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Protein could offer target to reduce lung damage from smoking-caused emphysema

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An international research team has identified a lung protein that appears to play a key role in smoking-related emphysema and have crafted an antibody to block its activity, Indiana University scientists reported.

The research, conducted in mice, suggests that the protein, a cytokine named EMAPII, could provide a target for drugs to treat emphysema, said Irina Petrache, M.D., associate professor of medicine at the Indiana University School of Medicine. The research was posted online May 16 for the June edition of *The* Journal of Clinical Investigation.

Emphysema, a form of chronic obstructive pulmonary disease (COPD) that affects nearly 5 million people in the U.S alone, is caused by the destruction of cells that transfer oxygen from the lungs to the blood, along with inflammation in the lungs. Cigarette smoking is the most common cause of emphysema.

The cytokine EMAPII – a type of cell-signaling molecule – is normally part of the process of early lung development. Research had previously found that EMAPII could cause the death of cells that line blood vessels – endothelial cells – and inflammation, but it had not been identified as the molecular culprit at work when cigarette smoking inflicted its damage on the lungs.

"The fact that we could have a single target affecting two major processes made us excited about looking for it in response to smoking," said Dr. Petrache, the Floyd and Reba Smith Investigator in Respiratory

Disease at IU.

When the researchers induced emphysema in mice exposed to cigarette smoke, tests showed the mice had elevated levels of the EMAPII cytokine. In other tests, the scientists also found elevated levels of the cytokine in the lungs of patients with COPD.

The researchers also found that the cell death caused by the EMAPII resulted in the release of enzymes that cause more production of EMAPII, causing a vicious cycle of elevated cytokine levels and more cell death.

Members of the research team, led by first author Matthias Clauss, Ph.D., IU associate research professor of cellular and integrative physiology, created an antibody designed to specifically target EMAPII and block its activity. The mice received an inhaled version of the antibody during their third month of smoking. They then were exposed to a fourth month of smoking without the treatment.

The mice receiving the treatment had significantly less cell death and inflammation and improved lung function compared to the smoking mice who did not receive the treatment. Moreover the benefits to the treated mice continued even after the treatment stopped.

Next steps include optimizing the duration of the antibody treatments to determine whether they continue to have an effect after the animals have stopped smoking, she said. Plans also call for work to measure levels of the cytokine in large numbers of human emphysema and COPD patients to determine whether it can be used as a biomarker to measure the presence, severity or type of lung disease.

Considerable research work remains before an EMAPII antibody might be ready for testing in humans, Dr. Petrache said.

Provided by Indiana University School of Medicine