A promising target to treat asthma

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An enzyme known for its role in heart disease may well be a promising target to treat asthma. Researchers from the University of Iowa have found that the enzyme, called CaMKII, is linked to the harmful effects of oxidation in the respiratory tract, triggering asthmatic symptoms. The finding could lead to the development of a drug that would target the CaMKII enzyme, the researchers say.

Asthma affects billions of people worldwide. In the United States, 8.5 percent of the population has asthma, which causes 3,000 deaths and more than $56 billion annually in medical and lost work costs, according to the federal Centers for Disease Control and Prevention. Despite its toll on health and productivity, treatment options remain confined to steroids, which have harmful, even life-threatening, side effects for those with severe cases.

Current treatments don't work well, noted Mark Anderson, professor and chair in internal medicine at the UI and a co-corresponding author on the paper, published July 24 in the journal *Science Translational Medicine*.

"It's a kind of an epidemic without a clear, therapeutic option," Anderson says. "The take-home message is that inhibiting CaMKII appears to be an effective anti-oxidant strategy for treating allergic asthma."

Anderson and co-corresponding author Isabella Grumbach knew from previous work that the CaMKII enzyme played a role in the oxidation of heart muscle cells, which can lead to heart disease and heart attacks. The

scientists surmised the same enzyme may affect oxidation in the respiratory system as well.

The team first tested the enzyme in airway muscle cells, but to little effect. They then tried to block the enzyme in the airway lining (epithelial) cells. They noticed that mice with the blocked enzyme had less oxidized CaMKII, no airway muscle constriction and no asthma symptoms. Similarly, mice without the blocked enzyme showed high "oxidative stress," meaning lots of oxidized enzymes in the epithelial cells, a constricted airway and asthma symptoms.

"[The study] suggests that these airway lining cells are really important for asthma, and they're important because of the oxidative properties of CaMKII," says Anderson, whose primary appointment is in the Carver College of Medicine. "This is completely new and could meet a hunger for new asthma treatments. Here may be a new pathway to treat asthma."

"Ten years ago, not much was known about what CaMKII does outside of nerve cells and muscle cells in the heart," says Grumbach, associate professor in internal medicine at the UI. "My lab has worked on investigating its function mainly in blood vessels with the long-term goal to use blockers of CaMKII to treat common diseases. We are constantly finding that CaMKII is interesting and important."

The researchers also took tissue samples from the airways of patients with asthma. True to their hypothesis, they found more oxidized enzymes in those patients than in healthy individuals. Taking a step further, the team found that mild asthma patients who inhaled an allergen had a spike in oxidized CaMKII in the epithelial cells just a day later.

"We have this very compelling association," Anderson says, adding that

more studies in patients are needed to validate the approach.

The researchers also plan to investigate inhaled drugs that could block the oxidation of theCaMKII enzyme, for treating heart disease and asthma. Anderson has a patent and is involved in a company, Allosteros Therapeutics, which is seeking to develop such a drug.

Provided by University of Iowa