Breathing easy: Biochemists offer first 3-D model of asthma-causing inflammation enzyme

February 2 2011

Inflammation is a healthy response in reaction to potentially harmful presences in the body. But when it starts in the lungs and builds up to a full-fledged asthma attack, it can be downright deadly. Chronic inflammation has been directly associated with heart disease and other physical ailments.

But LSU graduate student Nathanial Gilbert and Professor of Biological Sciences Marcia Newcomer, together with Associate Professor Sue Bartlett, have developed the first 3-D model of Human 5-Lipoxygenase, or 5-LOX, the molecule responsible for creating inflammatory compounds that provoke asthma. This model will serve as a target for the design of new, more effective asthma medication.

Their research was printed in *Science* on Jan. 14 and was the subject of an article in *Science Translational Medicine*.

"This molecule is responsible for starting the synthesis of compounds referred to as 'signaling molecules,' which cause inflammation," said Newcomer. "If we can look at this molecule in closer detail than we have previously been able to do so, then that will allow for the development of better asthma medications that are able to stop an attack more effectively."

Prior to their development, scientists had been unable to study this

molecule in detail because of its transient nature.

"It was really hard to work with," said Newcomer. "5-LOX is unstable. Before you could start your experiments, the enzyme would self-destruct."

The enzyme has an "Achilles' heel," which makes it prone to destabilization. But after working with another, hardier enzyme, Newcomer and her team were able to target the weak area, then bioengineer a replacement. Once they were able to apply this technique to 5-LOX, they were able to identify the complex pathway of how the molecule shuts itself off. The resulting molecule, complete with the engineered "heel," was then tested to verify that the output was precisely the same as its unaltered counterpart, and it was.

"Once we confirmed that it still produced the same thing, we essentially had a machine that makes the inflammatory compound but is stable enough so that we can study it," said Newcomer. "From there, we were able to determine the 3-D structure."

A better understanding of the structure allows for more effective targeting of the enzyme. This, in turn, should lead to fewer side-effects from drugs treating asthma.

"This work has so many implications," said Newcomer. "Our model is an important step toward actual application. The next step is to determine the structure of the machine in action with the substrates it operates on, but we cannot do this in the presence oxygen. This situation requires us to perform research in an oxygen-free environment. That's a tricky proposition, but this has really opened up the possibilities."

All preliminary work was done at CAMD, LSU's Center for Advanced Microstructures and Devices, by Gilbert, who is pursuing his Ph.D.

"We're excited to be a part of this big step forward in understanding 5-LOX and inflammation," said Newcomer.

Provided by Louisiana State University