Learning How Embryonic Stem Cells Become Heart Cells

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Heart muscle cells derived from human embryonic stem cells (DNA is stained blue, a structural protein is green, and a calcium-binding protein is stained red). *Credit: Juan Carlos Izpisúa Belmonte, Salk Institute for Biological Studies*

Three teams of San Diego scientists are collaborating on a comprehensive new systems-biology approach to learn how to prompt mouse embryonic stem cells to differentiate in the laboratory into cardiac muscle cells, results that could eventually be used to develop completely new treatments for human heart disease.

Doctors often say that every person dies with the heart he or she was born with because while the heart is the first organ to form as the embryo develops in the uterus, the heart also apparently lacks the ability to repair itself. However, the researchers hope that what they learn about mouse stem cell differentiation can be used as a blueprint for prompting human stem cells to differentiate in the laboratory into cells that could then be used therapeutically to repair damaged or diseased hearts.

Collaborating scientists at UC San Diego and the nearby Salk Institute for Biological Studies and Burnham Institute for Medical Research will use a new three-year grant to painstakingly detail all the biochemical steps and control mechanisms involved in the complex process by which mouse embryonic stem cells differentiate into heart muscle cells, or cardiomyocytes.

The National Heart, Lung and Blood Institute has awarded $3.1 million to the three research institutions to make use of a variety of recent biotechnology advances to detail the dozens of biochemical triggers that act in concert to control the differentiation of mouse cardiomyocytes. "The detailed measurements of signaling molecules and other proteins in these immature heart cells will help us reconstruct pathways of differentiation, an outcome that will help us find 'targets' for drugs to induce the same process in the laboratory production of heart muscle cells," said Shankar Subramaniam, a professor of bioengineering at UCSD and principal investigator of the project.

In the study, Subramaniam will collaborate with co-principal investigators Juan Carlos Izpisúa Belmonte, a professor in the Salk Institute for Biological Studies' Gene Expression Laboratory, and Mark Mercola, a professor in the Stem Cells and Regeneration Program at the Burnham Institute for Medical Research and associate director of the Burnham Institute's Del E. Webb Center for Neuroscience, Aging, and Stem Cell Research.

"This is an exceptional opportunity for leveraging the strengths of the three institutions, combining systems biology expertise from UCSD with the stem cell and cardiogenesis expertise of Salk and Burnham will lead to improved methods of producing heart muscle from stem cells," said Mercola.

The geographical proximity of the three teams is expected to increase the pace of progress toward meeting milestones established in the grant's three-year timeline. Coordination and interaction will be facilitated by meetings with a steering committee that includes Subramaniam, Mercola and Belmonte as well as pioneers in three scientific disciplines that overlap in the project. The three outside experts are: Richard Lee, a professor of medicine at Harvard Medical School who is a lecturer in bioengineering at the Massachusetts Institute of

Technology and a cardiologist at Brigham and Women's Hospital in Boston, MA; Fred Gage, a professor in the Laboratory of Genetics at the Salk Institute whose lab showed that humans can grow new nerve cells throughout life and that environmental enrichment and physical exercise can enhance the growth of new brain cells; and Bernhard Palsson, a professor in the UCSD Jacobs School of Engineering's Department of Bioengineering and a pioneer of the relatively new field of systems biology.

The researchers will make use of hundreds of prior studies that have documented thousands of individual steps involved in the differentiation of embryonic tissue. The signaling molecules involved in embryonic development are similar across many species. For example, the formation of avian heart tissue is orchestrated by the Hensen's node, a tiny knot of cells in the chicken embryo. The signaling chemicals released by the Hensen's node are similar to those found in humans and other species.

As part of the mouse stem cell study, researchers will closely monitor changes in the concentration of electrically charged calcium ions inside the developing mouse cardiomyocytes. Changes in calcium levels play a crucial signaling role in the initiation of an electrical rhythm; as the calcium levels in cardiomyocytes go up and down, cell contractility develops.

The researchers will use a variety of new biotechnology tools and techniques to identify signaling and control steps in cardiomyocyte differentiation, all of which will become the basis of a systems biology model of the cells. The investigators will share the final version of the model freely and publicly with other scientists.

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