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Team looks to experimental cancer drug to dampen bronchospasm

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UC San Francisco researchers have developed a new treatment strategy for asthma that acts in a completely different way than standard drugs that have been used for decades as "rescue" medicines.

The new type of drug treatment, which they tested in asthmatic lab mice and in tissue from cadaveric human lungs, appears to have an add-in effect to drug mainstays, like albuterol, and might potentially save lives, according to authors of the study, published online on Dec. 5, 2016, in the *Journal of Clinical Investigation*.

One in 12 adults has asthma, according to the Centers for Disease Control and Prevention. In 2009, asthma was found to be responsible for close to 500,000 hospitalizations, 1.9 million emergency department visits and 3,388 deaths.

"Our hope is that this will be a new, effective drug treatment strategy for dampening exaggerated airway responsiveness in asthma, even under circumstances in which existing interventions are ineffective," said Aparna Sundaram, MD, an assistant professor of medicine at UCSF and the lead author of the study.

The drug used in the experiments on mice had previously been tested in phase II clinical trials as a way to block blood-vessel growth within tumors. The UCSF researchers have begun working with pharmaceutical scientists on campus to develop more potent drugs.

Sundaram probed the intricacies of a biological mechanism that generates tension during "bronchospasm," the prolonged contraction of the smooth muscle that surrounds lung airways that occurs during an asthma attack, which results in narrowing of the air passages and oxygen deprivation.

Sundaram identified proteins that cause airway muscle cells to stick to the underlying cellular scaffolding and transmit the force generated by muscle contraction, and she found that she could disrupt these attachments and thereby decrease muscle contraction and relieve constriction of the airways.

'Little progress' for therapies that target muscle

The underlying cause of hyper-responsiveness of airway smooth muscle in asthma is an abnormal immune response. Steroid drugs have long been used to quiet the immune system in asthmatics. Newer drugs more specifically target immune responses that underlie the development of asthma. But these drugs act slowly and they do not work for all patients. Faster-acting rescue medicines, such as albuterol, a bronchodilator developed a half-century ago, target the contracting muscle that is the immediate cause of bronchospasm in asthma, allowing constricted airways to expand again. These remain standard treatment for asthma attacks.

"There has been very little progress in terms of therapies that target muscle," Sundaram said. In part, this is because the biological mechanism targeted by standard therapies plays a crucial role in cellular processes throughout the body, and efforts to improve old drug standbys have resulted in experimental drugs that often fail due to intolerable side effects, she said.

These standard therapies affect the movement of muscle filaments that

occurs during muscle contraction as a result of the interaction of the proteins actin and myosin, through well-understood mechanisms that have been described in myriad textbooks for generations.

"What is most exciting about this new work is that we showed we can modulate tension transmission in a way that does not depend on modulating actin and myosin," Sundaram said.

Sundaram designed the experiments and wrote the newly published study with senior author Dean Sheppard, MD, professor of medicine and Chief of the Pulmonary, Critical Care, Allergy and Sleep Division at UCSF.

Drug found to enhance airway-relaxing effect of standard treatment

Sundaram homed in on a specific member of a family of molecules known as integrins, a type of cell protein that spans the cell's outer membrane and plays a role in tethering cells to the underlying matrix of scaffolding proteins, but which also engages in bi-directional signaling to reshape this extracellular matrix in response to changing conditions. Just as there are many integrins, there also are a variety of distinct structural proteins that are incorporated within the extracellular matrix.

Through a series of experiments, Sundaram eventually determined that muscle tension in airway smooth muscle was largely determined by the attachment of a specific cellular integrin, called α5β1, to a specific scaffolding protein, called fibronectin.

In experiments on airway tissue from cadaveric human lungs, the UCSF researchers found that disrupting the matrix surrounding cells impaired contraction in response to administration of a type of asthma-inducing "cytokine" molecule that is secreted by immune cells. In addition, when the researchers administered the cancer drug to inhibit α5β1 directly into

the airways of mice, it also dampened the airway hyper-responsiveness caused by allergen challenge. Furthermore, using the drug to block α5β1 in mouse trachea also enhanced the airway-relaxing effect of the standard bronchodilator isoproterenol.

"Prevention of asthma through new biologic strategies that target the immune system is important, but regardless of an asthmatic patient's immune system characteristics, the treatment of bronchospasm in asthma will always be required," Sundaram said.

More information: Aparna Sundaram et al. Targeting integrin α5β1 ameliorates severe airway hyperresponsiveness in experimental asthma, *Journal of Clinical Investigation* (2016). DOI: 10.1172/JCI88555

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