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Arsenic metabolites in dermal cellular milieu: Molecular analysis

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Abstract

Contamination of drinking water by arsenic metabolites, which can occur naturally or due to human activities such as mining and industrialization, is an important public health issue in south Asia. More than 200 million are exposed to arsenic through drinking water. Chronic exposure to this metalloid has been associated with onset of many diseases, including cancer. There are 4 major molecular mechanisms through which arsenic disturbs cell health. They are (1) Arsenic contaminated water disturbs the gastric mucosal barrier thereby altering the cell stress hemostasis (2) It directly or indirectly interacts with energy synthesis pathway and induces cellular ROS generation (3) It inhibits the repair machinery (4) Finally, arsenic induces DNA abnormality. Understanding the molecular mechanisms of arsenic exposure and its subsequent health effects at cellular level will support efforts to reduce the worldwide health burden and encourage the development of strategies for managing arsenic-related diseases in the era of personalized medicine.
Keywords: Arsenic, Cell health, Dermal lesions, Signal transduction

1. INTRODUCTION

Arsenic (atomic number, 33; relative atomic mass, 74.92) has chemical and physical properties intermediate between a metal and a non- metal and is often referred to as a metalloid or semi-metal. It belongs to Group VA of the Periodic Table and can exist in four oxidation states: $^{-}3$, 0, $^{+}3$, and $^{+}5$. Arsenite, As^{III}, and arsenate, As^{V}, are the predominant oxidation states under respectively, reducing and oxygenated conditions. From a biological and toxicological perspective, there are three major groups of arsenic compounds: inorganic arsenic compounds, organic arsenic compounds, and arsine gas [1]. Arsenic and arsenic compounds have been produced and used commercially for centuries. Current and historical uses of arsenic include pharmaceuticals, wood preservatives, agricultural chemicals, and applications in the mining, metallurgical, glass-making, and semiconductor industries. Human exposure of arsenic occurs mainly by occupational route, dietary exposures and by inhalation. The epidemiological evidence on arsenic and cancer risk comes from two distinct lines of population studies, characterized by the medium of exposure to arsenic. One set of studies addresses the cancer risk associated with inhalation. These studies involve populations that are largely worker groups who inhaled air contaminated by arsenic and other agents, as a consequence of various industrial processes. The second set of studies was carried out in locations where people ingested arsenic in drinking-water at high concentrations over prolonged periods of time. During metabolism, pentavalent forms of arsenicals undergo repetitive reduction process whereas trivalent forms of arsenicals get oxidatively methylated. The reduction of pentavalent arsenicals is mediated by enzymes like glutathione- *S*-transferase, purine nucleoside phosphorylase, and certain mitochondrial enzymes. Due to its known toxicity there have been concerns about the metabolism of As_2O_3. The ADME profile suggests that As_2O_3 is readily converted to organic

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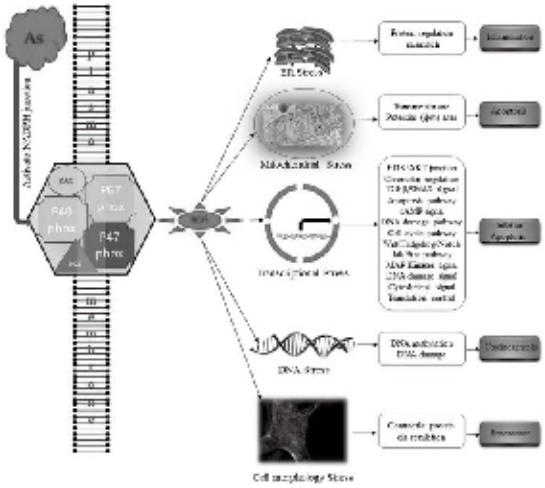
forms before it gets eliminated as seen in the study done on four APL patients by Wang et al. They studied the presence of arsenic in the urine samples of the patients that were injected with arsenite (As III) solution that contained 10 mg of As_2O_3 precursor.

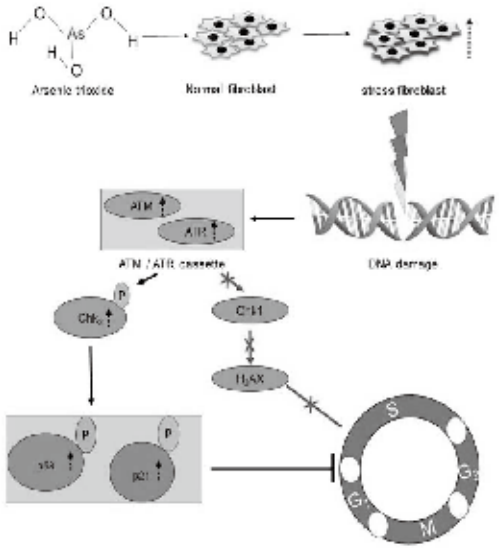
2. ARSENIC PATHOGENESIS IN CELL

Immediate cause of arsenic exposure to human body is the trigger of ROS in the cellular microenvironment and it leads to the activation of signal transduction in the cell. One such mechanism is explained in the following figure.



Arsenic entry to cell first reacts with lipid bilayer of the cell membrane. Lipid peroxidation occurs as cells are being stressed by reactive oxygen species leading to loss of membrane function and integrity thereby causing oxidative stress damage. Oxidative stress mediates many nocent effects of metals. The overproduction of reactive oxygen species (ROS) results in a significant increase in intracellular ROS, which leads to cellular damage, including lipid peroxidation, oxidative DNA modifications, protein oxidation and enzyme inactivation The imbalance between free radical generation and antioxidant defense systems resulting from oxidative stress is usually maintained in mammalian cells by key enzymes such as, superoxide dismutase (SOD), catalase (CAT), glutathione transferase (GST), glutathione peroxidase (GPx) and HO-1 that regulate intracellular ROS levels. Later stage of acute arsenic exposure leads to alterations in the cellular redox potential, cell shrinkage, loss of membrane lipid asymmetry and chromatin condensation. Finally, it is associated with the execution phase of apoptosis are characterized by activation of execution caspases and endonucleases, apoptotic body formation and cell fragmentation.

Another fate of cell disturbance due to arsenic is the overexpression of transcriptional factor signaling parameters like ATM/ATR pathways and is explained in the following figure.

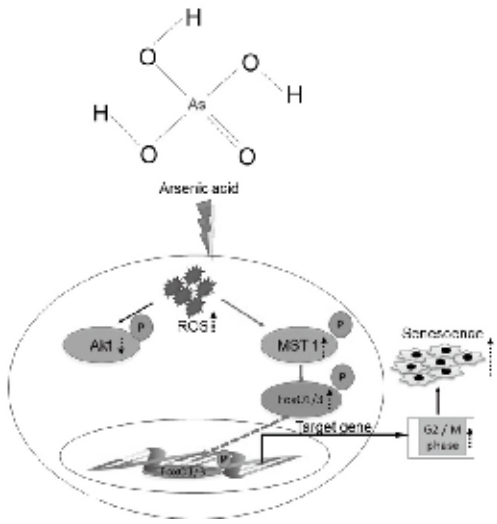


Oxidative DNA damage is a form of oxidative cellular stress and leads to two distinct, but mutually interacting, cellular responses: (1) when the DNA damage is relatively serious, such as a double-strand DNA break, ATM (ataxia telangiectasia mutated) and its downstream target Chk2 (check point kinase 2) are activated, thus leading to apoptosis or cell resistance to apoptosis and (2) when the DNA damage is relatively mild, such as an oxidative DNA modification or nick formation, ATR (ATM and rad3 related) and its downstream Chk1 are activated to repair the DNA damage. In the response to double-strand DNA break, histone H_2AX is phosphorylated by ATM [2]. And finally leading to the blocking of regular cell cycle or delay in the cell cycle.

In conclusion the study demonstrated the Thus study shows that exposure of normal skin fibroblast cells to As_2O_3 could lead to cell cycle arrest through ATM/ATR and DNA damage signaling pathways. In conclusion, we report here that arsenic trioxide increases cellular oxidative stress leading to shift in cell cycle and leads to DNA damage through ATM/ATR and the CHK-dependent signaling pathway.

Another classical pathway of diligent effect of arsenic is cell stress induced cell senescence. there are a variety of factors included in the process of cellular senescence. It is a complicated pathophysiological process, for instance the oxidative stress, shortening of telomere length, abatement of histone deacetylase and DNA methyltransferase and so on

The schematic of the arsenic induced cell senescence is explained in the flowing figure.



Organismal ageing is associated with increased chance of morbidity or mortality and it is driven by diverse molecular pathways that are affected by both environmental and genetic factors. The progression of ageing correlates with the gradual accumulation of stressors and damaged biomolecules due to the time-dependent decline of stress resistance and functional capacity, which eventually compromise cellular homeodynamics. FOXOs play a role in cell proliferation and survival by regulating the expression of genes involved in cellular processes, such as cell cycle arrest and DNA repair. FOXO family of transcription factors gained increased interest as pivotal elements of cell fate. It is implicated in diverse functions, from development, longevity, and aging, to control of cell survival or cell senescence. FOXO members are directly implicated in cell cycle control [3], through G1-related p130 and cyclin G2 or DNA damage-inducible gene 45α (GADD45α)

3. CONCLUSION

Both inorganic and organic form of arsenic has been shown to impair nucleotide excision repair and base excision repair processes. Both inorganic and organic arsenic exposure may cause carcinogenicity as it increases oxidative DNA damage and chromosomal aberration and interferes with cellular signaling pathways [4].

4. REFERENCES

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