MedicalXpress

Protein thought to protect against oxidative stress also promotes clogging of arteries

January 10 2011

UCLA researchers have found that a protein that plays an important role in some antioxidant therapies may not be as effective due to additional mechanisms that cause it to promote atherosclerosis, or clogging of the arteries.

Published in the January issue of the journal *Arteriosclerosis,* Thrombosis *and Vascular Biology*, the finding may give clues as to why some antioxidant therapies have not yielded more positive results.

The protein, called Nrf2, has been thought to be an important drug-therapy target for diseases such as cancer because it can induce chemopreventive activity by attaching to specific sequences of DNA, leading to the release of numerous antioxidant and anti-inflammatory genes and enzymes that can decrease or inhibit the effects of carcinogens.

Researchers reasoned that Nrf2, with its potent ability to boost antioxidants, might also be useful in combating the cell and tissue damage, or oxidation, that leads to atherosclerosis.

However, UCLA scientists found that while Nrf2 boosted antioxidant properties in an animal model, it also increased the development of atherosclerosis by raising plasma cholesterol levels and cholesterol content in the liver.

According to researchers, this is the first study to document these

additional effects on cholesterol metabolism in tandem with plaque formation in the arteries.

"We were very surprised at the finding," said principal investigator Dr. Jesus Araujo, director of environmental cardiology at the David Geffen School of Medicine at UCLA. "In fact, the atherosclerosis-producing factors were greater than the antioxidant benefits. The development of novel antioxidant therapies is quite important, and this research may help shed light on why treatments affecting this protein may not be as effective as we thought."

For the study, the team was able to isolate and identify Nrf2's actions by looking at what would happen in mice that were specially bred without the protein.

Researchers found that male mice without Nrf2 had decreased levels of antioxidants, as would be expected, but also exhibited a 53 percent reduction in atherosclerotic plaques in the aorta, compared with normal animals. Mice with only half the gene expression for Nrf2 exhibited the same degree of plaque formation as normal animals.

The team then tried to arrive at a better understanding of what was going on by evaluating several factors that could be affected by the Nrf2 protein.

Scientists found that the mice without any Nrf2 had lower levels of total cholesterol in the blood and lower amounts of cholesterol in the liver. The protein deficiency also led to reduced expression of the genes involved in synthesizing and storing fat and regulating glucose in the liver, which are part of the process of manufacturing cholesterol.

According to Araujo, the study findings point to new and important effects of the Nrf2 protein in regulating cholesterol production as well as

antioxidant pathways.

"The cholesterol effects may need to be taken into consideration when developing antioxidant therapies using this protein," said Fen Yin, a co-author of the study and a research associate in the division of cardiology at UCLA. "The dosage or level of this gene expression could be important to balance the two effects."

In addition, investigators found that most of the effects of Nrf2 were more highly prevalent in the male mice. More studies will be needed to examine whether these sex differences in the animal model would be similar in humans.

Araujo noted that more research will also assess whether other environmental, metabolic and genetic elements play a role in the impact of Nrf2 on cholesterol and antioxidants.

Provided by University of California - Los Angeles