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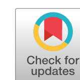
Enhanced H3K4me3 modifications are involved in the transactivation of DNA damage responsive genes in workers exposed to low-level benzene☆



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ABSTRACT

In this study, we explore whether altered global histone modifications respond to low-level benzene exposure as well as their association with the hematotoxicity. We recruited 147 low-level benzene-exposed workers and 122 control workers from a petrochemical factory in Maoming City, Guangdong Province, China. The internal exposure marker level, urinary S-phenylmercapturic acid (SPMA), in benzene-exposed workers was 1.81-fold higher than that of the controls ($P < 0.001$). ELISA method was established to examine the specific histone modifications in human peripheral blood lymphocytes (PBLCs) of workers. A decrease in the counts of white blood cells (WBC), neutrophils, lymphocytes, and monocytes appeared in the benzene-exposed group (all $P < 0.05$) compared to the control group. Global trimethylated histone 3 lysine 4 (H3K4me3) modification was enhanced in the benzene-exposed group ($P < 0.05$) and was positively associated with the concentration of urinary SPMA ($\beta = 0.103$, $P = 0.045$) and the extent of DNA damage (% Tail DNA: $\beta = 0.181$, $P = 0.022$), but was negatively associated with the leukocyte count (WBC: $\beta = -0.038$, $P = 0.023$). The *in vitro* study revealed that H3K4me3 mark was enriched in the promoters of several DNA damage responsive (DDR) genes including *CRY1*, *ERCC2*, and *TP53* in primary human lymphocytes treated with hydroquinone. Particularly, H3K4me3 modification was positively correlated with the expression of CRY1 in the PBLCs of benzene-exposed workers. These observations indicate that H3K4me3 modification might mediate the transcriptional regulation of DDR genes in response to low-dose benzene exposure.

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1. Introduction

Benzene is a ubiquitous environmental pollutant and a widely used chemical reagent. Occupational benzene exposure occurs in petrochemical plants, shoe and rubber factories, fuel transport, gas stations, and many other industries. Moreover, the general population may also become exposed to benzene originating from gasoline vapors, cigarette smoke, or vehicle exhaust (Arnold et al., 2013). Benzene exposure may cause acute myeloid leukemia (AML) and it has been recognized as a Group I carcinogen by the International Agency for Research on Cancer (1987). The US Occupational Safety and Health Administration and the European Commission's Scientific Committee recommend 1 ppm as the limit of occupational benzene exposure. Epidemiological studies have shown that a decrease in blood cell counts appears in populations with long-term exposure to benzene (Casale et al., 2016; Koh et al., 2015). Furthermore, accumulating evidence has revealed decreased

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counts of leukocytes, platelets, erythrocytes, as well as increasing risk of myelodysplastic syndrome in workers exposed to benzene less than 1 ppm. This indicates that low-level benzene exposure has an impact on the induction of hematotoxicity (Casale et al., 2016; Koh et al., 2015; Lan et al., 2004; Qu et al., 2002).

Meta-analysis has identified associations between childhood leukemia and several potential benzene exposure metrics (Carlos-Wallace et al., 2016). To assess the risks of benzene, a comprehensive outline of a mode of action (MOA) has been proposed, leading to the identification of several potential key events involved in benzene-induced leukemogenesis (McHale et al., 2012). Benzene is a genotoxic agent which is capable of causing DNA breaks, chromosomal damage and sister chromatid exchanges (Dean, 1985; Sasiadek et al., 1989). Lines of epidemiological studies suggest that exposure to benzene is association with genotoxic risk (Benites et al., 2006; Celi and Akbas, 2005; Celik et al., 2003). Although it is evident that genetic damage, error-prone DNA repair, oxidative stress and epigenetic alternations are relevant to benzene-induced leukemogenesis, the key events with respect to the aberrant epigenetic alterations remain largely unknown.

Epigenetic modification is considered "acquired inheritance" and is a consequence of the interaction between genes and environment (Jaenisch and Bird, 2003). Aberrant epigenetic modification could be used as an early biomarker for predicting adverse health effects in population exposure to environmental carcinogens (Koturbash et al., 2011). It has been revealed that epigenetic changes play important roles in benzene-related hematotoxicity and carcinogenicity (Bollati et al., 2007; Yu et al., 2011). For instance, benzene exposure leads to an alteration of DNA methylations, both in the global and gene-specific levels of human peripheral blood lymphocytes (PBLCs) (Bollati et al., 2007; Fustinoni et al., 2013; Li et al., 2017; Xing et al., 2010, 2013). Specific genes such as *p15*, *p16*, and *STAT3* are aberrantly methylated in benzene exposed populations (Bollati et al., 2007; Xing et al., 2010; Yang et al., 2014). These findings provide evidence that epigenetic mechanisms are critical for benzene-induced hematotoxicity. To date, more attention has been paid to DNA methylation and non-coding RNA (Fenga et al., 2016). Whether or not histone modifications are involved in benzene-induced hematotoxicity remains to be determined.

The acetylation of histone residue is typically associated with the activation of gene expression. Whether the methylation of histone is associated with transcriptional activation depends on the location of lysine in the histone tail (Berger, 2007). A number of recent studies have demonstrated that specific histone modifications altered in response to a variety of environmental pollutants such as metal-rich air particles, arsenic, benzo(a)pyrene, and cigarette smoke (Cantone et al., 2011; Chervona et al., 2012; Liang et al., 2012; Ma et al., 2016; Sundar and Rahman, 2016). However, it remains unclear whether histone modifications triggered by benzene exposure mediate the cellular response and the molecular mechanism of the transcriptional regulation of specific genes, particularly in context of population exposure to low-level benzene.

To address the epigenetic mechanism behind benzene-related hematotoxicity, this study examined the modifications of H3 methylation in the PBLCs of petrochemical workers. We also clarified the associations between the histone modifications and blood cell counts, and the extent of DNA damage. We identified H3K4me3 as a specific histone mark that might be involved in DNA damage response in workers exposed to low-level benzene.

2. Materials and methods

2.1. Subjects and sample collection

In this study, we recruited 269 workers from a petrochemical plant in the city of Maoming, Guangdong Province, China. Benzene-exposed workers ($n = 147$) were recruited according to the following criteria: (1) they had worked at least one year in workplaces exposed to benzene; (2) they had finished occupational health clinical examinations in accordance with the Technical Specifications for Occupational Health Surveillance GBZ188-2007, China. The 122 workers in the control group consisted of administrative staff unexposed to benzene. To avoid the impact of confounding factors, all subjects are non-smoking and non-drinking male workers. All participants were interviewed by trained personnel using a structured questionnaire that included questions on demographic characteristics, body weight and height, duration of employment, educational level, occupational history and disease history. The study protocol was approved by the Ethical Review Committee at Sun Yat-sen University and written informed consent was obtained from every worker.

We collected 5 mL of blood from every worker for isolation of peripheral blood lymphocytes (PBLCs) and extraction of histone protein. In addition, we collected 30 mL urine samples from each worker and stored them at -80 °C until determination of urinary SPMA and S-benzylmercapturic acid (SBMA), an internal marker for toluene exposure.

2.2. Measurement of benzene levels and determination of urinary SPMA and SBMA

Individual air sampling was conducted among 18 benzene-exposed workers selected from 7 representative workplaces in the petrochemical plant as well as 4 office workers from various parts of the administrative office. Each worker was equipped with an individual air sampler (Galian, USA) which used charcoal sampling tubes during a typical midweek shift, as described by Seow et al. (2012). The amounts of benzene and toluene were analyzed according to the method provided in *Occupational Exposure Limits for Chemical Hazards in the Workplace of China* (GBZ2.1-2007). The detection limits for benzene, toluene, ethylbenzene, and xylene (BTEX) were 0.01 mg/m^3, 0.02 mg/m^3, 0.02 mg/m^3, and 0.02 mg/m^3, respectively.

The urinary SPMA and SBMA were measured in a liquid chromatography/electrospray tandem mass spectrometry (LC–MS/MS) as described by Schettgen et al. (2008). The detection limits for urinary SPMA and SBMA were 0.01 μg/L and 0.03 μg/L, respectively.

2.3. Comet assay

Comet assay was performed under alkaline conditions following the protocol as described by Fracasso (Fracasso et al., 2010). A CometAssay® HT 20-well slide (Trevigen Inc., Gaithersburg, MD, USA) was used and the assay was conducted under dark conditions. DNA damage was quantified as the tail DNA intensity (% Tail DNA).

2.4. Cell treatments

Primary human lymphocytes (PHLCs) isolated from 20 mL whole blood were placed in 6 cm dishes at a density of 1×10^6 and treated with hydroquinone (HQ) at concentrations of 0, 0.1, 1.0, and 10.0 μM. The design of the dosage was based on a previous report which had shown that HQ concentrations in peripheral blood at a range of 20–120 ng/mL (0.2–1.1 μM) were similar to the levels of external environmental benzene ranging from 0.2 to 78.8 mg/m^3 (0.1–24.7 ppm) (Kerzic et al., 2010).

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