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Review

Epimutagenesis: A prospective mechanism to remediate arsenic-induced toxicity

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ABSTRACT

Arsenic toxicity is a global issue, addressed by the World Health Organization as one of the major natural calamities faced by humans. More than 137 million individuals in 70 nations are affected by arsenic mainly through drinking water and also through diet. Chronic arsenic exposure leads to various types of patho-physiological end points in humans including cancers. Arsenic, a xenobiotic substance, is biotransformed in the body to its methylated species by using the physiological S-adenosyl methionine (SAM). SAM dictates methylation status of the genome and arsenic metabolism leads to depletion of SAM leading to an epigenetic disequilibrium. Since epigenetics is one of the major phenomenon at the interface between the environment and human health impact, its disequilibrium by arsenic inflicts upon the chromatin compaction, gene expression, genomic stability and a host of biomolecular interactions, the interactome within the cell. Since arsenic is not mutagenic but is carcinogenic in nature, arsenic induced epimutagenesis has come to the forefront since it determines the transcriptional and genomic integrity of the cell. Arsenic toxicity brings forth several pathophysiological manifestations like dermatological non-cancerous, pre-cancerous and cancerous lesions, peripheral neuropathy, DNA damage, respiratory disorders and cancers of several internal organs. Recently, several diseases of similar manifestations have been explained with the relevant epigenetic perspectives regarding the possible molecular mechanism for their onset. Hence, in the current review, we comprehensively try to intercalate the information on arsenic-induced epigenetic alterations of DNA, histones and microRNA so as to understand whether the arsenic-induced toxic manifestations are brought about by the epigenetic changes. We highlight the need to understand the aspect of epimutagenesis and subsequent alterations in the cellular interactome due to arsenic-induced molecular changes, which may be utilized to develop putative therapeutic strategies targeting both oxidative potential and epimutagenesis in humans.

Contents

Abbreviations: WHO, World Health Organization; MPL, maximum permissible limit; NPDS, National Poison Data System; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; BD, Bowen's disease; iAs, inorganic arsenic; SAM, S-adenosyl methionine; ROS, reactive oxygen species; MMA, monomethyl arsonic acid; DMA, dimethyl arsinic acid; DNMT, DNA methyltransferase.

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1. Introduction

Arsenic consumption mainly through drinking water is one of the increasing pandemic concerns. Arsenic toxicity plagues more than 137 million individuals in nearly 70 countries of which the most affected regions includes the Ganga–Brahmaputra–Meghna basin of India and Bangladesh, parts of China, Japan, Taiwan, Argentina, and USA (Mondal et al., 2010; Bhattacharjee et al., 2013; Rahaman et al., 2013). According to the World Health Organization (WHO), the maximum permissible limit (MPL) for arsenic consumption through drinking water is 10 μg/L (WHO, 1996). In the state of West Bengal nearly 26 million individuals are at risk of arsenic exposure, where the mean arsenic content is above the recommended MPL (Guha Mazumder et al., 2012; Paul et al., 2013a). An estimated 19.6 million individuals are at risk in China consuming arsenic-contaminated drinking water (Rodríguez-Lado et al., 2013). The expanse of arsenic contamination has spread globally and is on the rise steadily. In a report by Mowry et al. (2013), 733 cases out of 9345 registered cases by American Association of Poison Control Centers National Poison Data System, USA (NPDS) had arsenic-related toxic exposure in 2012 (Mowry et al., 2013). This accounts for 7.84% of the registered cases, which was around 6.83% in 2002 as reported by the NPDS database (Watson et al., 2003). The source of arsenic in the environment may be either through natural processes or may be anthropogenic (Anawar et al., 2004; Pandey et al., 2006; Lin et al., 2008).

The metabolism of arsenic within the human body is a multi-step biotransformation that involves various enzymes and intermediates to ultimately form monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). These are the main end products along with some variants of trimethyl arsine oxides (TMAO), all of which are ultimately targeted towards excretion through urine and also via the hair and nails. The biotransformation of arsenic within the human body involves transmethylation reaction under the influence of arsenic (III) methyltransferase (AS3MT), which adds a methyl group to the inorganic arsenic species to subsequently form MMA and DMA (Foà et al., 1984; Apostoli et al., 1997; Mandal et al., 2001). It was observed that accidental arsine intoxication led to a gradual transition in metabolic forms of arsenic through the urine of which MMA and DMA were predominant (Apostoli et al., 1997).

In humans, skin is one of the most physiologically sensitive organs to bear the brunt of arsenic toxicity. Dermatological hyper-pigmentations, premalignant lesions like palmo-plantar hyperkeratosis as well as cancerous transforms like basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and Bowen's disease (BD) have been reported in arsenic-exposed human populations and are considered as hallmarks of chronic arsenic exposure (Tseng et al., 1968; Guha Mazumder et al., 1998; Karagas et al., 2001; Banerjee et al., 2007; Ghosh et al., 2007). Also cancers in the urinary bladder, lung and pancreas have been associated with arsenic exposure (Liu-Mares et al., 2013; Ferreccio et al., 2013; Tsuji et al., 2014). Besides arsenic have also been correlated with several other physiological end points like increase in the incidence of peripheral neuropathy, chronic lung disorders, hepatic and cardiovascular disorder (Das et al., 2012; Pesola et al., 2012; Barton and McLean, 2013; Paul et al., 2013a). The liver has an important role in the regulation of metabolic pathway of inorganic arsenic (iAs) within the human body. Chronic arsenic load hence induces hepato-toxicity within individuals (Das et al., 2012; Guha Mazumder, 2001). *In vivo* experiments in mice models show that administration of iAs can alter the gut microbiome microenvironment (Lu et al., 2014). Also, DNA damage has been one of the primordial concerns, associated with arsenic-induced toxicity. Metabolism of iAs within the human body readily bio-transforms it into its organic equivalents of methylated and/or thiolated forms using S-adenosyl methionine (SAM) and glutathione (GSH) (Naranmandura et al., 2006). This generates several reactive oxygen species (ROS), leading to oxidative DNA damage (Lee and Ho, 1994; Matsui et al., 1999). DNA damage detected in forms of chromosomal aberrations, breaks and micronuclei (MN) have been widely reported from all over the world in arsenic-exposed human population (Choudhury et al., 1997; Basu et al., 2002).

The metabolic activity of arsenic not only generates oxidative stress, but also depletes the cellular methyl pool by utilizing SAM to generate methylated species (MMA, DMA) which are excreted through urine (Coppin et al., 2008). This results in an observed global genomic hypomethylation (Reichard et al., 2007); but studies have demonstrated that certain gene specific promoter hypermethylation as well as hypomethylation occur upon arsenic exposure leading to altered degree of gene expression upon arsenic exposure (Chanda et al., 2013; Gribble et al., 2014). Over the years it has been difficult to detect toxic mechanism of arsenic within the human body. Very recently, the field of epigenetics has been associated with different toxic outcomes in humans. In the present review we have attempted to intercalate the recent advances in the field of arsenic toxicity research and related epigenetics in humans and tried to propose the plausible mechanism of arsenic toxicity by epimutagenic events.

2. Nature of arsenic-induced epimutagenesis

2.1. DNA methylation

According to the semi-conservative theory, DNA methylation occurs mostly in the newly synthesized strands during the S-phase, regulated by the methyltransferase enzymes found within the system (Geraci et al., 1974; Bird, 1978; Franchina et al., 2001). In fact, it was demonstrated that the splice variants of DNA methyltransferases within the peripheral blood leukocytes confirm the various methylation specificities within the cell (Zhao et al., 1997). This may be attributed to the variable genomic methylation index within the cellular microenvironment. In case of arsenic, several reports state that the DNA methyltransferases (DNMTs) show a variable degree of activity upon arsenic exposure. Zhao and his colleagues showed that a prolonged arsenic treatment *in vitro* resulted in a loss in the methyltransferase activity of DNMT1, due to depletion of the methyl pool even though the mRNA transcript in the arsenic-exposed TRL-1215 was higher than normal (Zhao et al., 1997). Thus, decrease in bioavailability of the methyl pool may deplete the methylation profile of the newly synthesized genome, leading to a global hypomethylated genome.

The adult multipotent stem cells in humans perform differentiation and biogenesis of several tissues like the fibroblasts and hematopoietic stem cells. They have well designated molecular signaling pathways which are epigenetically regulated (Oakley and Van Zant, 2007). In cancer, epigenetic deregulation has a profound effect in reprogramming of normal adult stem cells to cancer stem cells (Vecchio et al., 2013). Since arsenic mediated genomic hypomethylation have shown to reactivate several suppressed genes leading to an aberrant gene expression (Zhao et al., 1997; Liu et al., 2011); it may be hypothesized as one of the important aspects in arsenic-induced carcinogenesis. Nevertheless, research reports show that there are several instances where genes like *p53*, *p16*, and *CTNNA2* have hypermethylated promoters, resulting in a lower expression profile within the cell. Expression of tumor