $DMNT^{V}$ is produced. These by-products induce the production of ROS and RNS, leading to DNA genomic mutations and disrupting cell signalling pathways. Along this process, the expression of several genes (including tumour suppressor genes) is downregulated due to the hypermethylation of their promoter regions. SAM depletion, on the other hand, leads to hypomethilation of several proto-oncogenes.

4. Arsenic induce epigenetic modifications

Gene expression can be modulated by epigenetics modifications at DNA and protein levels leading to chromatin remodelling. In general, methylation induces repression of gene expression and acetylation has the opposite effect. DNA is methylated by the action of DNA-methyltransferases (DNMT), which uses SAM as a methyl donor. However, methylation of As^{III} also depends on SAM generating competition between As^{III}, and DNMT for methyl groups. As a result, this competition ends by changing the chromatin methylation pattern. In fact, different in vitro and in vivo lung cancer studies including people exposed to arsenic, showed hypermethylation of several tumour suppressor genes such as p53, CDKN2A, Ink4/Arf, p16 and RASSF1A (Hubaux et al., 2012; Bustaffa et al., 2014; Reichard and Puga, 2010). Interestingly, hypomethylation of DNA regions has also been observed, altering, for example, the methylation status of promoter CpG islands. As a consequence, protooncogenes such as c-myc and c-Ha-ras are up-regulated and the expression of other important genes such as RASSF1, E-cadherin and GSTP1 becomes abnormal (Bustaffa et al., 2014; Reichard and Puga, 2010) (Fig. 1).

Epigenetics changes by histone tail modifications are reflected by a reduction of H4K16 acetylation levels and changes in the methylation patterns of H3K4, H3K9, and H3K27– in malignant and non-malignant lung cell lines (Hubaux et al., 2012). Likewise, aberrant epigenetic modifications of histone proteins induce ectopic expression of WNT family genes, contributing to the malignant transformation behaviour (Hubaux et al., 2012). In short, these observations suggest two different scenarios after arsenic exposure: hypermethylation at a gene-specific level and hypomethylation at the genome-wide level (Reichard and Puga, 2010; Rozek et al., 2014).

5. Arsenic disrupts the normal function of several signalling pathways

Several important cellular pathways are deregulated by arsenic biotransformation (Fig. 2). For instance, acute exposure to As^{III} activates PI3K/AKT signalling pathway by inducing AKT through JNK/STAT3 signalling (Jensen et al., 2009). Under normal circumstances, PI3K/AKT signalling pathway is activated when an extracellular growth factor binds the receptor with tyrosine kinase activity (RTKs), triggering the dimerization of the receptor. Once the RTK is activated, PI3K is recruited and phosphorylated. This, in turn, drives the successive recruitment and activation of AKT and several downstream target proteins, leading to cell proliferation, metabolism, growth and survival (Templeton et al., 2014). Experiments using human bronchial epithelial cells (HBEC) showed that AKT activation by As^{III} induces the expression of vascular endothelial growth factor (VEGF), which is crucial for angiogenesis and tumour growth (Hubaux et al., 2012; Nyati et al., 2006). Moreover, As^{III} can suppress the action of PTEN, which is a phosphatase that inhibits and thus controls PI3K/AKT signalling. These observations indicate that acute exposure to As^{III} overactivates the PI3K/AKT signalling pathway inducing cell proliferation, anchorage-independent growth and survival (Hubaux et al., 2012). Evidence of the relationship between arsenic-PI3K/AKT signalling is compelling, but the mechanism is not yet fully understood.

The signal governed by the epidermal growth factor receptor (EGFR) can also be modulated by arsenic exposure. EGFR is overactivated in 50% of lung cancer, driving cell proliferation, differentiation, survival, invasion, angiogenesis and metastasis (Hecht, 1999; Nyati et al., 2006). Arsenic has the ability to disrupt the EGFR autoinhibitory feedback loop permanently activating the pathway even in absence of ligand. The constitutive activation occurs due to the ability of arsenic to stimulate c-Src, which in turn, interacts with EGFR producing its activation by two phosphorylation events at two tyrosine: Tyr85 and Tyr1101. Using lung epithelial cells exposed to arsenic, Hubaux et al. (2012) observed that the reactive oxygen produced activates EGFR and other pathway components such as Ras, Raf and MEK (Hubaux et al., 2012). This scenario is further complicated by the crosstalk between different pathways since malignant cells receive parallel signals to survive and proliferate.

So far, the evidence suggests that the molecular mechanisms driving lung cancer in smokers are related, but not identical, to the mechanism

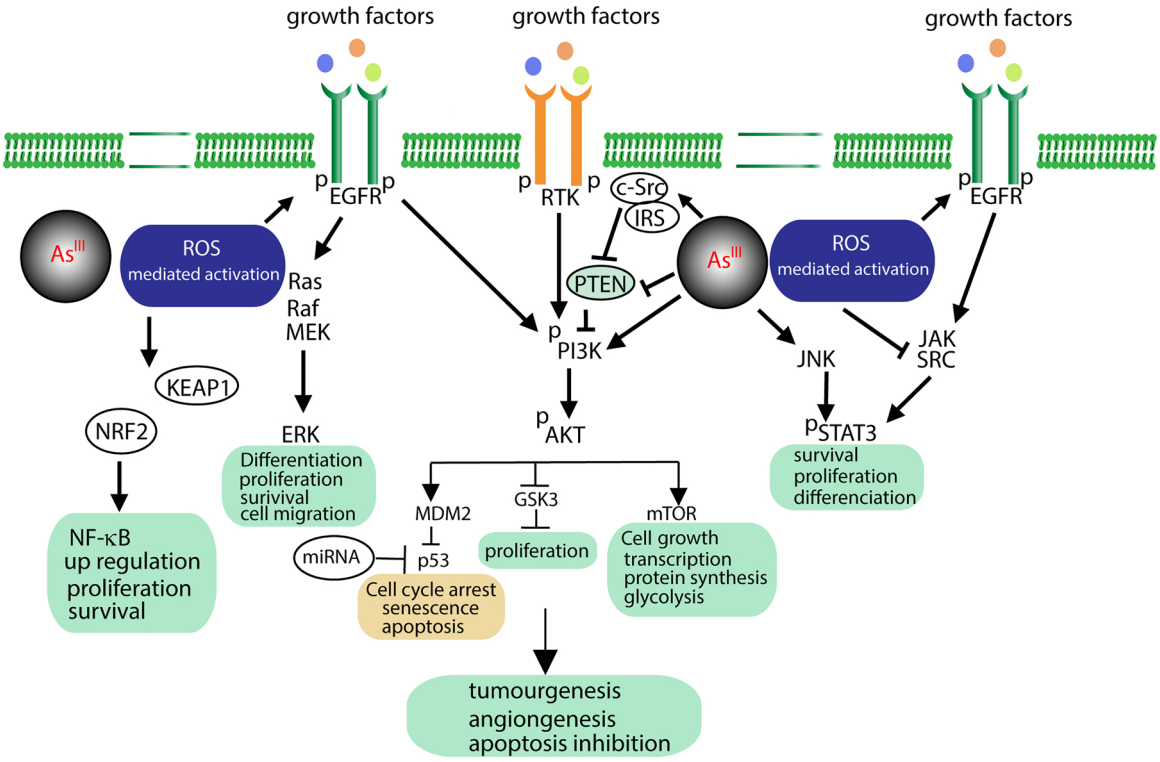

Fig. 2. Chronic arsenic exposure disrupts several signalling pathways leading to tumourgenesis. As^{V} is reduced to As^{III}, which is subject to oxidative methylation. As byproducts of this process reactive oxygen species (ROS), RNS and others free radical species are produced. Thus, increased concentration of As^{III} disrupts the EGFG, RTK/AKT and Nrf2-KEAP1 signalling pathways. The constitutive activation of the EGFR leads to the activation of Ras/Raf/MEK/ERK signalling inducing cell proliferation, migration and survival. Likewise, EFGR signalling pathway activates PI3K, which is reinforced by the RTK/AKT pathway and the block of PTEN, both by the action As^{III}. The activation of these pathway leads to inhibition of p53, and different process that contribute to tumourgenesis, such as cell proliferation, inhibition of apoptosis, angiogenesis, protein synthesis and gene transcription. miRNA such as miR200b and up regulation of MDM2 block the expression of the tumour suppressor p53. Others miRNA are also involved in the constitutive activation of AKT and its target proteins. Exposure to As^{III} induces the expression of STAT3 through JNK inducing cell survival, proliferation and differentiation. The permanent activation of the Nrf2-KEAP1 signalling pathway induces the up regulation of NF-κB contributing further to cell proliferation and survival. All these events contribute to events that facilitates tumour formation, survival and angiogenesis. Phosphorylation is indicated as "p".

accounting for lung cancer in non-smokers (Hecht, 1999). Smokers' lung cancer usually presents mutation in KRAS gene. As consequence, ligands of EGFR such as transforming growth factor-α (TGF-α) are release and Ras activates the PI3K–AKT signalling pathway. Conversely, EGFR mutations in never-smokers triggers the activation of the pathway. In spite of the activation mechanism - whether the activation occurs by KRAS or EGFR mutation - the final consequences are similar. Importantly, genes in the RTK/Ras/PI3K signalling pathways are not exclusively involved in lung cancer but also to many others, and genes such as BRAF, ERBB2 (HER2), have also the ability to activate these pathways (Hecht, 1999). Another way to trigger the release EGFR ligands is by oestrogens. Indeed, lung cancer tumours present oestrogen receptors and these tumours can growth and proliferate upon oestrogen stimulation (Hecht, 1999).

A further signalling pathway that is activated by arsenic derivative reactive oxygen is the Nrf2-KEAP1 pathway. When the pathway is not required, KEAP1 (Kelch ECH associating protein 1) binds to NRF2 (nuclear factor erythroid 2-related factor 2) and Cul3-based E3 ligase complex poly-ubiquitylates NRF2 inducing its degradation by the proteasome. When chemical, oxidative or electrophilic stress occurs, a protective response mechanism starts. This cytoprotective response begins with the dissociation of NRF2 from the KEAP1-CUL3 -based E3 ligase complex. Thus, the transcription factor NRF2 migrate to the nucleus inducing the expression of genes involved in the stress-related response. This protective response, however, fails when arsenic exposure becomes chronic producing a constitutive activation of the pathway (Hubaux et al., 2012; Kansanen et al., 2013). Likewise, mutations in KEAP1 or in proteins (such as p21 and p62) that affect the association of NRF2-KEAP1 lead to the same problem (Kansanen et al., 2013). In non-small cell lung cancer, overexpression of this pathway upregulates NF-κB, inducing the expression of genes involved in cell proliferation and survival (Kansanen et al., 2013; Hubaux et al., 2012). Furthermore, constitutive activation of NRF2-KEAP1 pathway results in resistance to chemotherapy and radiotherapy, worsening disease prognosis (Kansanen et al., 2013).

6. Arsenic deregulate the expression of microRNA

Experiments in human bronchial epithelial cells showed that chronic arsenic exposure downregulates the expression of miR200b by promoter methylation. This downregulation knocked down p53 and induced epithelial-to-mesenchymal transition (EMT) (Wang et al., 2011). Conversely, As^{III} exposure upregulates miR190 in a dose-dependant manner. This overexpression of miR190 represses the PH domain and Leucine-rich repeat Protein Phosphatases (PHLPP), an AKT negative regulator. Hence, the interaction of miR190 with the 3' UTR region of PHLPP leads to the constitutive activation of AKT and its target proteins (Beezhold et al., 2011). Another example is the deregulation of miR-9 and miR-181b in chick embryos. Cui et al, (2012) showed that 100 nM sodium arsenite injected into fertilised eggs caused a downregulation of miR-9 and miR-181b and an inducing angiogenesis and cell migration (Cui et al., 2012). Thus, it seems that miRNAs are key components of arsenic-induced tumour progression.

We are unveiling the different mechanisms by which arsenic exposure may lead to cancer. Future studies should focus on the synergic effect of different risk factors on molecular pathways and consider

possible alterations in epigenetic patterns.

7. How do we face the arsenic problem? A glance to future plans

To understand how an environmental factor such as arsenic exposure favours cancer development is complex. One of the main problems is that cancer develops several years after exposure (Steinmaus et al., 2013, 2014; Marshall et al., 2007; Roh et al., 2018; Rahman et al., 2018), which makes the design of strategies and health policies difficult. We have learnt this lesson by observing the relationship between tobacco consumption and the slow increase of new lung cancer cases – it takes 20 years for a new smoker to be at risk for lung cancer (Cairns, 1978).

As tobacco consumption, chemical exposure is framed in a more complex scenario, due to the combined action of unhealthy lifestyles such as lack of physical activity, alcohol abuse, unhealthy nutrition and obesity. The synergic action of these factors makes difficult the finding of a straightforward solution.

To face the arsenic contamination problem, we need to perform retrospective analyses of arsenic exposure in the most affected regions and predict their associated cancer risk. The studies must include the quality of the drinkable water at the sources. Likewise, it would be important to assess the contamination level of agriculture products in those regions and how this could affect their inhabitants. Thus, facilitating the design of decontamination plans in the near future.

The biotransformation of arsenic into arsenite and the subsequent oxidative methylation by SAM lead different by-products that are able to affect genomic integrity, producing mutations and the pattern of epigenetic modifications, which alter further the expression of genes. Moreover, different cell overactivated signalling pathways induce cell proliferation, growth, survival, motility and angiogenesis. The abnormal cell behaviour triggered by arsenic exposure may affect in different ways depending on the time and length of the exposure. The evidence suggests that during the embryonic development susceptibility to arsenic is higher (Hubaux et al., 2012). Considering that the adverse effect of the exposure is observed only later in childhood or adult life, it would be important to estimate how many pregnant women are at risk. Answering how arsenic affect population at different stages of development (foetus, infants, young and adults) would help to define the critical window time at which arsenic exposure is more dangerous for human health.

8. Concluding remarks

Molecular epidemiology has emerged as a fundamental tool to identify environmental risk factors and to understand why some populations are more susceptible than others to develop the disease. The study of the human genome will help to unveil polymorphisms associated with the susceptibility to develop lung cancer and to respond to certain risk factors. For example, Quiñones et al (2001) studies on Chilean population showed that combined mutations in two CYP1A1*2 A and GSTM1 alleles produce a higher estimated relative risk for lung cancer than mutations on any of these genes alone or than wild types (Quinones et al., 2001). Thus, the identification of these genetic marks may lead to the characterisation of environmental factors that could represent a greater risk for some population as well as to the definition of its effect on specific ethnicities.

In the last few years, it has become clear that patients show different genomic abnormalities and protein expression profiles, which influence their prognosis and response to treatments. Thus, in order to provide effective long- lasting treatments, we need to understand the molecular basis of the disease in each particular case and, according to this, analyse and predict the tumour behaviour, design a personalise treatment and new drugs. Future research should integrate the biological and social dimensions, understanding the profound implication related to arsenic exposure.

Acknowledgement

We would like to thank Nordiana Barruzzi, for revising and correct grammatically the article.

References

Argos, M., Kalra, T., Rathouz, P.J., Chen, Y., Pierce, B., Parvez, F., et al., 2010. Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study. Lancet 376 (9737), 252–258.

Baastrup, R., Sørensen, M., Balstrøm, T., Frederiksen, K., Larsen, C.L., Tjønneland, A., Overvad, K., Raaschou-Nielsen, O., 2008. Arsenic in drinking-water and risk for cancer in Denmark. Environ. Health Perspect. 116 (2), 231–237. https://doi.org/10.1289/ehp.10623.

Beezhold, K., Liu, J., Kan, H., Meighan, T., Castranova, V., Shi, X., et al., 2011. miR-190-mediated downregulation of PHLPP contributes to arsenic-induced Akt activation and carcinogenesis. Toxicol. Sci. 123 (2), 411–420.

Bustaffa, E., Stoccoro, A., Bianchi, F., Migliore, L., 2014. Genotoxic and epigenetic mechanisms in arsenic carcinogenicity. Arch. Toxicol. 88 (5), 1043–1067.

Cairns, John, 1978. Cancer and Society. W.H. Freeman and Company, San Francisco, pp. 56–60.

Cui, Y., Han, Z., Hu, Y., Song, G., Hao, C., Xia, H., et al., 2012. MicroRNA-181b and microRNA-9 mediate arsenic-induced angiogenesis via NRP1. J. Cell. Physiol. 227 (2), 772–783.

Dauphine, D.C., Ferreccio, C., Guntur, S., Yuan, Y., Hammond, S.K., Balmes, J., et al., 2011. Lung function in adults following in utero and childhood exposure to arsenic in drinking water: preliminary findings. Int. Arch. Occup. Environ. Health 84 (6), 591–600.

Ferreccio, C., Sancha, A.M., 2006. Arsenic exposure and its impact on health in Chile. J. Health Popul. Nutr. 24 (2), 164–175.

Ferreccio, C., González, C., Milosavjlevic, V., Marshall, G., Sancha, A.M., Smith, A.H., 2000. Lung cancer and arsenic concentrations in drinking water in Chile. Epidemiology 11 (November (6)), 673–679.

Hamdi, M., Yoshinaga, M., Packianathan, C., Qin, J., Hallauer, J., McDermott, J.R., et al., 2012. Identification of an S-adenosylmethionine (SAM) dependent arsenic methyltransferase in Danio rerio. Toxicol. Appl. Pharmacol. 262 (2), 185–193.

Hecht, S.S., 1999. Tobacco smoke carcinogens and lung cancer. J. Natl. Cancer Inst. 91 (14), 1194–1210.

Hosgood, H.D., Sapkota 3rd, A.R., Rothman, N., Rohan, T., Hu, W., Xu, J., et al., 2014. The potential role of lung microbiota in lung cancer attributed to household coal burning exposures. Environ. Mol. Mutagen. 55 (8), 643–651.

Hubaux, R., Becker-Santos, D.D., Enfield, K.S., Lam, S., Lam, W.L., Martinez, V.D., 2012. Arsenic, asbestos and radon: emerging players in lung tumorigenesis. Environ. Health 11, 89.

Hubaux, R., Becker-Santos, D.D., Enfield, K.S., Rowbotham, D., Lam, S., Lam, W.L., et al., 2013. Molecular features in arsenic-induced lung tumors. Mol. Cancer 12, 20.

IARC, 2004. IAERC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Some Drinking Water Disinfectants and Contaminants, Including Arsenic. pp. 41–156 84.

IARC Working Group, 2012. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans. Arsenic, Metals, Fibres, and Dusts. A Review of Human Carcinogens. 100 C: 1-888. Available online:. (Accessed on 19 December 2018). http://www.who.int/tobacco/global_report/2015/report/en/.

Jensen, T.J., Wozniak, R.J., Eblin, K.E., Wnek, S.M., Gandolfi, A.J., Futscher, B.W., 2009. Epigenetic mediated transcriptional activation of WNT5A participates in arsenical-associated malignant transformation. Toxicol. Appl. Pharmacol. 235 (1), 39–46.

Kansanen, E., Kuosmanen, S.M., Leinonen, H., Levonen, A.L., 2013. The Keap1-Nrf2 pathway: mechanisms of activation and dysregulation in cancer. Redox Biol. 1, 45–49.

Marshall, G., Ferreccio, C., Yuan, Y., Bates, M.N., Steinmaus, C., Selvin, S., Liaw, J., Smith, A.H., 2007. Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. J. Natl. Cancer Inst. 99 (12), 920–928 Epub 2007 Jun 12.

Martinez, V.D., Vucic, E.A., Lam, S., Lam, W.L., 2012. Arsenic and lung cancer in never-smokers: lessons from Chile. Am. J. Respir. Crit. Care Med. 185 (10), 1131–1132.

Nyati, M.K., Morgan, M.A., Feng, F.Y., Lawrence, T.S., 2006. Integration of EGFR inhibitors with radiochemotherapy. Nat. Rev. Cancer 6 (11), 876–885.

Pass, H.I., Ball, D., Scagliotti, G.V. (Eds.), 2014. The IASLC Multidisciplinary Approach to Thoracic Oncology. Classic Epidemiology of Lung Cancer. International Association For The Study Of Lung Cancer, Aurora CO, pp. 3–13.

Qin, X.J., Liu, W., Li, Y.N., Sun, X., Hai, C.X., Hudson, L.G., et al., 2012. Poly(ADP-ribose) polymerase-1 inhibition by arsenite promotes the survival of cells with unrepaired DNA lesions induced by UV exposure. Toxicol. Sci. 127 (1), 120–129.

Queirolo, F., Stegen, S., Restovic, M., Paz, M., Ostapczuk, P., Schwuger, M.J., et al., 2000. Total arsenic, lead, and cadmium levels in vegetables cultivated at the Andean villages of northern Chile. Sci. Total Environ. 255 (1-3), 75–84.

Quinones, L., Lucas, D., Godoy, J., Caceres, D., Berthou, F., Varela, N., et al., 2001. CYP1A1, CYP2E1 and GSTM1 genetic polymorphisms. The effect of single and combined genotypes on lung cancer susceptibility in Chilean people. Cancer Lett. 174 (1), 35–44.

Rahman, M., Sohel, N., Yunus, F.M., Alam, N., Nahar, Q., Streatfield, P.K., Yunus, M., 2018. Arsenic exposure and young adult's mortality risk: a 13-year follow-up study in Matlab, Bangladesh. Environ. Int. 123, 358–367. https://doi.org/10.1016/j.envint.2018.12.006.

Reichard, J.F., Puga, A., 2010. Effects of arsenic exposure on DNA methylation and epigenetic gene regulation. Epigenomics 2 (1), 87–104.
Roh, T., Steinmaus, C., Marshall, G., Ferreccio, C., Liaw, J., Smith, A.H., 2018. Age at exposure to arsenic in water and mortality 30–40 years after exposure cessation. Am. J. Epidemiol. 187 (11), 2297–2305. https://doi.org/10.1093/aje/kwy159.
Rozek, L.S., Dolinoy, D.C., Sartor, M.A., Omenn, G.S., 2014. Epigenetics: relevance and implications for public health. Annu. Rev. Public Health 35, 105–122.
Steinmaus, C.M., Ferreccio, C., Romo, J.A., Yuan, Y., Cortes, S., Marshall, G., et al., 2013. Drinking water arsenic in northern chile: high cancer risks 40 years after exposure cessation. Cancer Epidemiol. Biomarkers Prev. 22 (4), 623–630.
Steinmaus, C., Ferreccio, C., Acevedo, J., Yuan, Y., Liaw, J., Duran, V., et al., 2014. Increased lung and bladder cancer incidence in adults after in utero and early-life arsenic exposure. Cancer Epidemiol. Biomarkers Prev. 23 (8), 1529–1538.
Sun, S., Schiller, J.H., Gazdar, A.F., 2007. Lung cancer in never smokers–a different disease. Nat. Rev. Cancer 7 (10), 778–790.
Templeton, A.K., Miyamoto, S., Babu, A., Munshi, A., Ramesh, R., 2014. Cancer stem cells: progress and challenges in lung cancer. Stem Cell Investig. 1, 9. https://doi.org/10.3978/j.issn.2306-9759.2014.03.06.
Vahter, M., 2008. Health effects of early life exposure to arsenic. Basic Clin. Pharmacol. Toxicol. 102 (2), 204–211. https://doi.org/10.1111/j.1742-7843.2007.00168.x.
Wang, Z., Zhao, Y., Smith, E., Goodall, G.J., Drew, P.A., Brabletz, T., et al., 2011. Reversal and prevention of arsenic-induced human bronchial epithelial cell malignant transformation by microRNA-200b. Toxicol. Sci. 121 (1), 110–122.
World Health Organization, 2015. WHO Report on the Global Tobacco Epidemic. Raising taxes on tobacco. Available online:. (Accessed on 10 November 2016). http://www.who.int/tobacco/global_report/2015/report/en/.