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Review

Epigenetic mechanisms underlying the toxic effects associated with arsenic exposure and the development of diabetes

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ABSTRACT

Background: Exposure to inorganic arsenic (iAs) is a major threat to the human health worldwide. The consumption of arsenic in drinking water and other food products is associated with the risk of development of type-2 diabetes mellitus (T2DM). The available experimental evidence indicates that epigenetic alterations may play an important role in the development of diseases that are linked with exposure to environmental toxicants. iAs seems to be associated with the epigenetic modifications such as alterations in DNA methylation, histone modifications, and micro RNA (miRNA) abundance.
Objective: This article reviewed epigenetic mechanisms underlying the toxic effects associated with arsenic exposure and the development of diabetes.
Method: Electronic databases such as PubMed, Scopus and Google scholar were searched for published literature from 1980 to 2017. Searched MESH terms were “Arsenic”, “Epigenetic mechanism”, “DNA methylation”, “Histone modifications” and “Diabetes”.
Results: There are various factors involved in the pathogenesis of T2DM but it is assumed that arsenic consumption causes the epigenetic alterations both at the gene-specific level and generalized genome level.
Conclusion: The research indicates that exposure from low to moderate concentrations of iAs is linked with the epigenetic effects. In addition, it is evident that, arsenic can change the components of the epigenome and hence induces diabetes through epigenetic mechanisms, such as alterations in glucose transport and/or metabolism and insulin expression/secretion.

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1. Introduction

Arsenic is a common carcinogenic element of major health concern. A Considerable epidemiological evidence is available that link the exposure of organic arsenic and iAs to the various human ailments, particularly cancer and diabetes (Smith et al., 2002). Apart from inorganic exposure, humans are also exposed to the variety of organic arsenic compounds such as 'arsenobetaine' and 'arsenosugars', which are mostly found in foods obtained from the sea (Edmonds and Francesconi, 1997; Koopaei and Abdollahi, 2017). The different types of organic, inorganic and biological forms of arsenic are shown in Fig. 1. Out of these, all forms have specific toxicity profile and mechanism of action. The biotransformation and toxicity of both iAs and organic arsenical compounds differ from each other in a substantial ways. Inorganic derivatives of arsenic such as 'arsenite' and 'arsenate' are metabolized to 'methylarsonate' and 'dimethylarsinate' respectively, which are ultimately excreted by the kidneys in urine along with other inorganic forms of arsenics (Aposhian and Aposhian, 2006). 'Arsenobetaine' is considered as a nontoxic compound and is eliminated in urine as such (Sabbioni et al., 1991).

Arsenic is considered to be non-genotoxic as it does not cause mutations. It is generally considered as non-carcinogenic when administered to the experimental animals solely except the transplacental exposure in the mouse model (Kitchin, 2001; Waalkes et al., 2004a,b). However, the molecular mechanisms underlying the arsenic-induced diabetes and carcinogenesis are unclear and it is a new subject to exploring the exact mechanism. Although, there are several hypotheses regarding the possible etiologies of arsenic-induced endocrine disorders such as diabetes, including the interruption of the insulin signaling cascades, induction of the oxidative stress and epigenetic alterations (Huang et al., 2004; Kumagai and Sumi, 2007; Maqbool et al., 2016). Therefore, it is believed that iAs is non-carcinogenic when used in animal models as a single administered agent and also in the studies conducted on human subjects because of the complexity associated with the development of certain endocrine disorders, as the human populations are exposed to other toxic substances along with arsenic.

Various reports indicate that every year, millions of people suffer from different diseases such as diabetes and cancer associated with chronic consumption of iAs originated from contaminated drinking water. (Smedley and Kinniburgh, 2002; Maqbool et al., 2017). In the United Sates (US), there are approximately 13 million people residing in the areas where the water is contaminated with iAs at the concentration of 10 μg/l, which exceeds the standard set by the US Environmental Protection Agency for the expected concentration of arsenic in the drinking water supply (Usepa, 2001).

Arsenic increases the level of glucose and insulin in animal models when used in relatively high concentration (Rodríguez et al., 2016). The uptake of glucose was decreased in insulin sensitive cells and it inhibited the factors responsible for insulin signaling transduction and insulin sensitivity during *in vitro* studies. The maximal level of trivalent arsenicals may trigger the phosphatidylinositol-3-kinase (PI-3k) and PI-dependent phosphorylation of protein kinase B (PKB/Akt). Hence, it may decrease the action of insulin via activating the PKB/Akt-mediated glucose transport in the cells which expressing the glucose transporter 4 (GLUT4) (Izquierdo-Vega et al., 2006; Paul et al., 2007). In studies conducted in Bangladesh, Taiwan, and Mexico, it has been shown that the presence of high concentration of arsenic in the drinking water and chronic exposure to arsenic is closely associated with diabetes. Excessive arsenic exposure in the industrial areas and pesticides has also been correlated withthe increased level of glycated hemoglobin, a potential biomarker for the determination of blood glucose levels (Mostafalou and Abdollahi, 2017).

Nowadays, epigenetic is an appropriate choice for such studies and is considered to be one of the fast-growing fields of molecular biology. The description of DNA methylation at a single nucleotide, the identification of new histones alternatives and the introduction of nucleosome locations are the key aspects highlighting the fast-tracking speed of scientific discoveries in recent years (Portela and Esteller, 2010). The invention and improvement in already available technologies, along with the growing rate of advances in epigenetic fields make it more interesting. This will allow the redesigning of epigenetic basis, such as DNA methylation and modification of the histones. Although, it might be essential for regulating the gene and noncoding RNA expression assays (Esteller, 2008). In most cases, the pattern through which the epigenetic genes are being expressed and the related phenotypes continue through mitotic cell division or even through meiosis, with the fact that no changes have been observed in the basic sequence of DNA, are not identified yet. Therefore, in general terms, it was understood that epigenetics is the study of molecular mechanisms that primarily regulate the gene expression (Khan et al., 2016a,b).

Today, epigenetics provide the ideal basis for understanding the mechanisms underlying the toxicants induced diseases. Epigenetic concept and the application of epigenetics techniques in the area of human ailments have initiated an interest for researchers. Covalent modifications of cytosine bases and histone at the molecular level in association with the overall alterations in the nucleosomes positioning are termed as the key mechanisms of epigenetics. Such mechanisms are essential for proper regulations of the cellular events such as level of miRNA, gene expression and cell differentiation (Rideout et al., 2001). In this review article, we focused on current evidence that indicates the epigenetic mechanisms associated with arsenic exposure, especially based on the activity of DNA methyltransferases (DNMTs) and the development of diabetes.