Losing protein helps heart recover, scientists say

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When a person has a heart attack, portions of the heart muscle die in the next several days or even weeks if deprived of oxygen for long enough. The recovering heart slowly remodels itself, even fostering the growth of new blood vessels, in an attempt to regain some of its former function. But all too often, the remodeling is actually harmful, and the damaged heart is on an inevitable downward slide to heart failure.

Now, scientists at the Center for Translational Medicine at Temple University School of Medicine have identified a key target they hope will help stave off the potentially harmful effects of remodeling. They have shown that by turning off the activity of a protein, GSK-3α, in the heart cells of mice that have had a heart attack, they can prevent heart remodeling, preserve heart function and significantly improve survival.

Their findings offer new insights into processes underlying remodeling, and perhaps to eventual strategies against heart failure. They reported their results November 5, 2012, at the Late-Breaking Basic Science Oral Session at the American Heart Association's Scientific Sessions 2012 in Los Angeles.

"We need to find ways to prevent and slow down remodeling of the heart after a heart attack – that's the Holy Grail of heart failure," said senior author Thomas Force, MD, Professor of Medicine and Clinical Director of Temple's Center for Translational Medicine. "Our findings are important steps in understanding some of the mechanisms at play in remodeling, and hold promise to eventually lead to new interventions and

perhaps even help prevent heart failure."

Focusing on GSK-3α

The protein enzyme GSK3 – glycogen synthase kinase 3 – plays a key part in many cellular processes and diseases. It has two forms, GSK-3α and GSK-3β, both of which have particularly important roles in heart disease. While the exact role of GSK-3α in heart cells has been unclear, studies indicate that it is important in regulating the heart's growth, ability to contract, and its expansion in size associated with heart disease and heart failure.

To find out the role of GSK-3α specifically in heart cells, Dr. Force, first author Firdos Ahmad, PhD, a postdoctoral fellow in the Department of Pharmacology and the Center for Translational Medicine and their co-workers compared mice with normal levels of the protein in their heart cells to mice with heart cells lacking a working GSK-3α. All of the mice in both groups experienced the equivalent of a heart attack. The researchers found that the mice missing the protein in their heart cells had significantly better survival (100 percent) over the next several days or week compared to the normal mice (75 percent survival).

After two weeks, they found that both groups had comparable increases in heart chamber size and accompanying reductions in the heart's left ventricle's ability to pump blood effectively. Yet, at four weeks after a heart attack, the two groups began to separate, with the mice without GSK-3α in their heart cells showing significantly better preserved heart function. By that time, however, the left ventricle in the non-GSK-3α mice showed a much greater reduction in size than was seen in the hearts of the mice with the GSK-3α protein. As a result, the hearts of the mice without GSK-3α showed greater pumping ability.

Eight weeks after experiencing a heart attack, 92 percent of the mice

lacking GSK-3α were still alive compared to only 71 percent of the normal mice.

"During remodeling, the heart's ventricles dilate and the ventricle function deteriorates," explained Dr. Force. "Remodeling after a heart attack is the major cause of heart failure in the United States. We'd like to prevent this by finding something to modulate the process."

Surprising Results

The researchers were surprised by the results, since earlier studies have found the opposite – that is, heart attack-induced mice that lack the GSK-3α protein in all of the body's cells have an increased rate of mortality, along with a less effectively functioning heart.

"These results are very unexpected," Dr. Force said. "We think that since turning off GSK-3α activity in all of the cells causes so many cardiac problems, there must be other processes at work there that are causing these differences from what we see when the protein's activity is halted in only heart cells. We'd like to find the mechanisms involved in this."

"The results also suggest that inhibiting both GSK forms might be a way of controlling post-heart attack remodeling and retain heart function," Dr. Ahmad noted, pointing to earlier research showing that inhibiting GSK-3β was also beneficial.

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