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Scientists identify single microRNA that controls how heart chambers form

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Scientists at the Gladstone Institute of Cardiovascular Disease (GICD) and the University of California San Francisco (UCSF) have identified a genetic factor critical to the formation of chambers in the developing heart. The discovery of the role of a microRNA called miR-138, could offer strategies for the treatment of congenital heart defects.

The heart is one of the first and most important organs to develop. In fact, embryos cannot survive long with a functioning heart. In vertebrates (animals with backbones), special cells form a heart tube; that tube loops back on itself to form the atrium and ventricle and the canal and valve that separates them. This requires a complicated sequence of genes turning on and off. MicroRNAs are very small RNAs of 20 to 25 nucleotides that regulate numerous gene functions. Approximately 650 human miRNAs are known, but only a few have yet been studied to determine what they actually do in a cell.

Researchers, led by Sarah Morton, an MD/PhD student at UCSF and GICD Director Deepak Srivastava MD, examined zebrafish, which are an ideal model system for understanding genetic functions. Zebrafish are small, reproduce fast, and are essentially transparent so that that events of heart formation can be studied while they are still alive. Yet many of their systems are quite similar to those of humans. For example, miR-138 is exactly the same in zebrafish and humans.

"What's interesting is that a single microRNA is responsible for setting up the distinct patterning of a developing heart into separate chambers,"

said Dr. Srivastava, senior author of the study. "Since many congenital heart defects involve abnormalities in the formation of the chambers, this is important information in finding ways of treating or avoiding those defects."

The GICD scientists reported in today's issue of the *Proceedings of the National Academy of Sciences* USA, that miR-138 is present in the zebrafish heart at specific times and in specific places in the developing heart. Furthermore, they showed that it is required to insure that the cardiac chambers develop properly. When the scientists used genetic engineering techniques to eliminate miR-138, cardiac function was disrupted, and the ventricles did not develop correctly, with the muscle precursor cells failing to mature properly.

"The miR-138 function was required during a discrete developmental window that occurred 24-34 hours after fertilization," said Sarah Morton. The team also showed that the miRNA controlled development by regulating numerous factors that function jointly to define the chambers, including a key enzyme that makes retinoic acid.

Source: Gladstone Institutes