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Team finds cellular structural molecule can be toxic: Makes pneumonia worse

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A structural molecule and the cellular pump that regulates its levels influence the severity of pneumonia and could provide new ways of treating the lung infection, which is a leading cause of hospitalization and death, according to scientists at the University of Pittsburgh and the University of Iowa. Their findings are available online in *Nature Medicine*.

Despite decades of research, there has been little new information on what biological mechanisms make bacterial pneumonia get worse, said senior author Rama K. Mallampalli, M.D., a professor in the Acute Lung Injury Center of Excellence, University of Pittsburgh School of Medicine, and pulmonary division chief at the VA Pittsburgh Healthcare System.

"Our study reveals some of the molecular steps that can lead to lung injury after infection and shows us new avenues for pneumonia therapy that don't have to target bacteria, as antibiotics do," he said.

The researchers found that lung fluid from humans and mice with pneumonia contains abnormally high levels of cardiolipin, a structural molecule that is typically found in the membranes of energy-making mitochondria. A carrier protein called Atp8b1 transports the molecule from the lung fluid into the cell, acting as a pump that regulates cardiolipin levels.

Infection leads to the death of cells, and that releases cellular

components, including cardiolipin, into the surrounding fluid, Dr. Mallampalli explained. The carrier protein can become overwhelmed, allowing cardiolipin levels to climb. The excess cardiolipin disrupts the function of surfactant, a lubricant that is necessary for the proper expansion and contraction of the lungs during breathing, which can lead to more tissue damage.

When cardiolipin was administered to mice, their lung function became impaired and their lung tissue became damaged akin to what is seen with pneumonia. Similarly, mice with a mutation in the carrier protein gene were more likely to have severe pneumonia.

"This research was inspired by the knowledge that some people have a mutation in this protein, a condition called Byler's disease, and they are more likely to get pneumonia," Dr. Mallampalli noted.

In other experiments, mice with the gene mutation and pneumonia were treated with an engineered protein fragment that attached to the cardiolipin binding site, preventing the molecule from interacting with surfactant and ultimately reducing lung injury and improving survival.

"A similar strategy might work in people and could be a very useful option at a time when we have bacterial strains that are resistant to multiple antibiotics," said Mark Gladwin, M.D., chief of the Division of Pulmonary, Allergy and Critical Care Medicine, Pitt School of Medicine.

Dr. Mallampalli and his colleagues are now working on ways to deliver proteins into the lung that tightly bind cardiolipin with the goal of translating this approach for testing in pneumonia patients.

Provided by University of Pittsburgh