Protein variant may boost cardiovascular risk by hindering blood vessel repair

September 17 2014

Philip Shaul. Credit: UT Southwestern

Researchers at UT Southwestern Medical Center have found that the most common variant of the circulating protein apolipoprotein E, called apoE3, helps repair the lining of blood vessels. Individuals with another variant, called apoE4, do not get the benefit of this repair, putting them at higher risk for cardiovascular disease.

"We believe that we have identified one mechanism by which apoE3 promotes a healthy cardiovascular system and why a genetic variant,

apoE4, is detrimental," said Dr. Philip Shaul, Professor of Pediatrics and Vice Chair for Research in the Department of Pediatrics at UT Southwestern.

The team of researchers found that apoE3 binds to a receptor, ApoER2, and that together they act on endothelial cells, which are the guardian cells of blood vessels, to produce a molecule called nitric oxide (NO). Nitric oxide blunts inflammation, a process that contributes to a variety of vascular disorders.

Up to 15 percent of individuals possess the gene coding for apoE4, and why these individuals are at increased risk of atherosclerosis and coronary heart disease had previously been enigmatic. Using both cell culture and mouse models, researchers showed that in contrast to apoE3, apoE4 cannot activate endothelial cells to produce NO. The reparative and anti-inflammatory processes, therefore, do not occur. In fact, apoE4 prevents the actions of apoE3, explaining why even individuals with one copy of the apoE4 gene are at increased risk of vascular disease.

Using mutant proteins, the investigators further determined the structural feature of apoE4 that prevents the protein from having the favorable actions of apoE3 and instead causes it to antagonize cell responses to apoE3.

The findings, recently published online in the *Proceedings of the National Academy of Sciences,* also suggest a potential preventive treatment for cardiovascular disease in the high-risk individuals who have the apoE4 variant.

"An important mechanism that is lost when people possess apoE4 is the ability to produce NO, which leads to a loss of both the reparative and anti-inflammatory capacities of the endothelium," said Dr. Shaul, who holds the Associates First Capital Corporation Distinguished Chair in

Pediatrics. "Now, knowing this information, we believe such individuals may benefit from treatment with an NO donor. There is a form of aspirin, for instance, that is an NO donor," he added.

Whereas there is considerable understanding of the biology of the apoE-ApoER2 tandem in the central nervous system and in Alzheimer's disease, the basis for the cardiovascular impact of the receptor and apoE variants had been perplexing. The new findings on apoE and ApoER2 complement the team's prior work on ApoER2, which revealed an important role for the receptor in the blood-clotting disease known as the antiphospholipid syndrome.

Provided by UT Southwestern Medical Center