Prostaglandin receptor key to atherosclerosis development

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Atherosclerosis – a disease that includes the buildup of fatty, cholesterol-laden lumps of cells inside the artery wall – is the underlying cause of heart attacks and strokes.

A team of Vanderbilt University Medical Center investigators has now demonstrated that a receptor for prostaglandin-E2 plays a key role in the development of atherosclerosis. The findings, reported this month in Cell Metabolism, point to this receptor and its signaling pathways as molecular targets for modulating atherosclerosis development.

Atherosclerosis is widely accepted to be an inflammatory disease process, involving immune system cells called macrophages.

"The first visible lesion in atherosclerosis – looking under a microscope – is the accumulation of cholesterol in macrophages or foam cells," said MacRae Linton, M.D., professor of Medicine and Pharmacology and senior author of the current studies. Since a major product of activated macrophages is prostaglandin-E2 (an inflammation-related signaling molecule), Linton and colleagues reasoned that this compound may play an important role in atherosclerosis.

Mounting evidence supports roles for prostaglandins and their receptors in atherosclerosis, but only two – prostacyclin and thromboxane-A2 – have been considered in detail, he said.

Linton, first author Vladimir Babaev, M.D., Ph.D., co-senior author

Sergio Fazio, M.D., Ph.D., and colleagues focused on two receptors for prostaglandin-E2, called EP2 and EP4, because they were known to be expressed by cells in human atherosclerotic plaques.

To study the roles of these receptors in atherosclerosis, the investigators performed a modified bone marrow transplant to develop mice in which the blood cells lacked either the EP2 or the EP4 receptor. They transplanted the blood-forming cells into mice missing the LDL receptor – a widely used model for studies of atherosclerosis because these mice rapidly develop plaques when fed a high-fat diet.

The researchers found that the mice with macrophages lacking the EP4 receptor had a significant reduction in atherosclerosis compared to mice with the EP4 receptor. They also observed an increase in macrophage programmed cell death (apoptosis) in the atherosclerotic lesions of mice with EP4-deficient cells.

The team examined EP4 receptor signaling pathways and discovered that two pathways known to be involved in macrophage cell survival (PI3K/Akt and NF-kappaB pathways) had lower activity in the EP4-deficient mice, suggesting a mechanism for the increase in macrophage cell death.

"Our studies clearly show that prostaglandin-E2 plays an important role in atherosclerosis and in macrophage survival," Linton said. "Prostacyclin and thromboxane aren't the whole story."

The findings suggest the potential for modulating the development of atherosclerosis with inhibitors of prostaglandin-E2 synthesis, which are already being studied, and also by manipulating the EP receptors or their signaling pathways, Linton said.

The link between macrophage apoptosis and lesion development remains

unclear, he said.

There have been some reports that increased macrophage apoptosis in early lesions reduces the lesion area, Linton said. Other studies have suggested that macrophage apoptosis creates a pro-inflammatory environment that promotes the development of more complex lesions. Still other reports speculate that macrophage cell death promotes plaque rupture, causing heart attacks and strokes.

If the latter is true, Linton said, the current studies could offer a mechanistic explanation for how the drug Vioxx increased heart attacks in patients. Vioxx, a selective inhibitor of the enzyme cyclooxygenase-2 (COX-2), was withdrawn from the market because of concern about an apparent increase in cardiovascular risk.

The current findings suggest that because COX-2 inhibition would reduce prostaglandin-E2 levels (COX enzymes perform the first step in the production of prostaglandins), it might increase macrophage apoptosis and promote plaque rupture.

Linton said his team plans to pursue studies aimed at understanding how macrophage apoptosis impacts more advanced atherosclerotic lesions in terms of their complexity and stability.

Source: Vanderbilt University