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Gladstone scientists identify critical gene factor in heart development

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Researchers at the Gladstone Institute of Cardiovascular Disease (GICD) announced they have identified a critical genetic factor in the control of many aspects of heart form and function. As reported in the journal Cell, scientists in the lab of Deepak Srivastava, MD, have successfully deleted a genetic factor, called a microRNA, in animal models to understand the role it plays in cardiovascular differentiation and development.

MicroRNAS, or miRNAs, seem to act as rheostats or "dimmer switches" to fine-tune levels of important proteins in cells. To learn how microRNAs do this, the team led by Dr. Srivastava, deleted the gene responsible for one microRNA in mice and examined the effects of its loss on heart development and maintenance. "Knocking out" a gene is a favorite method for figuring out what a particular gene does in a cell by selectively removing it.

"Development of the heart requires very careful regulation of many factors, and that's one reason that microRNAs are so exciting to us," said Dr. Srivastava, GICD Director. "By knocking out the gene for one miRNA, we could determine exactly what it contributes to that complex process."

MicroRNAs exert their control by stopping protein production after the genes have directed them to be made. Previously, it was thought that all the control was at the level of the genes. Although only 20-22 nucleotides long, the microRNAs bind to the much longer messenger

RNAs and prevent their blueprint for building a protein from being used. They typically prevent many messenger RNAs from making proteins and therefore can affect myriad events.

The Gladstone team looked at one particular microRNA, miR-1-2, that was active specifically in the heart. A closely related and redundant microRNA miR-1-1 could not fully compensate for loss of miR-1-2. The team found that loss of miR-1-2 affected many functions in the heart, including heart morphogenesis and control of the number of cells in the heart. For example, half of the mice developed holes in the pumping chambers of the heart, which is the most common human congenital heart defect.

They also found that miR-1-2 influences electrical conduction of the heart, which is what regulates the heart beat. Defects in the heart rhythm frequently cause sudden death in humans and are the reason for pacemakers and defibrillators.

Loss of miR-1-2 also caused a breakdown of the control of cell division in the heart cells. This is potentially a very important finding. Adult heart cells do not divide. When a heart attack occurs, heart cells die and cannot be replaced. Understanding how cell division works in the heart may lead to ways to turn it back on or to use stem cells to fix the damaged heart.

Finally, the team was able to see all of the genes that a specific microRNA affects. Each microRNA is known to control more than one gene. Dr. Srivastava's team used genomic studies to examine all of the genes that were turned on or off by the loss of miR-1-2. This information will help to determine the global picture of microRNA control.

"Our results show that even small changes in microRNA dosage can have

large effects," said Yong Zhao, MD, PhD, postdoctoral fellow and lead author on the paper. "Although any therapies are a long way off, understanding the effects of miR-1-2 is very exciting," added Joshua Ransom, a graduate student who contributed equally to this work."

Source: Gladstone Institutes