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Protection against fine particle-induced pulmonary and systemic inflammation by omega-3 polyunsaturated fatty acids

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ABSTRACT

Background: Exposure to fine particulate matter, such as through air pollution, has been linked to the increased incidence of chronic diseases. However, few measures have been taken to reduce the health risks associated with fine particle exposure. The identification of safe and effective methods to protect against fine particle exposure-related damage is urgently needed.
Methods: We used synthetic, non-toxic, fluorescent fine particles to investigate the physical distribution of inhaled fine particles and their effects on pulmonary and systemic inflammation in mice. Tissue levels of omega-3 fatty acids were elevated via dietary supplementation or the fat-1 transgenic mouse model. Markers of pulmonary and systemic inflammation were assessed.
Results: We discovered that fine particulate matter not only accumulates in the lungs but can also penetrate the pulmonary barrier and travel into other organs, including the brain, liver, spleen, kidney, and testis. These particles induced both pulmonary and systemic inflammation and increased oxidative stress. We also show that elevating tissue levels of omega-3 fatty acids was effective in reducing fine particle-induced inflammation, whether as a preventive method (prior to exposure) or as an intervention (after exposure).
Conclusions: These results advance our understanding of how fine particles contribute to disease development and suggest that increasing tissue omega-3 levels may be a promising nutritional means for reducing the risk of diseases induced by particle exposure.
General significance: Our findings demonstrate that elevating tissue omega-3 levels can prevent and treat fine particle-induced health problems and thereby present an immediate, practical solution for reducing the disease burden of air pollution.
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1. Background

With the development of global industrialization and our increasing population, environmental pollution is becoming a more threatening issue for our planet. As a result, air quality has greatly suffered, imposing adverse risk factors on human health, in both developed and developing countries [1–4]. Within the composition of air pollution, fine particulate matter <2.5 μm in diameter (PM2.5) is considered to be especially harmful to health, as it remains suspended and uniformly dispersed in the air and can penetrate deeper into airways [5], causing detrimental effects worldwide. The World Health Organization estimated that exposure to fine particulate air pollution caused approximately two million deaths in 2011, and that the number will continue to climb [6]. Additionally, cohort studies have reported associations between PM2.5 exposure and increased cardiovascular morbidity and mortality [7,8], while further evidence shows that PM2.5 exposure could be the source of various health problems including cardiovascular disease [9,10], respiratory disease [11–13], heart failure [14,15], diabetes [16,17], lung cancer [18,19], and even premature death [20]. A recent study also points out that household air pollutants, including kerosene and solid fuels, have a higher risk of neonatal and child mortality [21]. These resulting illnesses are among the list of chronic diseases currently imposing the most severe threat on human beings of different ethnicities and ages throughout the world [22,23]. Given the systemic effects of exposure to fine particulate matter, it is thought that fine particles may be capable of penetrating the pulmonary barrier and traveling into other organs, but such particle distribution remains to be investigated. As the presence of fine particles in our environment only threatens to increase, understanding the impact of such pollution on disease development and identifying safe and effective methods for prevention and treatment of associated diseases is urgently needed.

The exact mechanisms underlying fine particle-induced damage are currently not well understood. The diseases associated with fine particle

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exposure are believed to be influenced by inflammatory processes, including cytokine release, increased oxidative stress, and vascular permeability with concomitant neutrophil recruitment [24–26]. As an essential nutrient, omega-3 polyunsaturated fatty acids (PUFA) are known to be involved in multiple physiological functions and have beneficial effects on human health, including anti-inflammatory and antioxidative properties [27–31]. We hypothesized that omega-3 fatty acids could ameliorate the adverse health effects of fine air pollution by suppressing the body's inflammatory response to fine particulate matter, and thereby reduce the risk for chronic disease development.

In this study, we first investigated the distribution of inhaled fine particles in the body using a synthetic, fluorescent fine particle compound. Next, we examined whether increasing the tissue levels of omega-3 fatty acids can reduce fine particle-induced inflammation and oxidative stress, using two approaches: (1) supplementation of animals with omega-3 fatty acids as a therapeutic treatment following fine particle inhalation and (2) utilization of a transgenic fat-1 mouse model with endogenously elevated tissue levels of omega-3 fatty acids [32] to evaluate the preventive potential of omega-3 fatty acids prior to fine particle inhalation.

2. Results

2.1. Fine particle distribution in the organs following inhalation

To obverse the distribution of fine particulate matter in vivo, fine particle inhalation was simulated by administering non-toxic, fluorescent carboxylate microspheres (1.75 μm in diameter) through oropharyngeal aspiration for 6 weeks, and after sacrifice, tissues were sectioned in sliding microtome and examined with fluorescence microscopy. Fine fluorescent particles were observed not only in the lungs but also in other organs, including the brain, liver, kidneys, spleen, and testes (Fig. 1). These results demonstrate, for the first time, that fine particles can penetrate the pulmonary barrier after accumulating in the lungs and travel to other organs, potentially inducing systemic illnesses.

2.2. Omega-3 intervention alleviates pulmonary inflammation, systemic inflammation, and oxidative stress induced by fine particles

To evaluate the effects of fine particle inhalation on pulmonary inflammation and whether this damage could be ameliorated by dietary intervention with omega-3 fatty acids, wild-type (WT) mice with or without fine particle exposure (PM and control group, respectively) were maintained on a control Western diet, and half of the fine particle-exposed mice were supplemented with omega-3 PUFA (PM + ω3 group) for 2 months. We then examined pulmonary inflammation status by measuring the white blood cell count in bronchoalveolar lavage (BAL) liquid, macrophage infiltration in lung tissue, key inflammatory cytokine levels and related gene expression, and phagocytic oxidative burst by in vivo imaging. We found that the mice exposed to fine particulate matter exhibited a marked increase in the BAL total cell count (Fig. 2A, C) and macrophage infiltration in both BAL (Fig. 2B, C) and lung tissue (Fig. 2D), BAL levels of inflammatory cytokines, including TNF-α, IL-6, IL-1β, and MCP-1 (Fig. 2E), and lung tissue gene expression of the inflammatory cytokines (Fig. 2F), compared to the control group without fine particle exposure. However, these parameters of pulmonary inflammation were all significantly reduced in the fine particle-exposed mice given omega-3 PUFA supplementation (Fig. 2A–F). Furthermore, to measure phagocytic oxidative burst, a marker of inflammatory response, myeloperoxidase (MPO) activity was assessed by intravenous injection of Lumino-R and detection of fluorescent signals using a spectrum animal imaging system. The mice exposed to fine particulate matter showed high levels of MPO activity, but those given omega-3 PUFA supplementation had lower levels MPO activity, comparable to the control group (Fig. 2G). These findings indicate that fine particle exposure can induce pulmonary inflammation, and omega-3 supplementation is capable of significantly alleviating the degree of pulmonary inflammation.

We then examined the effects of fine particle exposure on systemic inflammation and oxidative stress, and the potential benefits of omega-3 PUFA supplementation, by measuring plasma levels of key inflammatory cytokines and endotoxins, total antioxidant capacity, and related gene expression. Compared to the control group, mice exposed to fine particulate matter had higher circulating levels of pro-inflammatory cytokines (Fig. 3A), lower antioxidant capacity (Fig. 3B), and greater levels of lipid peroxidation, DNA damage, and endotoxins (Fig. 3C, D, E). When fine particle-exposed mice were given omega-3 PUFA supplementation, however, the inflammatory effects of fine particulate matter were largely reversed (Fig. 3A–E). Accordingly, the splenic mRNA expression of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, and MCP-1; Fig. 3F) and oxidant-related genes (SOD, GSH-px; Fig. 3G) was elevated in the fine particle-exposed mice but significantly reduced in the fine particle-exposed mice supplemented with omega-3 PUFA. Thus, these results demonstrate that intervention with omega-3 PUFA was able to

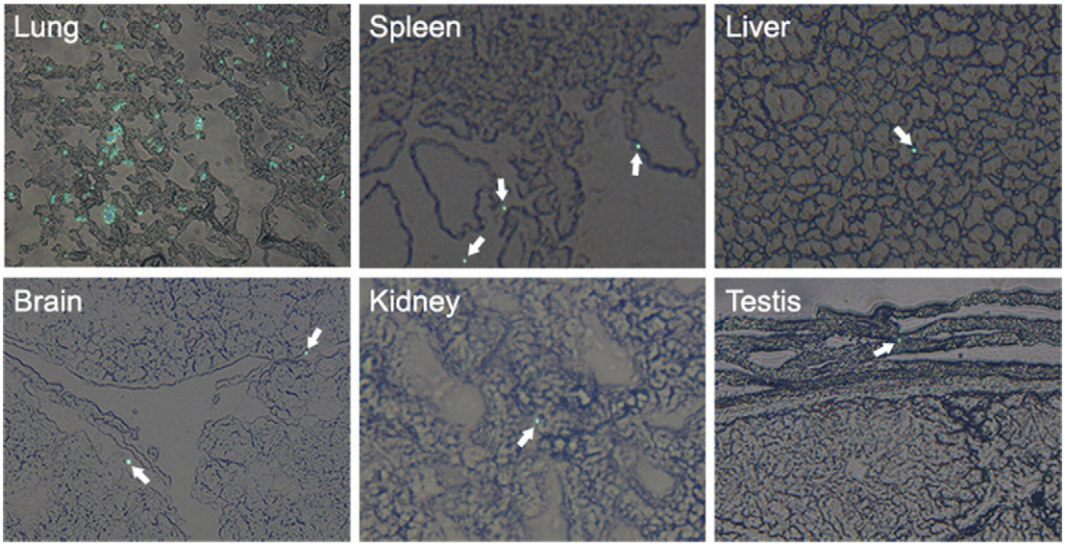

Fig. 1. Fine particle distribution *in vivo*. Fine particulate matter in the form of non-toxic, fluorescent carboxylate microspheres (1.75 μm in diameter) were administered by oropharyngeal aspiration for 6 weeks, and after sacrifice, tissues were sectioned in sliding microtome and examined with fluorescence microscopy. Fluorescent fine particles (indicated by arrows) were observed not only in the lung tissue but also in other organ tissues, including the brain, liver, kidneys, spleen, and testes (×200 magnification).

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