SOUTHWESTERN NEWS

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RESEARCHERS FIND PROTEIN MECHANISM FOR POTENTIAL ATHEROSCLEROSIS DEVELOPMENT

DALLAS – April 11, 2003 – Inactivating a protein that helps regulate the proliferation of vascular cells increases the chance of developing atherosclerosis, a major cause of heart disease, researchers at UT Southwestern Medical Center at Dallas have discovered.

Vascular vessels endure constant pounding and considerable stresses associated with blood flow. Vascular smooth muscle cells play an important role in the development of blood vessels, providing structural integrity and the ability to dilate and constrict. The low-density lipoprotein receptor-related protein (LRP1) helps regulate the proliferation and movement of these smooth muscle cells, presumably because LRP1 forms a complex with the receptor for platelet-derived growth factor (PDGF).

In findings reported in today's issue of *Science*, a UT Southwestern research team led by Dr. Joachim Herz, professor of molecular genetics and in the Center for Basic Neuroscience, discovered that inactivating LRP1 in vascular smooth muscle cells caused the overexpression of PDGF receptor and abnormal PDGF receptor signaling in mice. Smooth muscle cells proliferated and the vessel wall became highly susceptible to cholesterol buildup.

"We used gene targeting to unravel a mechanism that controls and holds smooth muscle cell proliferation and migration in check," said Dr. Philippe Boucher, postdoctoral researcher in molecular genetics and first author of the study. "This process is hyperactive in atherosclerosis."

The absence of LRP1 is unlikely to occur in humans, Herz said, but the research emphasizes the importance of PDGF signaling in the development of atherosclerosis.

Atherosclerosis is a buildup of cholesterol and fatty substances in the lining of arteries. Smooth muscle cells respond to this buildup by proliferating and taking up more cholesterol, resulting in plaque formation. Continued expansion of this plaque leads to arterial obstruction, which often results in heart attack or stroke.

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"We wanted to find out whether the smooth muscle cells would abnormally proliferate after LRP1 was inactivated. They do, and the vessel wall is very susceptible to high cholesterol," said Herz.

The researchers also discovered that Gleevec – a drug used successfully to treat chronic myeloid leukemia – significantly reduced the development of the vessel abnormalities that lead to atherosclerosis. In cancer cells, Gleevec blocks certain signals and prevents a series of chemical reactions that cause cells to rapidly grow and divide.

"We effectively found that Gleevec could reduce atherosclerosis in our mouse models by about 50 percent," Herz said.

Herz cautioned that the use of Gleevec in this research does not imply it is an alternative therapy for people with high cholesterol.

"It's better to keep cholesterol levels down and prevent these pathways from being activated," he said. "The key to preventing atherosclerosis has not changed. People need to keep their blood pressure down, control cholesterol and control diabetes."

Other UT Southwestern researchers involved in the study were Dr. Wei-Ping Li, assistant professor of cell biology; Dr. Richard Anderson, chairman of cell biology; and Dr. Michael Gotthardt, former postdoctoral researcher at UT Southwestern and now an assistant professor at the Max-Delbrück Center in Berlin.

The research was supported by the National Institutes of Health, the Alzheimer's Association and the Perot Family Foundation.

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