GLADSTONE NEWS

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GLADSTONE SCIENTISTS IDENTIFY GENES INVOLVED IN EMBRYONIC-HEART DEVELOPMENT

– Findings Important to Understanding Congenital Heart Defects –

SAN FRANCISCO – April 16, 2011 – Scientists at the Gladstone Institutes have identified networks of genes that play an important role in embryonic-heart development, advancing knowledge of how healthy hearts develop—and offering clues about how to combat a common birth defect known as congenital heart disease.

Congenital heart disease affects nearly 1 out of every 100 babies born worldwide and is the most common cause of death from a birth defect. In the disease, cells in the embryo often fail to get the right instructions while the heart is being formed. Many genes and proteins must be deployed at just the right time and in the right amounts for healthy heart formation to occur. Disruption of the correct dosage of proteins can lead to congenital heart defects.

One way cells control the amount of protein made from genes is through a recently discovered molecule called a microRNA. MicroRNAs are tiny strands of genetic material that do not encode the information to make enzymes and proteins, as most RNAs do. Instead, microRNAs inhibit other RNA molecules from producing protein. In recent years, scientists have discovered that each microRNA inhibits protein production from hundreds of RNAs, regulating almost every process in every cell of the body by fine-tuning the dosage of key proteins.

“MicroRNAs provide an extra layer of regulation that helps ensure that the correct amount of protein is made from a particular gene at the right time,” said Isabelle King, a Gladstone scientist and an assistant professor of pediatrics at the University of California, San Francisco. Dr. King is the lead author on the study, the results of which were published in the April 17 issue of *Developmental Cell*. “In the fetal heart, subtle changes in gene dosage and timing can yield heart defects in children.”

While microRNAs are powerful, it has been challenging to identify the hundred or more genes that each microRNA regulates. To overcome this problem, the researchers devised a simple genetic test in fruit flies, a classic organism for genetic studies. By examining the impact of thousands of genetic mutations on the function of a muscle-specific microRNA, the scientists were able to better understand how the fly heart develops and found that the same genes were important in the mouse heart. These

results may provide insight into what happens in humans because genes common to mouse and fly hearts are also typically critical for heart formation in humans.

“Flies and humans have a lot in common in terms of how their cells work, and so flies represent a powerful tool to explore human diseases,” said Dr. King.

To examine genes that influence fetal-heart development, the Gladstone investigators created mutant flies with too much of a muscle-specific microRNA called miR-1. Flies and other animals without miR-1 are known to have heart defects. By selective breeding, the researchers found more than three regions in the flies’ genome that made the effects of excess miR-1 even worse—suggesting that genes in these regions work in concert with miR-1.

The identity of these genes will help researchers better understand why muscle and heart cells need miR-1, how birth defects develop in the fetal heart and where to target any potential therapies to prevent those defects. For example, one of the genes tells the cell which side should face up and which should face down, which is a critical event as heart cells come together to form an organ.

While the techniques used in this research revealed important information for heart research, a similarly structured experiment could also be used to reveal new knowledge about the function of microRNAs in other organs and tissues.

“The assay system we developed gives us a valuable tool to identify microRNA-responsive genes involved in other developing organs or disease states,” said Deepak Srivastava, MD, director of the Gladstone Institute of Cardiovascular Disease and the study’s senior author.

Gladstone scientists Joseph Shieh, Yu Huang and Chulan Kwon, and University of California, San Francisco scientist J. Liang, all contributed to this study. The National Institutes of Health, Gladstone, the California Institute for Regenerative Medicine, and the Younger Foundation all provided funding for this study.

Dr. Deepak Srivastava directs all cardiovascular research at Gladstone. He is also a professor of pediatrics and biochemistry and biophysics, and the Wilma and Adeline Pirag Distinguished Professor in pediatric developmental cardiology at the University of California, San Francisco.

About the Gladstone Institutes
Gladstone is an independent, nonprofit biomedical research organization dedicated to accelerating the pace of scientific discovery and biomedical innovation to prevent illness and cure patients suffering from cardiovascular disease, neurodegenerative disease, or viral infections. Gladstone is affiliated with the University of California, San Francisco.

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