MedicalXpress

# Gene therapy reprograms scar tissue in damaged hearts into healthy heart muscle

January 4 2013

A cocktail of three specific genes can reprogram cells in the scars caused by heart attacks into functioning muscle cells, and the addition of a gene that stimulates the growth of blood vessels enhances that effect, said researchers from Weill Cornell Medical College, Baylor College of Medicine and Stony Brook University Medical Center in a report that appears online in the *Journal of the American Heart Association*.

"The idea of reprogramming scar tissue in the heart into functioning heart muscle was exciting," said Dr. Todd K. Rosengart, chair of the Michael E. DeBakey Department of Surgery at BCM and the report's corresponding author. "The theory is that if you have a big heart attack, your doctor can just inject these three genes into the scar tissue during surgery and change it back into heart muscle. However, in these animal studies, we found that even the effect is enhanced when combined with the VEGF gene."

"This experiment is a proof of principle," said Dr. Ronald G. Crystal, chairman and professor of genetic medicine at Weill Cornell Medical College and a pioneer in gene therapy, who played an important role in the research. "Now we need to go further to understand the activity of these genes and determine if they are effective in even larger hearts."

During a heart attack, blood supply is cut off to the heart, resulting in the death of heart muscle. The damage leaves behind a scar and a much weakened heart. Eventually, most people who have had serious heart attacks will develop heart failure.

Changing the scar into heart muscle would strengthen the heart. To accomplish this, during surgery, Rosengart and his colleagues transferred three forms of the vascular endothelial growth factor (VEGF) gene that enhances blood vessel growth or an inactive material (both attached to a gene vector) into the hearts of rats. Three weeks later, the rats received either Gata4, Mef 2c and Tbx5 (the cocktail of transcription factor genes called GMT) or an inactive material. (A transcription factor binds to specific DNA sequences and starts the process that translates the genetic information into a protein.)

The GMT genes alone reduced the amount of scar tissue by half compared to animals that did not receive the genes, and there were more heart muscle cells in the animals that were treated with GMT. The hearts of animals that received GMT alone also worked better as defined by ejection fraction than those who had not received genes. (Ejection fraction refers to the percentage of blood that is pumped out of a filled ventricle or pumping chamber of the heart.)

The hearts of the animals that had received both the GMT and the VEGF gene transfers had an ejection fraction four times greater than that of the animals that had received only the GMT transfer.

Rosengart emphasizes that more work needs to be completed to show that the effect of the VEGF is real, but it has real promise as part of a new treatment for heart attack that would minimize heart damage.

"We have shown both that GMT can effect change that enhances the activity of the heart and that the VEGF gene is effective in improving heart function even more," said Dr. Crystal.

The idea started with the notion of induced pluripotent stem cells – reprograming mature specialized cells into stem cells that are immature and can differentiate into different specific cells needed in the body. Dr.

Shinya Yamanaka and Sir John B. Gurdon received the Nobel Prize in Medicine and Physiology for their work toward this goal this year.

However, use of induced pluripotent stem cells has the potential to cause tumors. To get around that, researchers in Dallas and San Francisco used the GMT cocktail to reprogram the scar cells into cardiomyocytes (cells that become heart muscle) in the living animals.

Now Rosengart and his colleagues have gone a step farther – encouraging the production of new blood vessels to provide circulation to the new cells.

Provided by Weill Cornell Medical College