Researchers discover signaling pathway crucial to acute lung injury

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Researchers at National Jewish Health have discovered a signaling pathway that is crucial to the devastating effects of acute lung injury (ALI). The data, obtained from cells, animals and ALI patients, suggest several potential therapeutic targets. Experimental blockade of one of the targets significantly reduced flooding of the lungs that is the hallmark of ALI.

"Acute lung injury is a devastating disease, with 40 percent mortality and no beneficial therapies," said first author James Finigan, MD, Assistant Professor of Medicine at National Jewish Health. "Our study identifies several promising targets for therapy, including HER2, which is already targeted by existing breast-cancer medications."

About 200,000 people in the United States suffer acute lung injury (ALI) every year. It is caused by either direct injury to the lungs or as a result of other conditions, often pneumonia or systemic infection. In ALI, large amounts of protein-rich fluid flow from the capillaries into the lungs, leading to flooding of the airspaces and reduced ability to deliver oxygen to the blood. Severe ALI is often referred to as acute respiratory distress syndrome or ARDS. Currently there is no approved therapy for the disease. Care of ALI patients is supportive only, in which doctors try to maintain blood-oxygen levels. Approximately 40 percent of patients with ALI, or 90,000 people per year in the US, die.

Dr. Finigan and his colleagues had previously shown that HER2, a receptor involved in cell development and growth, participates in

recovery of mice from chemically-induced lung injury. They hypothesized that it may also play a role in the earlier inflammatory phase of lung injury, which resembles ALI in mice. The researchers also knew that the inflammatory molecule interleukin-1β is a central player in ALI and the permeability of capillaries.

In a series of experiments in cell culture and animal models they connected interleukin-1β to HER2, which triggers a cascade of signals within epithelial cells. Those signals cause blood vessel walls to become permeable and allow the flood of fluid into the lung airspaces. When researchers blocked production of NRG-1, one of the molecules in the signaling pathway, they reduced flow of molecules through a cellular barrier by 52 percent.

The researches then examined lung fluid from ALI patients, and found heightened levels of NRG-1, adding clinical evidence to their data supporting an important role for this pathway. They published their findings January 19 in the online version of the Journal of Biological Chemistry

Two existing medications, herceptin and tykerb, already target a malfunctioning HER2 in some cases of breast-cancer. Several medications targeting ADAM17 are also in development.

"Our work suggests several very promising avenues of research that may finally bring help to ALI patients," said senior author Jeffrey Kern, MD, Professor of Medicine at National Jewish Health.

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