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GENES THAT CONTROL EARLY HEART FORMATION MAY LEAD TO NEW THERAPIES FOR CONGENITAL, ADULT HEART DISEASE

DALLAS — June 3, 1997 — Researchers at UT Southwestern Medical Center at Dallas have provided the first glimpses into the earliest events that control formation of the heart. They hope that by understanding how the heart is formed, new therapies will be developed to prevent or rectify the congenital heart anomalies found in one percent of all live births.

Dr. Eric Olson, chairman of molecular biology and oncology, and his colleagues recently published three papers describing their studies of the genes *GATA4*, *MEF2C* and *dHAND* and the closely related *eHAND*, all of which control early steps in a series of complex stages leading to formation of the heart. Olson directed the *GATA4* study, published in the April 15 issue of *Genes and Development*, and the *MEF2C* study, described in the May 30 issue of *Science*. Dr. Deepak Srivastava, assistant professor of pediatrics and molecular biology and oncology, directed the study of the regulation of cardiac development by *dHAND* and *eHAND*, published in the June issue of *Nature Genetics*.

In all three studies, the researchers used similar molecular techniques to create mice that lacked one of the genes. By following the growth of the fetal heart in the mice, they were able to determine at what stage the missing gene blocked cardiac development. Previous studies have shown that the genes that control cardiac development are very similar for many different species — from fruit fly to mouse to man.

Although the molecular pathways that control heart development are still being uncovered, the descriptive formation of the heart, the first organ to form in vertebrates, is well known. In the embryo, a primitive linear heart tube is formed from the longitudinal folding of specialized precardiac tissue. The tube then further differentiates as the middle

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segment loops to the right to form what becomes the right ventricle. This process of looping is the first sign of cardiac asymmetry and is essential for proper heart formation and chamber position. After looping, the various chambers of the heart become physically distinguishable. Each chamber expresses a distinct set of cardiac muscle genes that allows it to accomplish its unique function.

When the *GATA4* gene is absent, the mouse embryo does not create a linear heart tube. In this lethal condition, two independent linear hearts develop because the longitudinal folding and movement of embryonic tissue necessary to form the single linear heart tube does not occur.

The *MEF2C* factor, normally present in all stages of heart development, is considered by Olson, director of the Nancy B. and Jake L. Center for Basic Research in Cancer and holder of the Nancy B. and Jake L. Hamon Distinguished Chair in Basic Cancer Research, to be the central regulator of cardiac muscle differentiation and heart formation. When the *MEF2C* gene is altered and no *MEF2C* is produced, there is no cardiac looping, no right ventricle formed and no expression of a subset of cardiac muscle genes. Fruit flies also have an *MEF2* gene, and it, too, is required for differentiation of heart muscle cells.

"This tells us that this gene is more than 600 million years old, and it dates all the way back to a common ancestor of the fruit fly," said Olson.

The lack of *dHAND* is also a lethal event for the mouse. In this case, a linear heart tube is formed, but no looping occurs and no morphological right-sided ventricular chamber is developed.

"Clearly *dHAND* specifies the identity of the right ventricle," said Srivastava. These studies provide proof that development of the two ventricular chambers are controlled by different molecular determinants. Olson and Srivastava believe that *dHAND* and *eHAND*, which is expressed in the left ventricle, are probably either directly involved in congenital diseases in which children are born without a left or right ventricle or in the pathways leading to those diseases.

"Two years ago we did not know even a single gene involved in the regulation of

cardiac formation. Now it is a matter of putting this handful of really important genes into pathways, finding out what they regulate and what regulates them," said Olson.

Srivastava believes that the first application of their efforts will be in adults, who have more than 500,000 heart attacks yearly. Heart attacks kill heart muscle, which has no means of regenerating.

"What we have to do is go back in time and turn on the critical set of genes that is turned on in the fetus. They should be able to make more heart muscle," said Srivastava.

The *HAND* genes are good candidates because they are active only during the proliferative stage of heart formation, whereas *GATA4* and *MEF2C* are present throughout fetal heart development and in the adult heart.

Olson and Dr. Qing Lin, former graduate student, participated in all three studies. Other investigators involved in the *GATA4* study were UT Southwestern research fellow Dr. Jeffery Molkentin and Dr. Stephen Duncan of Rockefeller University. Tiffani Thomas, a pediatrics research assistant, and Doris Brown, graduate student, were co-authors of the *dHAND* study. Dr. Margaret Kirby of the Medical College of Georgia School of Medicine also participated in the *dHAND* study. Additional investigators on the *MEF2C* study were Dr. John Schwarz of UT Medical School at Houston and Dr. Corazon Bucana of UT M.D. Anderson Cancer Center.

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