SOUTHWESTERN NEWS

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EMBARGOED UNTIL 11 A.M. CST, TUESDAY, MARCH 15, 2005

Molecule that usually protects infection-fighting cells may cause plaque deposits inside arteries

DALLAS – March 15, 2005 – A molecule that usually protects the body's infection-fighting cells might also contribute to fatty buildups that coat arteries and lead to heart disease, UT Southwestern Medical Center researchers have found.

The molecule, called apoptosis inhibitor of macrophage or AIM, inhibits cell death in macrophages, which circulate in the bloodstream and help the body fend off infection and foreign substances. The AIM-protected macrophages go on to encourage buildup of fats on the interior walls of arteries, according to Dr. Toru Miyazaki, senior author of a study that appears in the March issue of the journal *Cell Metabolism*.

"We found that AIM is highly expressed in certain macrophages and that lack of AIM dramatically decreased early atherosclerotic lesion development in mice," Dr. Miyazaki said. "These results may imply a novel therapeutic application of AIM regulation for prevention of atherosclerosis in the future. Most importantly and attractively for patients, this approach may not need dietary restriction"

Dr. Miyazaki, associate professor in the Center for Immunology and of pathology, and his colleagues first discovered the protective role of AIM six years ago. In the current study, scientists exposed mice lacking AIM to a fatty diet that would normally induce atherosclerosis. After several weeks, researchers found little to no atherosclerotic lesions. Comparatively, in mice that had normal AIM function, there was marked presence of plaque deposits in the arteries following a diet of high-fat food.

"This was dramatic evidence that showed suppressing AIM function translates into prevention of atherosclerosis," Dr. Miyazaki said.

Atherosclerosis, known as "hardening of the arteries," occurs when the inside walls of an artery become thicker and less elastic. This narrows the space for blood flow and can lead to angina

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and heart attacks in some people. Fatty buildups occur on the inner lining of an artery and gradually thicken into a plaque. As plaque grows, it narrows the artery more and more. When the plaque ruptures, blood clots form that can block the artery entirely.

Low-density lipoprotein is transported inside arteries by macrophages, which engulf the cholesterol through a process called oxidation. Macrophages produce pro-inflammatory substances, which cause a secondary effect, encouraging other cells to accumulate and worsen plaque buildup in arteries.

"The oxidized lipids are cleared out by macrophage cells, but the lipids themselves are very toxic to cells and promote apoptosis (cell death)," Dr. Miyazaki said. "Therefore AIM production is a self-defense mechanism for macrophage cells, but interestingly, is in turn detrimental for the body."

Atherosclerosis is a contributing factor to a number of cardiovascular diseases – the No. 1 cause of death among people in the United States. It is also highly associated with other risk factors such as smoking, obesity and diets high in fat and cholesterol.

UT Southwestern researchers involved in the study included Dr. Satoko Arai, postdoctoral researcher in the Center for Immunology; Angie Bookout, researcher; John Shelton, research scientist in internal medicine; and Dr. David Mangelsdorf, professor of pharmacology and Howard Hughes Medical Institute investigator. The University of California, Los Angeles, also contributed to this study.

The two-year study was funded by the Juvenile Diabetes Research Foundation and the National Institutes of Health.

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