To predict atherosclerosis, follow the disturbed blood flow

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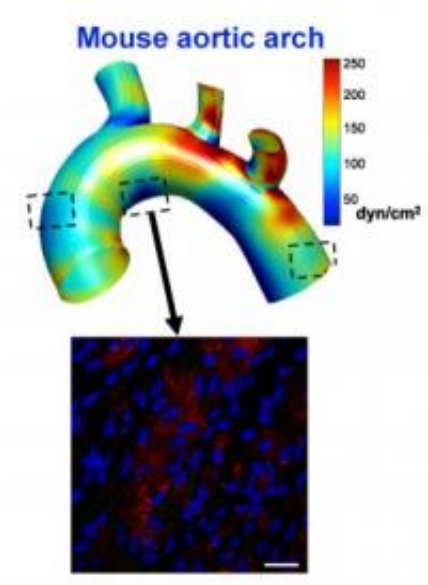

The gene LMO4 is turned on in the middle boxed region, but not the other two, because of "disturbed flow" in that area of the aorta. Credit: Hanjoong Jo

A new animal model of atherosclerosis has allowed researchers to identify a host of genes turned on or off during the initial stages of the process, before a plaque appears in the affected blood vessel.

The results were published June 15 in *Blood,* the journal of the American Society of Hematology.

The model is the first to definitively show that disturbances in the

patterns of blood flow in an artery determine where atherosclerosis will later appear, says senior author Hanjoong Jo, PhD, Ada Lee and Pete Correll professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

The first author of the paper is Chih-Wen Ni, a graduate student in biomedical engineering.

Atherosclerosis describes a process where the arterial walls thicken and harden, because of a gradual build-up of white blood cells, lipids and cholesterol. This process can lead to plaque formation, and eventually to heart attacks and strokes.

Jo says his team's results could provide insight into how aerobic exercise, known to provide protection against atherosclerosis, improves the patterns of blood flow and encourages protective genes to turn on in blood vessels.

Scientists have previously observed that atherosclerosis occurs preferentially in branched or curved regions of arteries, because of the "disturbed flow" branches and curves create. Constant, regular flow of blood appears to promote healthy blood vessels, while low or erratic flow can lead to disease.

The standard laboratory model of atherosclerosis has scientists feeding a high-fat diet to mice with mutations in a gene (ApoE) involved in removing fat and cholesterol from the blood. Even then, atherosclerosis usually takes a few months to develop. In these models, clogs in a mouse's arteries tend to appear in certain places, such as the aortic arch, but flow patterns are set up at birth and thus are poor gauges of cause and effect, Jo says.

"We have developed a model where we disturb blood flow in the carotid

artery by partial ligation, and atherosclerosis appears within two weeks," he says. "This rapid progression allows us to demonstrate cause and effect, and to examine the landmark events at the beginning of the process."

Jo says that endothelial cells, which form the inner lining of blood vessels, are equipped with sensors that detect changes in fluid flow.

"Disturbed flow is what causes the endothelial cells to become inflamed," he says.

The inflammation resulting from "bad flow" conditions in a stretch of artery causes white blood cells to accumulate there, followed by buildup of cholesterol and lipids and plaque formation.

Just 48 hours after blood flow in the carotid arteries was disturbed, Ni and colleagues dissected the carotid arteries from the mice and used genome-wide microarray technology to identify hundreds of genes that were turned on or off in the endothelial cells.

In past experiments, scientists grew endothelial cells in dishes to probe how different patterns of fluid flow affected their patterns of genes. However, growing cells in dishes alters them enough that many of the genes Jo's team found have not been identified before in this context.

For example, the team showed that the gene LMO4 - not previously known to be involved in atherosclerosis -- is turned on in their mouse model and also in human coronary arteries. Scientists studying breast cancer think LMO4 is involved in tumor migration and invasion, making an interesting parallel between atherosclerosis and cancer, Jo says.

He says his laboratory is now probing which of the newly identified genes are most important in atherosclerosis and searching for ways to

manipulate them with drugs or genetic techniques, with an eye towards possible diagnostic and pharmaceutical applications.

More information: References:

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