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PM2.5 induce NLRP3 inflammasome activation and Lung fibrosis

Tian Xia
University of California Los Angeles, USA

Airborne fine particulate matter (PM2.5) is known to cause respiratory inflammation such as chronic obstructive pulmonary disease and lung fibrosis. NLRP3 inflammasome activation has been implicated in these diseases; however, due to the complexity in PM2.5 compositions, it is difficult to differentiate the roles of the components in triggering this pathway. We collected eight real-life PM2.5 samples, 4 samples each before and after the beginning of district/public heating in Zhengzhou, a big city in northern China. Northern Chinese cities operate with a centrally controlled district/public heating system, with most cities cranking up the heat, mostly by coal, in mid-November. Using these PM2.5 samples, we compared their effects on NLRP3 inflammasome activation in vitro and lung fibrosis in vivo. In vitro assays showed that although the PM2.5 particles did not induce significant cytotoxicity at the dose range of 12.5 to 100 μg/mL, they induced potent TNF-α and IL-1β production in PMA differentiated THP-1 human macrophages and TGF-β1 production in BEAS-2B human bronchial epithelial cells. PM2.5 triggers NLRP3 inflammasome activation by inducing lysosomal damage and cathepsin B release, leading to IL-1β production. This was confirmed by using NLRP3- and ASC-deficient cells as well as a cathepsin B inhibitor, ca-074 ME. Interestingly, samples collected during the public heating induced higher IL-1β production than that were collected before the beginning of district/public heating. Administration of PM2.5 via oropharyngeal aspiration at 2 mg/kg induced significant TGF-β1 production in the bronchoalveolar lavage fluid and collagen deposition in the lung at 21 days post-exposure, suggesting PM2.5 has the potential to induce pulmonary fibrosis. The ranking of in vitro IL-1β production for all samples correlates well with the in vivo total cell count, TGF-β1 production, and collagen deposition in the lung. In summary, we demonstrate that PM2.5 is capable of inducing NLRP3 inflammasome activation, which triggers a series of cellular responses in the lung to induce lung fibrosis in vivo.

Biography

Tian Xia is a professor in Division of Nano Medicine, Department of Medicine at UCLA. His main research area is on studying particulate matter collected from air pollution, wildfire, electronic cigarettes, and marijuana as well as engineered nanoparticles and their effects to the lung. Research findings on particle-induced toxicity have been used for the safer design of nanomaterials for biomedical applications including adjuvant, particles that can induce immune tolerance for allergy and autoimmune diseases, and antimicrobials based on these structure-activity relationships. He is an elected Councillor in the Southern California Chapter of Society of Toxicology and he is Associate Editor in Nano toxicology, a flagship journal in the nanomaterial field. He has published over 150 articles with total citation of over 50,000 and H factor of 75 in Google Scholar and he was named Highly Cited Researcher in Chemistry three times by Web of Science of Clarivate Analytics.