Protein could prevent blocked arteries

December 9 2008

A soluable N-cadherin plaque with more stable phenotype features.

(PhysOrg.com) -- For the first time, researchers have found that a modified form of a naturally occurring protein, N-cadherin, could prevent blocked arteries. Blocked arteries are a major cause of heart attacks and strokes.

The thickening of the artery wall, which occurs due to the build-up of fat and cells in the artery wall leads to the formation of an atherosclerotic plaque. Plaques can eventually break open, or rupture, leading to the formation of a blood clot that can block the artery and possibly lead to a heart attack or stroke. Doctors Cressida Lyon and Sarah George at the Bristol Heart Institute (BHI) have found by making a modified form of cadherin they can stabilise the plaques and prevent them from rupturing.

In this University of Bristol study, published in *Arteriosclerosis, Thrombosis and Vascular Biology* and funded by the British Heart

Foundation (BHF), Dr Lyon investigated the effects of a protein – called N-cadherin – that is produced by cells in the plaque. This protein helps neighbouring cells stick tightly together.

The researchers designed a smaller, soluble, form of N-cadherin that could be transported in the blood stream. They found that soluble cadherin stabilised the plaques, making them less likely to rupture.

Drs Lyon and George said: “This study is the first demonstration that reduction of cell death with soluble N-cadherin can reduce the likelihood of plaque rupture. It highlights soluble N-cadherin as a potential therapeutic for blocked arteries and thereby heart attack and stroke.”

The cellular composition of the plaque is an important factor in the likelihood of plaque rupture. There are two main cell types involved – smooth muscle cells, and inflammatory ‘bad’ white blood cells, called macrophages. Stable plaques contain high numbers of smooth muscle cells while unstable plaques container fewer smooth muscle cells. The smooth muscle cells form a protective cap over the top of the plaque and provide strength to prevent ruptures from occurring. Smooth muscle cell death, which occurs during unstable plaque development, causes a weaker cap and increases the likelihood of rupture. Death of macrophages leads to the attraction of further inflammatory cells, which increases the incidence of plaque rupture.

The researchers found soluble N-cadherin reduced the death of both smooth muscle cells and macrophages in culture and in a model of atherosclerotic plaque formation. This reduction in cell death protected the plaques from rupture and caused a more stable plaque type; the size of the smooth muscle cell-rich cap was increased and fewer macrophages were present.

Dr George added: “Further studies are of course essential, and therefore

we and our colleagues are performing longer term experiments and attempting to reduce the size of the molecule to make it more suitable for clinical use."

The paper: Soluble N-cadherin over-expression reduces features of atherosclerotic plaque instability; Lyon, C.B., Johnson, J.L., Williams, H., Sala-Newby, G.B., and George, S.J, Arteriosclerosis, Thrombosis, and Vascular Biology 2008; (epub). Published online before print November 13, 2008.

Provided by University of Bristol