SOUTHWESTERN NEWS

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UT Southwestern researchers unravel control of growing blood vessels

DALLAS – Aug. 1, 2005 – Researchers at UT Southwestern Medical Center have discovered a basic mechanism by which smooth muscle cells that line the blood vessels can grow – sometimes abnormally – suggesting methods of treatment for various coronary diseases.

Abnormal growth of cells inside blood vessels is involved in hypertension, coronary artery disease, tumors called leiosarcomas and other conditions.

"By understanding this detailed mechanism, it is now possible to begin to design therapies to interfere with it and thereby potentially prevent various vascular disorders in humans," said Dr. Eric Olson, chairman of molecular biology and senior author of the paper. The work appears in the August issue of the journal *Developmental Cell.*

There are three types of muscles in the body – skeletal, cardiac and smooth. Smooth cells make up the stomach, intestine, blood vessels and other organs. Unlike the skeletal and cardiac muscles, smooth muscle cells can either rest in their final form, which allows vessels to contract, or they can divide into new cells.

Researchers have known about several signals that can stop smooth muscle cells from dividing and enable them to contract, but little is known about how this cascade of interactions works. The protein myocardin, discovered in Dr. Olson's lab in 2003, is known to bind to DNA and stimulate the expression of genes that control muscle contraction. How myocardin is controlled, however, has been a mystery, said Dr. Olson, director of the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer and the Nearburg Family Center for Basic Research in Pediatric Oncology.

He and fellow researchers focused on a molecule called Foxo4, to see whether it might control myocardin; they found that it turns off myocardin, thus allowing smooth muscle cells to stop contracting and grow. The level of Foxo4, in turn, increases or decreases depending on what kind of signals the smooth muscle receives.

This complexity suggests many pathways for future treatments. For instance, a treatment

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might directly control the level of Foxo4, or it may involve one of the signals that control Foxo4.

"Now that we understand the 'nuts and bolts' of this problem, we can use that information to find ways of disrupting the disease process," Dr. Olson said. "We have several ideas in this regard, which we intend to test in mice in the near future."

Other UT Southwestern researchers involved in the study were Drs. Zhi-Ping Liu, assistant professor of internal medicine, Zhigao Wang, postdoctoral researcher in biochemistry, and Hiromi Yanagisawa, assistant professor of molecular biology.

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