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Ambient PM2.5 caused cardiac dysfunction through FoxO1-targeted cardiac hypertrophy and macrophage-activated fibrosis in mice

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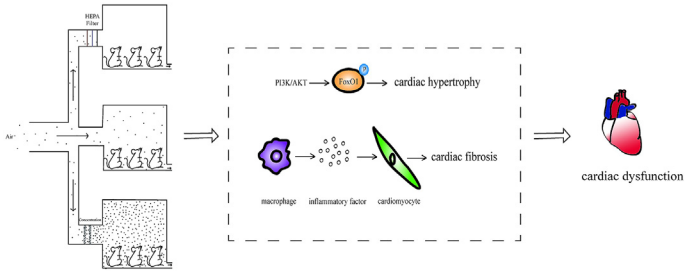
HIGHLIGHTS

- Real-time PM2.5 inhalation induced cardiac hypertrophy and fibrosis.
- FoxO1 might be a regulator of cardiac hypertrophy after PM2.5 exposure.
- Cardiac fibrosis induced by PM2.5 might be linked with macrophage activation.

GRAPHICAL ABSTRACT



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ABSTRACT

Plenty of epidemiological evidences have shown that ambient particulate matter (PM2.5) exposure increased the prevalence of cardiovascular disease, but the potential mechanism has not been known clearly. We established mice models by ambient PM2.5 exposure system to explore the adverse effects of PM2.5 on cardiac function in mice. Forty-eight C57BL/6 mice were randomly divided into 3 groups and exposed to filtered air (FA), unfiltered air (UA) and concentrated PM2.5 air (CA) for 8 or 16 weeks, 6 hours per day, 7 days per week, respectively. The changes of cardiac structure and function, histological analysis and related mechanism were investigated. The main manifestations of cardiac structure were cardiac hypertrophy and fibrosis in a dose- and time-dependent manner after PM2.5 exposure, which led to the decrease of cardiac systolic function. Cardiac hypertrophy in mice might be regulated by PI3K/Akt/FoxO1 signal. Cardiac fibrosis might be attributed to inflammatory infiltration caused by macrophage activation. Consequently, our data indicated that cardiac hypertrophy and fibrosis might be important factors of PM2.5-induced cardiac dysfunction in mice.

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1. Introduction

Ambient air pollution poses a serious hazard to global public

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health in recent years. According to the report of Global Burden of Disease (GBD) 2017, environmental particulate matter pollution becomes the eighth largest risk of death in the world Global Burden of Disease (2018). Epidemiological studies had demonstrated that the increased risk of cardiovascular diseases (CVDs) were associated with exposure to fine particulate matter (PM2.5) (Feng et al., 2019; Huang et al., 2019; Kirrane et al., 2019; Wang et al., 2019). CVD has been the main cause of death worldwide in 2016 Global Burden of Disease (2017a). Especially, there were more than 17 million premature deaths from worldwide, it was worth noting that more than 3 million of these deaths (19% of all cardiovascular deaths) were attributable to air pollution Global Burden of Disease (2017b). A 10 $\mu g/m^3$ increase in the 2-day moving average of PM2.5 concentration was associated with a 0.55% increase in daily cardiovascular mortality (Liu et al., 2019). Toxicological studies confirmed that PM2.5 could deposit in the lungs. Fine particles (nanoparticles) could pass through the air-blood barrier in the acinar region and enter the blood circulation, inducing damages in the extrapulmonary organs (Kreyling et al., 2014; Li et al., 2019a). Epidemiological evidence suggested that long term air pollution was associated with subclinical damage to left ventricular performance, which might be a risk factor for heart failure (Yang et al., 2017). Chronic exposure to PM2.5 impaired cardiovascular function, which might aggravate the condition of patients with cardiac arrhythmia, myocardial infarction, arterial hypertension, and heart failure (Zheng et al., 2018; Dirgawati et al., 2019; Huang et al., 2019; Malik et al., 2019). It was demonstrated that air pollution was closely related to increased morbidity and mortality of cardiovascular disease in human (Hamanaka and Mutlu, 2018; Parker et al., 2018), but the exact mechanism had not been known clearly. Therefore, further research is required to clarify the mechanism which could provide public health suggestions for reducing the occurrence and development of cardiovascular disease.

Cardiac morphological and functional parameters are important biomarkers for predicting health and cardiac disease prognosis. Epidemiological evidences suggested that air pollution exposure caused changes in left ventricular quality and function (Van Hee et al., 2009). Air pollution might be associated with the development of human left ventricular hypertrophy (Lazzeroni et al., 2016; Aronow, 2017). PM2.5 exposure caused cardiac hypertrophy in susceptible animal model such as spontaneously hypertensive rats (Ying et al., 2015). During the pathological process of cardiac hypertrophy, most myocardial proteins achieved a dynamic balance between phosphorylation and dephosphorylation through the action of multiple kinases and phosphatases. Protein kinase B (Akt), as a key kinase to promote cell metabolism and remodeling, could be activated by phosphatidylinositol (3, 4, 5)-trisphosphate (PIP3) synthesized after phosphatidylinositol-3-kinase (PI3K) activation. PI3K/Akt signal had long been considered to be a key participant in hypertrophy signal transduction (Latronico et al., 2004; Zhou et al., 2015). In early genetic and biochemical studies, Akt was identified to be a major regulator of Forkhead box transcription factors, O subfamily (FoxO) function in different organisms (Tzivion et al., 2011). FoxO transcription factors were involved in the regulation of a variety of cell functions, including differentiation, metabolism, proliferation and survival (Huang and Tindall, 2007), which play important roles in regulating cardiac hypertrophy (Skurk et al., 2005; Ni et al., 2006). Therefore, it is hypothesized that PM2.5 deregulated the PI3K/Akt drove the FoxO signal to promote cardiac hypertrophy and then led to cardiac dysfunction.

Furthermore, cardiac fibrosis is another major reason of cardiac dysfunction induced by PM2.5 (Qin et al., 2018; Wang et al., 2018). It is well known that the fibrosis was triggered and developed by chronic inflammation (Haertel et al., 2014). PM2.5 exposure induced inflammation in the heart of mice, which related with the macrophage polarization and NLRP3 inflammasome activation (Du et al., 2019). In cardiac tissue, macrophages could integrate a variety of environmental signals to remove necrotic debris and matrix remodeling during heart injury (Frieler and Mortensen, 2015). Myocardial macrophages were closely related to collagen-producing myofibroblasts, and then usually were used as regulators of fibrosis after myocardial stress (Hulsmans et al., 2016). Macrophages were involved in systemic inflammatory response and activation of proinflammatory cytokines (Du et al., 2019), which regulated the development of cardiac fibrosis in mice. We assumed that PM2.5 exposure might induce cardiac fibrosis by promoting inflammation through macrophages.

In this study, a PM2.5 exposed mice model was established to explore the effect of PM2.5 on cardiac function and its possible mechanism. We hypothesized that the mechanism of cardiac dysfunction induced by PM2.5 exposure might be due to cardiac hypertrophy mediated by PI3K/Akt/FoxO signaling pathway and cardiac fibrosis infiltrated by inflammatory factors after macrophage activation. Our findings could provide a new idea for the clinical correlation between long term PM2.5 exposure and human cardiac disease.

2. Materials and methods

2.1. Animals and PM 2.5 treatment

Six-week-old male C57 L/6 J mice were purchased from Vital River Laboratory (Beijing Vital River Laboratory Animal Technology Co., Ltd, Beijing, China). All of the mice were housed in cages under standard conditions (22.11 ± 1.51 °C, 49.67 ± 8.92% RH) with a 12 h light−dark cycle, the mice had free access to standard food and water. The weight of mice was monitored weekly. After a week of acclimatization, forty-eight mice were divided randomly into 3 groups and exposed to filtered air (FA), unfiltered air (UA) and concentrated air PM2.5 (CA) for 8 or 16 weeks, 6 h per day, 7 d per week, respectively. The FA and UA mice were exposed to air in the chamber with or without three-layers of high-efficient particulate air (HEPA) filters, respectively. CA mice were exposed to concentrated PM2.5 by the PM2.5 concentration enrichment system (Beijing Huironghe Technology Co., Ltd, Beijing, China). We monitored continuously the real-time concentrations of PM2.5 in exposure chambers by aerosol monitor (TSI instrument Co., Ltd, Minneapolis, USA) and the distribution of the particulate matters by ultraviolet aerodynamic particle sizer (TSI instrument Co., Ltd, Minneapolis, USA). Simultaneously, we used the gas detector GasAlertMicro 5 PID (BW Canada) to monitor the levels of NO_2, SO_2 and O_3 in the chambers, respectively. Cardiac function was measured with echocardiography after the final exposure for 24 h. The mice were anesthetized with 1% pentobarbital sodium (0.1 mL/10 g body weight) and sacrificed after electrocardiogram recording, and blood samples were collected from abdominal vein. The hearts were quickly removed, washed, weighed, fixed, sliced into pieces and stored at −80 °C for subsequent analyses. The protocol of animal procedures was conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and was approved by the Committee of the Ethics Animal Experiments of Hebei medical University (IACUC-Hebmu-20170116).

2.2. Echocardiographic assessment

Heart function and structure were assessed by echocardiography using a Vevo 2100™ high-resolution small animal ultrasound system equipped with 18−38 MHz MS400 high frequency probe (Visual Sonics, Toronto, Ontario, Canada). The mice were