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Urinary polycyclic aromatic hydrocarbon metabolites, Club cell secretory protein and lung function

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ABSTRACT

Background: Exposure to polycyclic aromatic hydrocarbons (PAHs) has been associated with lung function decline. However, the underlying mechanisms for the association remain unclear.
Objectives: To explore potential role of a lung epithelial biomarker, Club cell secretory protein (CC16), in associations between PAH exposures and lung function decline.
Methods: We investigated 3384 adults from the Wuhan-Zhuhai cohort, and followed up at three years after first examination. Linear mixed models was used to quantify dose-response relationships between urinary monohydroxylated PAH metabolites (OH-PAHs) and lung function, as well as OH-PAHs and plasma CC16. Mediation analysis was conducted to investigate role of CC16 in the association between OH-PAHs and lung function. We also estimated the relationships between OH-PAHs and lung function change in three years among participants with different levels of CC16.
Results: Each 1-unit increase of log-transformed total urinary high and low molecular weight OH-PAHs (ΣHMW OH-PAH and ΣLMW OH-PAHs) were associated with a 22.59 and 25.25 ml reduction of FEV_1 respectively, while ΣHMW OH-PAH was associated with a 30.38 ml reduction of FVC. Moreover, these negative associations between OH-PAHs and lung function levels were significant only among low CC16 group (< 15.83 ng/ml). CC16 concentration decreased monotonically with increased high molecular weight OH-PAHs (ΣHMW OH-PAHs) when ΣHMW OH-PAH concentration was over 0.67 μg/mmol Cr. CC16 mediated 22.13% of the association between ΣHMW OH-PAH and FVC among individuals with higher ΣHMW OH-PAH. After three years of follow-up, subjects with low level of plasma CC16 had a significant decline of FVC when exposed to high level of ΣHMW OH-PAH.
Conclusions: CC16 play an important role in the association between high molecular weight PAHs and FVC. Individuals with low plasma CC16 level might suffer a decline in lung function when exposed to high level of high molecular weight PAHs.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are one kind of the most widespread environmental contaminants in air, water, and soil. Exposure to PAHs not only link to raised risks for certain cancers, but also may result in nonmalignant health effects, especially respiratory effects such as chronic obstructive pulmonary diseases (COPD) and asthma (Burstyn et al., 2003; Al-Daghri et al., 2013; Zhou et al., 2016). We recently observed that elevated urinary monohydroxylated PAH metabolites (OH-PAHs) were significantly associated with lung function decline (Zhou et al., 2016). However, the underlying mechanism linking PAH exposures and lung function decline remain largely unknown. It has been reported that activation of oxidative stress and inflammation were involved in the process of PAH-induced damage on the structural integrity of the lung epithelium (MacNee, 2001; Gerritsen et al., 2005; Ahmadi-Abhari et al., 2014; Farzan et al., 2016), which

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might play important roles in the pathogenesis of lung function decline.

Club cell secretory protein (CC16) has been recognized as a biomarker of integrity of lung epithelium. It is secreted in abundance in airways by non-ciliated bronchiolar Club cells and increasingly appears to protect the respiratory tract against oxidative stress and inflammation (Van Vyve et al., 1995; Benson et al., 2005). Lower CC16 level was found to be linked with lung function decline or development of respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD) (Martin et al., 2006; Park et al., 2013; Guerra et al., 2015). Therefore, CC16 has emerged as a key biomarker to help confirm the diagnosis and define the prognosis in some respiratory disorders (Lomas et al., 2008; McAuley and Matthay, 2009; Park et al., 2013; Guerra et al., 2015), Many noxious environmental pollutants such as wood smoke, cigarette smoke and arsenic, can alter CC16 levels through damaging Club cells (Robin et al., 2002; Timonen et al., 2004; Stockfelt et al., 2012; Beamer et al., 2016). Previous studies reported that Club cells were more susceptible to PAHs than other airway epithelial cells due to highly expressed aryl hydrocarbon receptor (AhR), which is a ligand-activated transcription factor involved in PAH-induced immunotoxicity (Plopper et al., 1992; Chang et al., 2006). However, few studies focused on the association between PAHs and CC16. One in vivo study showed that naphthalene (a simplest PAH) exposure could reduce both the number of Club cell and the expression of CC16 mRNA and protein (Yildirim et al., 2008). Whether CC16 plays a potential role in lung function decline induced by PAH exposures has not been studied to date.

Therefore, we hypothesized that PAH exposures can decrease lung function through lowering CC16 concentration (Fig. 1). To assess the associations of PAH exposures with the levels of lung function and CC16, we determined urinary OH-PAHs as biomarkers for PAH exposures, and measured levels of plasma CC16 and lung function for 3384 adults in a Chinese general population. We further investigated the mediating role of CC16 on the associations between OH-PAHs and lung function alteration. We also estimated the relationships between OH-PAHs and lung function change in three years among participants with different levels of CC16 to assess whether individuals with low level of CC16 had poor lung function after PAH exposures.

2. Material and methods

2.1. Study design and population

All participants were from the Wuhan-Zhuhai (WHZH) cohort, which has been described elsewhere (Song et al., 2014). Briefly, the cohort included 4812 residents aged 18 to 80 who lived in Wuhan or Zhuhai city for more than five years. Participants underwent standardized questionnaires and physical examination including anthropometric and lung function measurement in 2011–2012, and followed to 2014–2015. Whole blood and early morning urine samples were collected for determination of CC16 and OH-PAHs levels, respectively. For the cross-sectional investigation, we excluded those failed to complete lung function test (N = 106), plasma CC16 (N = 971) or OH-PAHs determination (N = 687), and a total of 3384 participants were included in the baseline investigation. We followed up the participants three years later, and 2760 participants completed the second investigation. After excluding those who without performing lung function test (N = 1017), a total of 1743 subjects were included in the longitudinal analysis. All participants in this study gave written informed consent. The research protocol was approved by the Ethics and Human Subject Committee of Tongji Medical College, Huazhong University of Science and Technology.

2.2. Urinary OH-PAHs determinations

Concentrations of ten detectable urinary OH-PAHs including nine low molecular weight OH-PAHs (1-hydroxynaphthalene, 2-hydroxynaphthalene, 2-hydroxyfluorene, 9-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 4-hydroxyphenanthrene, 9-hydroxyphenanthrene) and one high molecular weight OH-PAH [1-hydroxypyrene (1-OHP)], were measured by an Agilent 5975B/6890N GC–MS System (Agilent, CA, USA). This method was performed as described (Li et al., 2012). The limits of detection (LOD) for the OH-PAHs ranged from 0.1 to 0.9 μg/l. Concentrations below the LOD were replaced by 50% of the LOD value. Valid OH-PAHs concentrations were calibrated to the levels of urinary creatinine and calculated as μg/mmol creatinine (Cr).

2.3. Lung function test

Lung function test was conducted by specialists using electronic spirometers (CHEST Ltd., Tokyo, Japan) as described previously (Zhou et al., 2016). Three acceptable volume-time curves of forced vital capacity (FVC) or forced expiratory volume in 1 s (FEV_1) were obtained and recorded according to the American Thoracic Society recommendations (Society, 1995).

2.4. Plasma CC16 measurements

Plasma CC16 concentration was measured by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, MN, USA) according to manufacturer's instructions, with the range of 0.8–50 ng/ml and the sensitivity of 0.217 ng/ml. All the samples were replicated two times.

2.5. Statistical analysis

We calculated the concentrations of total high or low molecular weight OH-PAHs (i.e. ΣHMW OH-PAH or ΣLMW OH-PAHs), respectively. OH-PAHs and CC16 concentrations were log-transformed due to right-skewed distributions; while FEV_1 and FVC were not statistically transformed because they were approximately normally distributed.

Both continuous and categorical analysis were conducted to quantify association of OH-PAHs with lung function parameters (FEV_1 and FVC) and CC16 concentration by using linear mixed models including residence as a random effect, with adjustment for sex, age, height, weight, income, occupational hazard exposure, smoking amount, passive smoking amount, alcohol consumption, regular physical activity, cooking meals at home. All participants were further separated into

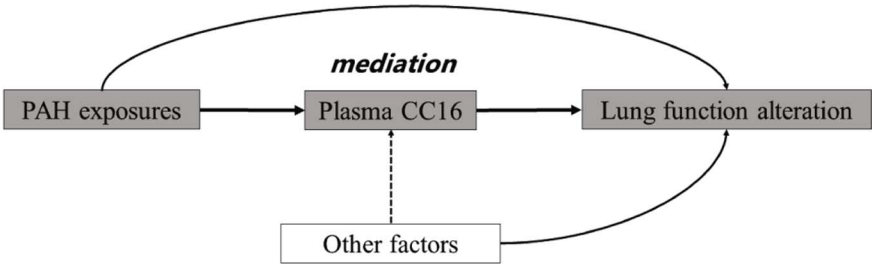

Fig. 1. Simple conceptual model for mediation assessment in the context of the present study.