Discovery could lead to new therapies for asthma, COPD

January 27 2011

Researchers have proved that a single "master switch" enzyme, known as aldose reductase, is key in producing excess mucous that clogs the airways of people with asthma and chronic obstructive pulmonary disease (COPD). The enzyme's action can be blocked by drugs whose safety has been shown in clinical trials for other diseases – a discovery that could improve therapies for the 510 million people worldwide suffering from asthma and COPD.

The findings are from a University of Texas Medical Branch at Galveston study published in the online journal *PLoS One*.

Using cell culture and laboratory mouse experiments, the researchers showed that the enzyme, aldose reductase, is essential to a process known as goblet cell metaplasia that is seen in both asthma and COPD. In goblet cell metaplasia, exposure to allergens such as pollen, mold and dust mites initiates a series of biochemical reactions that causes the cells that line the air passages of the lungs to change from their normal state into so-called "goblet cells," which produce substantial amounts of excess mucus. Healthy individuals' lungs contain very few goblet cells, but patients who die from asthma — an estimated 5,000 people annually — have significantly higher numbers of these cells.

"Aldose reductase is key to a whole range of inflammation disorders, so it comes as no surprise that it should be crucial to the inflammatory processes that drive disease in asthma and COPD," said UTMB Health biochemistry and molecular biology professor Satish Srivastava, senior

author of the paper. "The discovery that aldose reductase regulates mucus production and goblet cell metaplasia makes inhibition of this enzyme an attractive therapeutic option to reduce mucus-related airway obstructive diseases — and for the first time gives us a real chance to alter the course of the underlying disease in asthma and COPD."

According to Srivastava, aldose reductase inhibitors have a number of potential advantages over current therapies for asthma and COPD.

"Existing therapies for airway obstructive diseases provide relief by preventing allergic airway inflammation, but none of these drugs specifically address the problem of excessive mucus production; further, there is no convincing evidence that current therapies significantly reduce mortality associated with chronic asthma and COPD," Srivastava said. "Also, aldose reductase inhibitors can be given orally, unlike current inhaler-based treatments, so medication compliance could be better. And finally they can provide an alternative to steroid treatment for patients who either can't take steroids or find that steroids have no effect on their disease."

The next step, Srivastava said, is clinical trials of the drugs as a therapy for asthma and COPD — a process that should be expedited since aldose reductase inhibitors have already undergone Phase III clinical trials for diabetic neuropathy. The UTMB Health Center for Technology Development views Srivastava's research as so promising that it has applied for patents to cover their use as potential treatments for asthma, COPD and other inflammation-related disorders.

"Working closely with Professor Srivastava and other UTMB faculty, the next step is to prove the safety and efficacy of aldose reductase inhibitors for these conditions and develop them to improve the health of millions of people," said Jason Abair, associate vice president of the center. "We are looking forward to identifying appropriate partners in

industry to help us reach this goal."

Provided by University of Texas Medical Branch at Galveston