Scientists Identify Novel Way to Prevent Cardiac Fibrosis

April 22, 2008

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In a study that points to a new strategy for preventing or possibly reversing fibrosis - the scarring that can lead to organ and tissue damage - researchers at the University of California, San Diego School of Medicine have determined that a molecule called Epac (Exchange protein activated by cAMP1), plays a key role in integrating the body's pro- and anti-fibrotic response. The research will be published in the online edition of the *Proceedings of the National Academy of Science (PNAS)* the week of April 21.

Inflammation is the body's response to injury in tissues, prompting healing that leads to scars, whether on the skin, or in organs such as the heart, liver or lungs. Such scarring has beneficial properties, but there's also the risk of excessive scarring, or tissue fibrosis, that can lead to organ damage and loss of function.

The UC San Diego researchers looked at cardiac fibrosis, which can occur in patients who have suffered an infection of the heart muscle or a heart attack. Such fibrosis causes the heart to stiffen so that it cannot adequately fill with blood and then empty itself, a condition known as diastolic dysfunction.

"An old heart is a stiff heart and some injured hearts are stiff as well," said Paul A. Insel, M.D., UCSD professor of pharmacology and medicine, and principal investigator of the study. "Much of the decrease in cardiovascular function that occurs with aging or, in some patients after a heart attack, can be explained by fibrosis. We wondered: What is responsible for excessive fibrosis? Is there a way to decrease or possibly reverse it?"

It was previously known that a messenger molecule inside of cells, called cAMP, can block fibrosis in the heart. Insel and colleagues explored the mechanism leading to the anti-fibrotic effect, and discovered that the Epac molecule mediates cAMP actions that are involved in cardiac fibrosis. Epac also helps regulate other proteins that contribute to cell death, division, migration and motility.

"We found that Epac activation exerts a very important impact on the function of fibroblasts, the cells responsible for making and secreting collagen and thus for producing tissue fibrosis," said Insel. "Most exciting was our discovery that multiple agents that promote fibrosis decrease the expression and activation of Epac in fibroblasts from several different tissues - not only in the heart but also in lung, liver and skin."

The researchers found decreased Epac expression in regions near the site of heart attacks in rats and mice. In addition, they found that by increasing Epac expression, they were able to block the ability of agents to promote fibrosis.

Because increases in cAMP levels can decrease the function of fibroblasts after cell injury, stimulation of the cAMP signaling pathway is a potential way to blunt fibrosis. Increases in Epac expression may provide a novel way to do this, especially in cardiac fibroblasts, Insel added. To test this possibility, the scientists treated fibroblast cells in culture in ways that altered Epac expression, increasing Epac expression using an adenoviral construct.

"Using this strategy to overexpress Epac, we produced an anti-fibrotic effect, thereby inhibiting the synthesis of collagen" said Insel. "Other experiments showed that decreasing Epac expression favored fibrosis; in other words, were pro-fibrotic. Overall, the results show the central role of Epac in determining pro-fibrotic and anti-fibrotic response."

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The study supported by grants from National Institutes of Health, the Ellison Medical Foundation and the American Heart Association.

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