A particulate matter: How environmental irritants and particulate matter increase sensitivity to bacterial respiratory tract infections. Commentary for "Underground railway particulate matter and susceptibility to pneumococcal infection"

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Respiratory tract infections (RTIs) are a leading cause of morbidity and mortality and deaths attributed to antibiotic resistant organisms are increasing. In 2019, close to 500 million cases of lower RTIs and approximately 2.5 million deaths occurred, making RTIs the 4th leading cause of morbidity and mortality worldwide.[1] Pneumonia caused by *Streptococcus pneumoniae* (the pneumococcus) is the leading cause of these infections and responsible for almost half of all deaths.

Asymptomatic colonization with respiratory bacterial pathogens, such as *S. pneumoniae*, is common in young children and other susceptible populations[2] and a prerequisite for subsequent infection. Colonization is initiated by pneumococcal adherence to a multitude of host receptor structures, of which platelet activating factor receptor (PAF-R) is a major one,[2] followed by organization into well-organized microbial communities (biofilms) that are inherently more tolerant to anti-bacterial agents and host immunity.[3] Infection is triggered upon changes to the host environment, where infection with respiratory viruses, changes in the microbiota composition, or exposure to environmental irritants or particles, can induce dissemination of bacteria from the nasopharynx to other body sites, such as the lung.[2,3]

Exposure to environmental irritants in the form of particles, such as air pollutants, diesel exhaust, passive smoking, welding fumes, inorganic dust, and chemicals have been shown to increase both colonization rates of respiratory pathogens[4] and the hospitalization rate and mortality from infectious pneumonia.[1,5,6] The risk of lobar pneumonia and pneumococcal pneumonia were even higher in these studies and the risk for mortality is long-lasting.[5] The mechanisms associated with this risk have not been extensively studied, although initial studies have proposed that some particulate matter (PM; traffic-related and welding fumes, respectively) lead to an increased adherence through the PAF-R.[7,8] Other studies have proposed a role for lung injury and poor bacterial clearance in animal models.[9]

In a recent issue of *eBioMedicine*, Myiashita et al.[10] expand on the current mechanistic information about particulate matter (PM) and its role in pneumococcal colonization and disease. The authors provide novel evidence for an effect of PM of size lower than 10 μm (PM_{10}) from the London underground on pneumococcal adherence to epithelial cells, associated with colonization, and their risk for inducing pneumococcal infection. The composition of PM from the underground platforms is somewhat different, containing increased levels of iron and other metallic oxides, rather than material from combustion of fossil fuels seen in the traffic-related PM and air pollution.

The authors first show that similar to traffic-associated PM_{10}, particulate matter from two London underground platforms induced expression of the PAF-R on epithelial cells from the respiratory tract with a resulting increase in both adherence to and internalization into these cells. The increased adherence could be abrogated by addition of a PAF-R inhibitor but also thorough inhibition of oxidation by N-acetyl cysteine, suggesting that oxidative stress was required for PAF-R expression and subsequent increased adherence.

Next, outbred mice were exposed intranasally to PM_{10} from the London underground or with vehicle alone. Treatment with London underground PM_{10} resulted in an increased PAF-R expression in the nasal epithelium as well as the presence of particles in the lungs based on histology. The mice were then challenged intranasally with pneumococci in such a way that vehicle alone-treated animals remained asymptomatic throughout the study period of 7 days. However, the mice exposed to PM_{10} from the London underground showed rapid dissemination of pneumococci into the

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lungs to cause pneumonia and subsequently into the bloodstream resulting in sepsis and significant mortality. Using the PAF-R inhibitor a significant reduction in blood counts of bacteria was observed, suggesting a role for the PAF-R in the disease process.

This research highlights the importance of environmental irritants and inhaled particulate matter in increasing the risk of respiratory disease and provides mechanistic information linking this risk to PAF-R receptor expression and oxidative stress. The use of primary nasal and bronchial epithelial cells for the *in vitro* adherence assays as well as the use of relevant animal models for pneumonia and sepsis significantly strengthens the findings of this work. However, a comparison with traffic-related PM or other environmental irritants in this model would have facilitated a generalization of the effects of particulate matter in pneumonia sensitivity. Similarly, blocking PAF-R not only in the bloodstream but also in the nasopharynx and lung would have provided a better understanding of the functional role of the receptor in disease progression. Thus, as the PAF-R has been shown to be involved in cellular adherence and increased infection risk induced by PM of various types (traffic-related, welding fumes and now from iron oxide rich air in the London underground), a more detailed understanding of how PAF-R expression is regulated by PMs, its association with oxidative stress and how this results in lung injury and bacterial dissemination into the bloodstream will be important future questions to address. In conclusion, this work provides a solid and mechanistic approach to better understand the major risk factor of particulate matter for increased sensitivity to respiratory tract infections.

Contributors

APH researched the topic and wrote the manuscript.

Declaration of interests

The authors have no conflict of interests to declare.

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