How cadmium-induced inflammation increases the severity and mortality of lung infections

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A key mechanism of cadmium-linked inflammation that increases severity and mortality of lung infections has been described, offering a promising therapeutic target to limit lung injury and death.

This study, led by University of Alabama at Birmingham researchers Jennifer L. Larson-Casey, Ph.D., and A. Brent Carter, M.D., is based on an underserved, primarily African American community that is proposed as a National Priorities List area by the United States Environmental Protection Agency, due to heavy metals, including cadmium, in the soil and air that have caused lung disease. This North Birmingham, Alabama, community historically housed people who worked in mines, coke plants and heavy industries.

Air pollution from tiny particulate matter less than 2.5 microns in size is linked to respiratory infections, and this pollution is often tainted with cadmium, a poisonous heavy metal emitted from sources like smelters, coal fired plants, coke factories and forest fires. Environmental cadmium is associated with higher risk of death from flu and pneumonia, and it doubles the risk of lung disease; but the mechanism of cadmium's influence was not known.

Lower respiratory tract infections, including bacterial pneumonia, are the fourth-leading cause of death worldwide, with 120 million to 156 million cases and 1.4 million deaths a year. Streptococcus pneumoniae accounts for more than 55 percent of those deaths.

The UAB research, published in the journal *JCI Insight*, focused on bone marrow-derived macrophages that are recruited in large numbers to the lungs during infection to defend against respiratory pathogens. These immune cells are initially inflammatory to fight the pathogen, and then should become anti-inflammatory as the disease is controlled, so that continued inflammation does not damage the lung tissue. The Carter lab had previously shown that cadmium-mediated lung injury resulted in the persistence of the inflammatory, classically activated lung macrophages by inhibiting the nuclear localization of the transcription factor PPAR-gamma. Active PPAR-gamma is a negative regulator of the inflammatory response by inhibiting production of pro-inflammatory

cytokines and reactive oxygen species.

An enzyme called extracellular signal-regulated kinase, or ERK, has been known to play a pivotal role in lung inflammation and mouse models of lung injury; but how it acts was not known. In the present study, Larson-Casey, Carter and UAB colleagues used a mouse model to describe how cadmium or S. pneumoniae infection impairs the activation of PPAR-gamma in macrophages that were recruited to the lungs.

The exposure to cadmium or S. pneumoniae led to ERK activation in only the recruited macrophages. Activated ERK increased the post-translational phosphorylation of PPAR-gamma at its serine 112 amino acid. That change led to PPAR-gamma degradation, canceling its anti-inflammatory role.

The researchers also showed that the experimental drug BVD-523—an inhibitor of ERK that is currently in clinical testing to treat cancer—protected mice from lung injury after cadmium exposure or infection. They further found that human subjects, who live in industrial North Birmingham, had increased cadmium levels in their lung fluid. Those residents also showed PPAR-gamma inhibition, as compared to controls who live elsewhere, that was mediated, at least in part, by ERK activation.

"Although lung injury after respiratory infection is often unavoidable, identifying modifiable risk factors that predispose individuals to severe pneumonia is an unmet need," Carter said. "Our observations suggest that the regulation of PPAR-gamma in monocyte-derived macrophages is a novel target to protect against the severity of lower respiratory tract infections secondary to lung injury mediated by air pollution."

In the mouse model, mice were instilled intratracheally with cadmium

chloride or saline, and S. pneumoniae was given five days later. All mice that were given just saline or cadmium alone were alive 15 days later; but only about 80 percent of the mice given saline and S. pneumoniae survived, and less than half the mice given both cadmium and S. pneumoniae survived. Cadmium-exposed mice had increased numbers of macrophage cells in the lungs, and that number increased further after the cadmium-exposed mice were given S. pneumoniae. Both cadmium- and S. pneumoniae-exposed mice showed lung injury, and the lung injury was significantly greater in cadmium-exposed mice that were infected with S. pneumoniae.

In other details, the UAB researchers used single-cell RNA sequencing of cells from the lung to show that the PPAR-gamma gene was expressed predominantly in macrophage cells rather than 13 other cell types detected from the lung. That gene expression was about the same in macrophages exposed to cadmium or S. pneumoniae alone, or to cadmium and S. pneumoniae together.

The researchers also found that cadmium and S. pneumoniae increased the production of pro-inflammatory TNF-alpha and interleukin-6, and decreased production of the anti-inflammatory interleukin-10. Activated PPAR-gamma is known to inhibit production of TNF-alpha and interleukin-6, and it increases expression of interleukin-10.

Carter is a professor and Larson-Casey an assistant professor in the Division of Pulmonary, Allergy and Critical Care Medicine in the UAB Department of Medicine.

Co-authors with Carter and Larson-Casey in the study, "Impaired PPARɣ activation by cadmium exacerbates infection-induced lung injury," are Shanrun Liu, UAB Department of Medicine, Division of Clinical Immunology and Rheumatology; Jennifer M. Pyles and Suzanne E. Lapi, UAB Department of Radiology; Komal Saleem and Veena B.

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More information: Jennifer L. Larson-Casey et al, Impaired PPARγ activation by cadmium exacerbates infection-induced lung injury, *JCI Insight* (2023). DOI: 10.1172/jci.insight.166608