Preventing or reversing inflammation after heart attack, stroke may require 2-pronged approach

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Researchers at Albany Medical College are releasing results of a study this week that they say will help refocus the search for new drug targets aimed at preventing or reversing the devastating tissue inflammation that results after heart attack and stroke.

In the March 5 issue of the Journal of Biological Chemistry, lead author Alejandro P. Adam and his colleagues at the college's Center for Cardiovascular Science are reporting that vascular cells' ability to properly regulate fluid movement is not necessarily affected solely by the activity of an enzyme that for years has been in the crosshairs of scientists and pharmaceutical developers.

"Learning the mechanisms of inflammation is a key step in the development of new and better therapies to improve the outcome of widespread pathologies, such as stroke, heart attack, septic shock and pulmonary edema," said Adam, a postdoctoral fellow at the cardiovascular center. "To determine which are the best targets for treatment, we need to understand exactly what role each molecule is playing in the regulation of the vessel walls, and we found that the enzyme Src may be needed to get changes in barrier function but by itself is not sufficient."

Blood vessels, which form a tight barrier between blood and the surrounding tissues, are composed of endothelial cells that act as

gatekeepers, controlling how, when and where molecules of water, solutes and blood cells pass through them into the body's tissues.

Previous studies have shown blocking the enzyme Src altered the structure of a protein known to hold the endothelial cells together, thus, keeping their barriers tight and limiting tissue damage caused by fluid accumulation, or edema.

"We found that Src indeed adds several phosphates to this protein, but this addition of the phosphates did not alter barrier function of the endothelial cells," explained professor Peter A. Vincent, who oversaw the team's research. "These findings suggest other pathways are needed for Src to change permeability and open the door to future studies to determine what these other signals are."

There are many "adhesion molecules" involved in holding endothelial cells together and many signaling molecules that tell the adhesion molecules when to hold onto or release each other. Vincent's team is moving forward with what he calls a "two-hit model" - the idea that endothelial cells require two different signals to open up cell-cell connections and allow the passage of fluids.

"Many factors lead to a complex array of signals inside the endothelial cells to promote this loss of barrier function," Adam said. "A two-hit model would explain much better than a single-hit model the regulation of the vascular permeability. On the pharmacological side, it would allow us to propose other drug targets to prevent or reverse inflammation and edema."

By being named a "Paper of the Week" by the *Journal of Biological Chemistry*, the article by Adam and Vincent, graduate student Amy L. Sharenko and associate professor Kevin Pumiglia has been categorized in the top 1 percent of papers reviewed by the journal's editorial board in

terms of significance and overall importance.

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