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Researchers identify key mechanism that guides cells to form heart tissue

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Researchers at the Keck School of Medicine of the University of Southern California (USC) have identified a key cellular mechanism that guides embryonic heart tissue formation -- a process which, if disrupted, can lead to a number of common congenital heart defects.

Heart tissue forms in two distinct phases known as the First Heart Field, which includes the left ventricle and portions of both atrial chambers, and the Second Heart Field (SHF), which consists of the right ventricle and outflow tract. In humans, the process occurs within the fourth week of development. Using animal models, Keck School of Medicine researchers found that retinoic acid (RA), a derivative of vitamin A, regulates the SHF tissue formation and the septation, or division, of the outflow tract into the ascending aorta and the pulmonary artery.

The study appears in the March 16 issue of the journal *Developmental Cell*.

"This study provides us with a much deeper understanding of the biology of second heart field development," said principal investigator Henry Sucov, Ph.D., associate professor of Cell and Neurobiology at the Keck School of Medicine and a researcher at the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC. "We now know that vitamin A is a critical regulator of this process, and too much or too little RA can lead to common congenital defects."

RA is a signaling molecule that causes progenitor cells (cells that have

the capacity to differentiate into many different kinds of cells) to take the first step towards differentiating into heart tissue. Using specific molecular markers, researchers were able to observe the process by which the cells moved to the outflow tract and began to form essential heart tissue.

The process of moving cells to form the outflow tract is similar to a conveyer belt, Sucov explained. However, in animal models that were mutated to have an RA receptor deficiency, the entire process was halted, resulting in an outflow tract that was shortened and misaligned.

When development of the SHF is compromised, alignment defects such as double outlet right ventricle (DORV; the aorta and pulmonary trunk both exit from the right ventricle) or overriding aorta (when the aorta straddles the interventricular septum) occur. Problems in SHF development can also compromise the septation process resulting in a single outflow vessel—a condition known as persistent truncus arteriosus. These malformations occur commonly in human infants.

"This exciting research shows how retinoic acid, a vitamin A derivative, acts to guide cells in the embryo to form parts of the heart and the major blood vessels that emerge from it," said Martin Pera, Ph.D., director of the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC. "Defects in this developmental pathway can result in serious congenital malformations of the heart in the fetus and newborns, that may be fatal if not corrected surgically."

Further research is needed to examine how the findings may be used to correct human heart defects, Sucov said, noting that specific treatments suggested by these results and testing in animal models will soon be underway.

"Through this research, preventative strategies that prevent the

occurrence of these defects may be realized," he said.

More information: Peng Li, Mohammad Pashmforoush and Henry M. Sucov, "Retinoic Acid Regulates Differentiation of the Secondary Heart Field and TGFβ-Mediated Outflow Tract Septation." Developmental Cell. D-09-00178R4.

Provided by University of Southern California