Researchers find evidence of mature heart cell potential in embryonic stem cells

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In a new study, UC Davis researchers report the first functional evidence that heart cells derived from human embryonic stem cells exhibit one of the most critical properties of mature adult heart cells, an important biological process called excitation-contraction coupling.

The finding gives scientists hope that these cells can one day be coaxed into becoming functionally viable cells safe for transplantation into the damaged hearts of patients with end-stage disease, potentially avoiding the necessity of a heart transplant. Currently, there are nearly 3,000 people on heart transplant lists around the nation, including more than 300 in California.

UC Davis research scientist Ronald Li and his colleagues write in their study, “Functional Sarcoplasmic Reticulum for Calcium-Handling of Human Embryonic Stem Cell-Derived Cardiomyocytes: Insights for Driven Maturation,” that they observed cells that had begun the maturation process toward becoming heart cells. The article, available online in *Stem Cell Express*, stemcells.alphamedpress.org/ , will be published in the December issue of the journal *Stem Cells*.

“Previous experiments were able to derive heart cells from human embryonic stem cells,” said Li, who is an associate professor of cell biology and human anatomy at UC Davis School of Medicine and senior author of the study, “but those cells always remained too immature to be of any therapeutic use and actually could cause lethal arrhythmias in animal models. Now, what we’ve been able to do is push the therapeutic

potential of human embryonic stem cells further so that eventually they might be used safely, and with enhanced efficacy, in transplantation cases."

The main function of the heart is to mechanically pump blood in a highly coordinated fashion throughout the body. To do this, heart cells must receive electrical signals and contract in response to those signals. This link, called the excitation-contraction coupling, is dependent on the cells' ability to move calcium ions across an internal organelle known as sarcoplasmic reticulum, or the so-called "calcium store." The ability to handle calcium is disrupted in the cells of patients who experience heart failure. For future stem-cell based therapies to work, scientists will need to have heart cells that exhibit mature excitation-contraction coupling.

Until now, researchers studying heart cells (also called cardiomyocytes) derived from human embryonic stem cells have been unable to find evidence of functional calcium stores. Li found protein functions that are involved in the early stages of this coupling process. He and his colleagues now plan to move on and engineer the calcium-handling properties in order to enhance contractile properties in cardiomyocytes for both improved safety and functional efficacy.

In the current study, Li and his colleagues took human embryonic stem cells and grew them in cultures, allowing them to differentiate, or develop, into heart cells. Once they had these tiny, pulsing masses, the investigators energized the cells with small amounts of electrical current and chemicals, including caffeine. They then measured how the amount of intracellular calcium changed and looked for the presence of proteins and cellular structures known to be involved in excitation-contraction coupling.

Li and his colleagues are the first to find evidence of the functional calcium stores for excitation-contraction coupling, They also found four

of the seven key proteins that play key roles in handling calcium in the cell, as well as functional sarcoplasmic reticulum.

The UC Davis researchers used different cell lines than those utilized in previous studies, which they say may explain why they were able to achieve a breakthrough in their investigation where others had not.

The UC Davis group also looked at a smaller number of cells during various stages of development, enabling them to more accurately dissect the different population subsets. The authors said that differences in cell culture and experimental conditions could also account for the results not seen in previous efforts.

According to Li, the fact that different cell lines exhibit different potentials for differentiation and maturation underscores the need to develop new and additional stem cell lines in order to advance critical research into potential therapies for patients.

“This is a good example of the type of exciting, bench-to-bedside research now under way at UC Davis and the potential it has for new treatments,” said Jan Nolta, director of the UC Davis Stem Cell Program in Sacramento “As additional embryonic stem cell lines become available for research, we’ll be able to more fully explore the possibilities inherent in this powerful field of bioscience.”

Li’s study is a first step toward deriving cardiomyocytes with fully functional contractile properties from human embryonic stem cells. With heart transplants being the current treatment of last resort due to severe shortages of donor organs and the complexity of transplantation, the long term goal of researchers like Li is to come up with alternatives that are both safe and effective.

“Our latest study gives us great hope of eventually achieving a

breakthrough where stem cell therapy could be used in the types of cases that today require a heart transplant," concluded Li.

Source: University of California - Davis