The key to repairing heart tissue damage after a heart attack or cardiac surgery may be to inhibit an enzyme known to play a role in congestive heart failure, says a Duke University researcher. His latest studies, reported this week at the New York Academy of Sciences, show that blocking the enzyme beta-adrenergic receptor kinase (bARK) reduces damage to left ventricular function after heart attack.

This bolsters work published a year ago, which suggested the same protective effect in hearts that stop and then resume beating. The Duke team hopes that the findings may ultimately lead to new enzyme-blocking drugs that could be given either after heart attack or heart surgery, or prophylactically in people at high risk for heart attacks.

Walter Koch and his team used gene therapy on rabbits to inhibit bARK, which is present in failing hearts typically at three to five times normal levels. Using a modified adenovirus as a vector, Koch introduced the gene for bARKct, which blocks bARK, into the rabbits' heart cells. At the same time, the investigators also placed a loop around one of the arteries before closing the chest and allowing the animals to recover. Later, they triggered a heart attack by pulling on the loop, and then measured heart functions for 45 minutes.

The bARK-inhibited hearts showed "significantly attenuated" ventricular function compared to that usually observed under such conditions, said Koch. The results are as yet unpublished.

The experiment builds upon the team's previous work, which showed first that gene therapy with bARKct could heal damaged tissue even three weeks after a heart attack, and then showed that bARKct hearts were better able to withstand the damage associated with cold cardioplegic arrest, the customary method of stopping hearts during bypass operations and harvesting and transport before heart transplant.

Koch and his collaborators "have now amassed a convincing body of evidence" to support the therapeutic strategy of targeting bARK in naturally occurring heart failure, says Gerald Dorn, who is director of cardiology at the University of Cincinnati.

At the New York meeting, Koch also presented unpublished results from his lab's microarray research on DNA from mice that had been genetically engineered to have heart failure, which bolster the rabbit experiments. "We were able to blindly predict the difference between the normal and heart failure mouse based solely on their gene expression," says Burns Blaxall, who conducted the experiment.

Earlier experiments showed that cross-breeding mice prone to heart failure with mice that expressed bARKct "rescued" the offspring; the heart-failure phenotype was prevented. In microarray experiment, Blaxall was able to discern genetic differences between heart failure mice and "rescued" mice.

Dorn says this suggests "bARKct is somehow directly..."
addressing the causative factor" and "acting at the genetic level to prevent some of the critical molecular perturbations of heart failure, not just generally enhancing myocardial function."

The Duke experiments show potential for either gene therapy with bARKct, Dorn told BioMedNet News, or for creating an analogous drug.

"The precise mechanisms of how bARKct prevents heart failure and enhances post-ischemic myocardial function will no doubt be worked out in the coming months and years," Dorn predicted. Whether the work is relevant to humans remains to be seen; Koch is planning clinical trials of the gene-therapy approach, starting with end-stage heart failure patients.

The Duke team feels the gene therapy approach is not the most practical for humans. They are hoping to encourage drug companies to search for small-molecule bARK inhibitors. Koch says a number of biotech firms are already looking into receptor kinases.

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