CORNELL CHRONICLE

Kotlikoff part of international research effort to prevent heart arrhythmia

By Tom Fleischman | May 8, 2018

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The most common and potentially lethal complication following a heart attack is the heart's inability to do one of its most basic jobs: beat at a normal rate.

Following myocardial infarction, heart muscle cells are replaced by fibroblasts and new blood vessels, which do not conduct electricity and leave the heart susceptible to ventricular tachycardia – an excessive heart rate that can result in sudden death. These non-heart cells disrupt the normal pattern of electrical conduction that is critical for effective pumping. If there were a way to make these cells electrically active, one could bridge the conduction block to a certain degree, and greatly decrease dangerous post-infarction complications.

Michael Kotlikoff

Provost **Michael Kotlikoff** (https://www2.vet.cornell.edu/research/faculty/michael-kotlikoff-vmd-phd) – a professor in the Department of Biomedical Sciences in the College of Veterinary Medicine – is part of an international collaboration that is aiming to bridge that gap in damaged hearts with a simple gene-therapy approach.

Their paper, "**Overexpression of Cx43 in Cells of the Myocardial Scar: Correction of Post-infarct Arrhythmias Through Heterotypic Cell-Cell Coupling** (https://www.nature.com/articles/s41598-018-25147-8)," was published May 8 in Nature Scientific Reports. The team was led by Bernd

Fleischmann, M.D., professor and chairman of the Institute of Physiology at the University of Bonn, with whom Kotlikoff has collaborated for almost 30 years.

Also on the team was Wilhelm Roell, M.D., from the University of Bonn Department of Cardiac Surgery, and Guy Salama, professor of cardiology from the University of Pittsburgh.

Their work demonstrates a dramatic reduction of post-infarction arrhythmias following the transfer of a single gene, Connexin43, which electrically couples non-excitable cells to undamaged heart cells.

In a paper in 2007

Bernd Fleischmann

(http://news.cornell.edu/stories/2007/12/embryonic-cells-implanted-damaged-hearts-prevent-arrhythmias), this same team reported that by transplanting living embryonic heart muscle cells into cardiac tissue of mice that had suffered heart attacks, the mice became resistant to cardiac arrhythmias. The key to the finding: the Connexin 43 (Cx43) protein, expressed by the transplanted embryonic heart cells, improved electrical connections to other heart cells.

This time, instead of transplanting embryonic cells, the group delivered the Cx43 via a single virus injection into the scar tissue of infarcted mice. The Cx43 protein electrically couples cells to each other, and its expression in the non-heart cells of the scar greatly enhanced conductivity, resulting in long-lasting protection from arrhythmia.

Optical mapping of the mouse hearts in vivo confirmed the finding. Fleischmann said the group took a nonconducting section of tissue and basically made it more like heart tissue by expressing the protein that allowed these cells to connect with normal heart cells, a process known as heterotypic cell-cell coupling.

“We’ve created a bridge for the electrical signal,” Fleischmann said. “We suspected it would work. We suspected that the cells we were putting in were actually working in this way, but it is really exciting.”

The group's excitement is tempered by the reality that these are mouse hearts, with induced, regularly shaped infarctions that are fractions of the size of those in humans. The spatial difference, Kotlikoff said, is not trivial.

"Whether this will work in humans, or even in larger animals, that's still a question and my colleagues in Germany are pursuing this," Kotlikoff said.

Still, he said, what's most exciting about this is the ease with which this procedure could be done, if tests on larger animals prove successful.

"It could be a very simple medical procedure," Kotlikoff said. "One could imagine a relatively noninvasive procedure in which the gene is introduced through a catheter, resulting in long term protection."


Wilhelm Roell

Also contributing from Cornell were Jane Lee, research support specialist in the Kotlikoff Lab, and Robert Doran, formerly of the Kotlikoff lab.

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