Researchers identify drug target for atherosclerosis

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(Medical Xpress) -- UC Davis researchers have made a significant step forward in the search for ways to reduce heart attack and stroke risk.

Published in the July 5 issue of Circulation, their study shows that a protein known as nonmuscle myosin light chain kinase — or nmMLCK — causes cells that normally seal the inner surface of blood vessels to contract, creating gaps that allow fats and cell debris to leak through tissue barriers and form plaques inside arterial walls. Eventually, the plaques harden and narrow blood vessels, leading to atherosclerosis and greatly increasing the likelihood of coronary and neurovascular events.

"It is well known that the cells forming the interface between circulating blood and vascular tissues — the endothelium — is transformed during atherosclerosis," said Sarah Yuan, a UC Davis physician, professor of surgery and senior author of the study. "But the specific processes that make this change happen aren't well understood. Our outcome clarifies that nmMLCK compromises the natural barrier function of endothelial cells, leaving arteries susceptible to injury."

Yuan and UC Davis assistant project scientist Chongxiu Sun previously discovered that nmMLCK increased the permeability of blood vessel walls in response to inflammation. That initial outcome led them to consider that this protein could also play a role in plaque formation.

To find out if this was the case, Yuan and Sun "knocked out" the gene that produces nmMLCK in mice, and then fed them diets high in fat and

cholesterol. They fed the same diet to mice with no genetic alterations. After 12 weeks, the knock-out mice developed aortic lesions less than half the size of lesions in mice with unaltered nmMLCK gene.

The team also measured fat-carrying lipid and monocyte levels in blood and aortas and found that these key plaque-forming agents penetrate the endothelial barrier more easily in mice with intact nmMLCK genes. The knock-out mice had far less lipid content and fewer macrophage deposits (created when monocytes migrate through the endothelium) in their arterial walls.

"Eliminating nmMLCK significantly reduced the severity of arterial damage," said Sun, lead author of the current study. "The protein turns cells that are normally very protective into heart disease facilitators."

Sun and Yuan are planning to further characterize the contributions of nmMLCK to atherosclerosis by determining the unique structure of the protein. This research will give scientists the tools they need to develop drugs that block nmMLCK. They are particularly interested in a molecular pathway called Src (pronounced "sarc") that is activated by nmMLCK. Src is known to be involved in other diseases, including osteoporosis and certain cancers.

"We need to fully profile this protein and its interactions with other molecules to identify the best possible way to block its function," said Yuan, whose research focuses on the cellular and molecular regulation of cardiovascular functions. "Understanding exactly how it works is critical to providing new treatment options for patients."

Provided by UC Davis