Editorial

Mechanism of ambient particulate matter and respiratory infections

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Air pollution is an important risk factor for respiratory infections. One of the main components of air pollution is particulate matter (PM), a mixture of solid particles and liquid droplets suspended in the air. Acute respiratory infections are one of the leading causes of death worldwide, therefore, it is critical to understand the mechanism by which PM increases the risk of infections (1).

PM air pollution increases the risk of respiratory infections

There are several proposed mechanisms by which PM can increase respiratory infections. First PM can serve as a carrier of bacteria (2). Once PM arrives into the airway lands on the airway surface liquid and can quickly adsorb and impair peptides and proteins responsible for the airway antimicrobial activity (3,4). Also, PM can decrease mucociliary transport (5), and dampen the expression of antimicrobial peptides such as defensins (6,7). Alveolar macrophages are also responsible for the clearance of particles. PM can inhibit the phagocytic ability of macrophages against pathogenic bacteria such as *Pneumococcus pneumoniae* (8). Furthermore, our group and Liu *et al.* observed that PM promotes bacterial growth of airway pathogens. One mechanism might involve iron in PM, serving as an important nutrient for bacterial growth (4,9).

Lung injury by disruption of the epithelial barriers by PM

PM is noxious to the lung causing acute lung injury by mechanisms independent of infection. For example, epidemiologic data showed that high PM exposure increased the risk of culture negative pneumonia (10). Potential mechanisms include: (I) PM is directly cytotoxic; (II) PM increases the number of airway inflammatory cells; (III) and PM increases airway inflammatory markers. Also, it has been proposed that endotoxin and transition metal are implicated in this process (11,12). However, one of the central hypothesis in PM induced lung injury is the production of reactive oxygen species (ROS) which result in oxidative stress and cell/tissue damage. The mechanisms by which PM causes oxidative stress are not completely understood but evidence support that generation of free radicals might come from the particle surface, release of transition metals from the particle such as iron that catalyzes Fenton-type reactions and generate hydroxyl radicals, and activation of inflammatory cells (13).

The airway and alveolar epithelial barriers are crucial for a healthy non-injured lung. An intact epithelial barrier prevents airborne pathogens from reaching the bloodstream and cause systemic damage. The barrier consists mainly of tight junctions (TJs), and adherens junctions (AJs). TJs are closer to the apical side and regulate paracellular transport of ions and other molecules, and AJs initiate and

maintain cell-cell adhesion. (14). PM can also disrupt the airway epithelial barrier by affecting both TJs and AJs. Our group and others demonstrated that PM-induced ROS disrupted TJs by internalization of occludin from the plasma membrane into endosomal compartments and dissociation from Zonula Occludens 1 (15,16). PM also affected TJ protein claudin 1 but not claudin 5 in bronchial epithelial cells (9,17). AJs are also affected by PM. Exposure of PM to bronchial epithelium caused lysosomal membrane permeabilization, oxidative stress, and lipid peroxidation. Epithelial cells underwent mesenchymal transition, including loss of cell morphology, and decreased E-cadherin expression (18).

PM impairs other mechanisms of epithelial integrity. For example, PM exposure decreased membrane septin-2 and cortical actin. Septin-2-actin interactions and actin rearrangement are required to reinforce the barrier in response to noxious stimuli, therefore, increasing paracellular permeability (19).

PM and invasive disease

Liu *et al.* elegantly demonstrated in an *in vivo* mouse model that PM can increase lung injury, bacterial lung burden, and consequently lead to Pseudomonas bacteremia in a concentration dependent manner (9). Other studies may confirm these finding in humans. In a time-stratified, case-crossover analyses of patients presenting to an emergency department with pneumonia, short term PM exposure was positively correlated with severe pneumonia, intensive care unit admissions, and inpatient mortality (20). Other studies have shown that sulfur dioxide (SO_2), a component of air pollution, was related to increased risk of invasive pneumococcal disease (21,22). In contrast, another study did not find an association between 30-day PM exposure levels and sepsis (23). However, they consider sepsis from all sources and not only the ones related to the lung infection. Furthermore, as PM has been shown to increase oxidative stress, Liu *et al.* used the antioxidant N-acetylcysteine (NAC) to reduce epithelial barrier disruption.

In conclusion, we consider that air pollution is a preventable cause of lung injury, respiratory infection, and probably increased the risk of bacteremia via increased bacterial growth and disruption of the airway epithelial barrier. Further studies in humans are required to confirm this association and explore the role of NAC to treat PM-induced lung injury.

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Footnote

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