Researchers discover new culprit in atherosclerosis

9 January 2012

A new study by NYU Langone Medical Center researchers identified a new culprit that leads to atherosclerosis, the accumulation of fat and cholesterol that hardens into plaque and narrows arteries. The research, published online by *Nature Immunology* on January 8, 2012, explains why cholesterol-laden, coronary artery disease-causing cells called macrophages, accumulate in artery plaques.

"We have discovered that macrophages that accumulate in plaques secrete a molecule called netrin-1," said Kathryn J. Moore, PhD, senior author of the study and associate professor in the Departments of Medicine and Cell Biology at NYU Langone Medical Center. "Our study shows that netrin-1 blocks the normal migration of macrophages out of arteries, causing these immune cells to accumulate and promote the progression of atherosclerosis."

Artery plaques that break off causing vessel blockages, or potentially fatal heart attacks and strokes are known to have high macrophage cell content. Atherosclerosis is fueled by the presence of these cholesterol-laden macrophages in the artery wall. Typically, the immune system sends macrophages to clean up cholesterol deposits in arteries, but once they fill up with the unhealthy form of cholesterol they get stuck in the arteries, triggering the body's inflammatory response. The bloated macrophages then become major components of plaque lining artery walls. Until now, the mechanism by which macrophages become trapped has remained unknown.

In this new study, researchers show why macrophages remain in artery plaques leading to atherosclerosis. Netrin-1 promotes atherosclerosis by retaining macrophages in the artery wall. In fact, netrin-1 signals macrophages to stop migrating and as a result these cells accumulate within the plaque. In addition, study experiments show, genetically deleting netrin-1 can minimize atherosclerosis, reduce the level of macrophages in plaque and promote the migration of macrophages from plaques.

In the study researchers used a florescent tracking technique to label and monitor the movement of macrophage cells in and out of plaques. This experiment showed how macrophages were immobilized and retained in plaque by netrin-1 expression and also demonstrated macrophage emigration from plaque after the deletion of netrin-1.

"Our study identifies netrin-1 as a novel target for future therapeutic intervention for the treatment of atherosclerosis and cardiovascular disease," said Janine M. van Gils, PhD, lead author of the study and a post-doctoral researcher in the Marc and Ruti Bell Vascular Biology and Disease Program, Leon H. Charney Division of Cardiology, Department of Medicine at NYU Langone Medical Center. "This discovery provides new clues to help reduce the amount of plaque in arteries and the threat of atherosclerosis, a major cause of mortality in Western countries. The development of a new strategy to diminish macrophage accumulation in plaque offers great promise to reducing the occurrence of fatal cardiac events."

Provided by New York University School of Medicine