SOUTHWESTERN NEWS

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GENE COULD HOLD KEY TO PREDICTING, COMBATING LIFE-THREATENING ABNORMAL HEART GROWTH

DALLAS – Aug. 23, 2002 – Researchers at UT Southwestern Medical Center at Dallas have identified a gene they believe could predict risk for developing enlarged hearts and lead to treatments to control life-threatening heart growth.

In a study published in today's edition of *Cell*, a team led by Dr. Eric Olson, chairman of molecular biology at UT Southwestern, reports that the gene *HDAC9* limits abnormal heart-muscle growth.

Olson said doctors have long understood that the heart becomes enlarged – a condition called cardiac hypertrophy – when it responds to stresses, including irregular heartbeat and high blood pressure.

Enlarged hearts frequently become dilated – their inner chambers stretched beyond normal size – and work less efficiently. The excess muscle also can disrupt the electrical signals that control heart rhythm. Cardiac hypertrophy frequently is a cause of sudden death among young athletes, who suffer cardiac arrest due to enlarged hearts without ever knowing they had the condition.

"Stress accelerates hypertrophic growth, and *HDAC9* functions to restrict cardiac growth," said Olson. "If *HDAC9* isn't present, it's like you have no brakes and the heart grows uncontrolled."

The new research also shows that *HDAC9* specifically restricts cardiac growth in response to stress, but it does not restrict normal cardiac growth during development or in response to exercise.

Previous research had demonstrated that when the heart works harder than normal, a calcium sensor called calcineurin is activated and drives heart-muscle growth. The researchers showed that *HDAC9* counteracts the calcineurin activity to short-circuit muscle growth.

While the gene doesn't completely stop heart enlargement, UT Southwestern researchers showed that *HDAC9*'s presence significantly slows growth. Olson said the next step is to look at human subjects to see if abnormalities in *HDAC9* coincide with abnormal heart growth.

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"This gene exhibits the properties of a susceptibility gene for hypertrophy," Olson said. "In principle we eventually could identify people who don't have enlarged hearts but have mutations in that gene and tell them they're at risk."

During the study Olson's team created mouse models that lacked *HDAC9* and compared their heart development to that of normal mice. After one month under normal conditions, the hearts of the normal and *HDAC9*-negative mice were about the same size. But the hearts of the mice lacking the gene were, on average, 46 percent larger than normal by eight months of age.

Making the heart work harder than normal produced dramatic disparities.

The researchers first constricted the thoracic aortas in both the normal and *HDAC9*-negative mice to see how working harder to pump blood would affect heart growth. After three weeks, left-ventricle mass had increased by 56 percent in the normal mice and by 105 percent in mice missing the gene.

The researchers also artificially activated calcineurin in normal and *HDAC9*-negative mice. Four weeks later, heart mass in the normal mice had increased by 130 percent on average, compared to an average increase of 220 percent in the *HDAC9*-negative mice.

The research now will proceed on two fronts: The Donald W. Reynolds Cardiovascular Clinical Research Center at UT Southwestern eventually will screen participants in the Dallas Heart Study with enlarged hearts to see if they carry mutations in their *HDAC9* genes as part of the center's effort to identify the set of genes involved in heart disease; and Myogen Inc., a Denver-based biotechnology company that Olson co-founded, has licensed the research in order to start investigating drug-development possibilities.

"Now that we know that *HDAC9* is a key regulator of heart growth, we can use it to develop assays to find small molecules that could be developed into drugs," Olson said.

Other researchers from UT Southwestern's Department of Molecular Biology were Dr. Timothy A. McKinsey, a former postdoctoral researcher now at Myogen, and student research assistants Christopher L. Antos, Shurong Chang and Chun Li Zhang, the first author of the study. The University of Iowa College of Medicine also participated in the study.

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