Researchers identify agent responsible for protection against early stages of atherosclerosis

December 12 2011

Researchers from Boston University School of Medicine (BUSM) have identified for the first time the A2b adenosine receptor (A2bAR) as a possible new therapeutic target against atherosclerosis resulting from a diet high in fat and cholesterol. The findings, which appear on-line in *Circulation*, may have significant public health implications.

Adenosine is a metabolite produced naturally by cells at low levels, and at higher levels during exercise or stress. Adenosine binds to and activates cell surface receptors, one of which is the A2bAR. Previous studies have described the A2bAR as anti-inflammatory and protective against kidney ischemia, cardiac reperfusion injury and restenosis, typically via bone marrow cell signals.

In mouse models, BUSM researchers found atherosclerosis induced by a high-fat diet was more pronounced in the absence of the A2bAR. They also found bone marrow transplantation experiments indicated that A2bAR bone marrow cell signals alone were not sufficient to elicit this effect. "A2bAR genetic ablation led to elevated levels of liver and plasma cholesterol and triglycerides, and to fatty-liver pathology typical of steatosis, assessed by enzymatic assays and analysis of liver sections," explained senior author Katya Ravid, MD, a professor of medicine and biochemistry at BUSM.

The researchers also identified the mechanism underlying this effect in

the liver, involving the control of the transcription factor SREBP-1 and its downstream targets-regulators of lipid synthesis. They found restoration of the A2bAR in the liver of A2bAR null mice reduced the lipid profile and atherosclerosis. "Most importantly, in vivo administration of a pharmacological activator of the A2bAR in control mice on a high fat diet reduced lipid profile and atherosclerosis. Thus, this study provides the first evidence that the A2bAR regulates liver hyperlipidemia and atherosclerosis, suggesting that this receptor may be an effective therapeutic target against earlier stages of atherosclerosis," Ravid added.

Provided by Boston University Medical Center