Engineering excitable cells for studies of bioelectricity and cell therapy

July 19 2011

By altering the genetic makeup of normally "unexcitable" cells, Duke University bioengineers have turned them into cells capable of generating and passing electrical current.

This proof-of-concept advance could have broad implications in treating diseases of the nervous system or the heart, since these tissues rely on cells with the ability to communicate with adjacent cells in order to function properly. This communication is achieved through the passage of electrical impulses, known as action potentials, from cell to cell.

The researchers achieved this transformation by introducing genes into the cells that result in the formation of ion channels which are openings, or gates, on the surface of cells. Ion channels allow the flow of electrically charged molecules, or ions, to exit or enter the cell thus enabling the transfer of electric current from one cell to its neighbor.

"By introducing only three specific ion channels, we were able to give normally electrically inactive cells the ability to become electrically excitable," said Rob Kirkton, graduate student in the laboratory of senior investigator Nenad Bursac, associate professor of biomedical engineering at Duke's Pratt School of Engineering.

"We also demonstrated proof-of-concept experiments in which these modified cells were able restore large electrical gaps within and between rat heart cells," Kirkton continued. "This approach to genetically engineering electrical excitability may stimulate the development of new

cell or gene-based therapies for excitable tissue repair."

The results of the Duke experiments were published in the journal *Nature Communications*. The researchers are supported by the National Science Foundation, the American Heart Association and the National Institutes of Health.

"We believe that our approach opens the door to a wide range of novel studies involving electrical communication between cells and may also help us to understand and develop treatments for disorders of electrically active tissues," Bursac said. "For example, genetically engineered excitable cells could be important in treating heart attacks, in which damaged portions of heart muscle become electrically disconnected and are unable to contract in synchrony with neighboring healthy cells."

The Duke researchers hypothesized that a few key ion channels are sufficient to enable cell excitation. They determined that three particular channels could do the job, including those carrying potassium ions, sodium ions, and a gap junction channel, a highly specialized structure that enables cell-to-cell electrical communication.

"All three of these ion channels play critical roles in the generation and propagation of electrical activity in the mammalian heart," Kirkton explained.

After demonstrating that their genetic manipulations made unexcitable human kidney cells excitable, they tested whether groups of such cells could carry electrical signals from heart cell to heart cell, both in two-dimensional and three-dimensional cell culture models.

In a key set of experiments, the researchers created an "S"-shaped pathway, with clusters of normal, living rat heart cells at either end. The space between the two clusters was filled with a population of either

unexcitable cells (the control), or the genetically engineered cells. When an electrical stimulus was applied to a heart cell cluster at one end of the setup, an electrical impulse traveled throughout these heart cells but immediately stopped and disappeared at the entrance to the "S"-shaped path containing the unexcitable control cells.

"However, when we used the genetically modified cells, the electrical impulse was rapidly regenerated and carried throughout the three-centimeter long pathway, eventually triggering the second cluster of cells to fire on the other side," Kirkton said. "Alternatively, if we applied the stimulus to the modified cells in the center of the pathway, the electrical impulse travelled outwardly in both directions toward the heart cells and electrically activated them."

The Duke scientists also said that their engineered excitable cells can be continuously and easily grown in the lab, are genetically and functionally identical to each other, and also have the capacity for further modifications to change their electrical or structural behavior.

"These cells can be used in the laboratory as a platform for investigating the roles that specific ion channels have in tissue-level bioelectricity as well as testing the effectiveness of new drugs or therapies on bioelectrical activity," Kirkton said. "They could potentially also be helpful in the design of new biosensors to detect disease or environmental toxins.

Provided by Duke University