Study shows underlying connection between 'good' cholesterol and collagen in heart health

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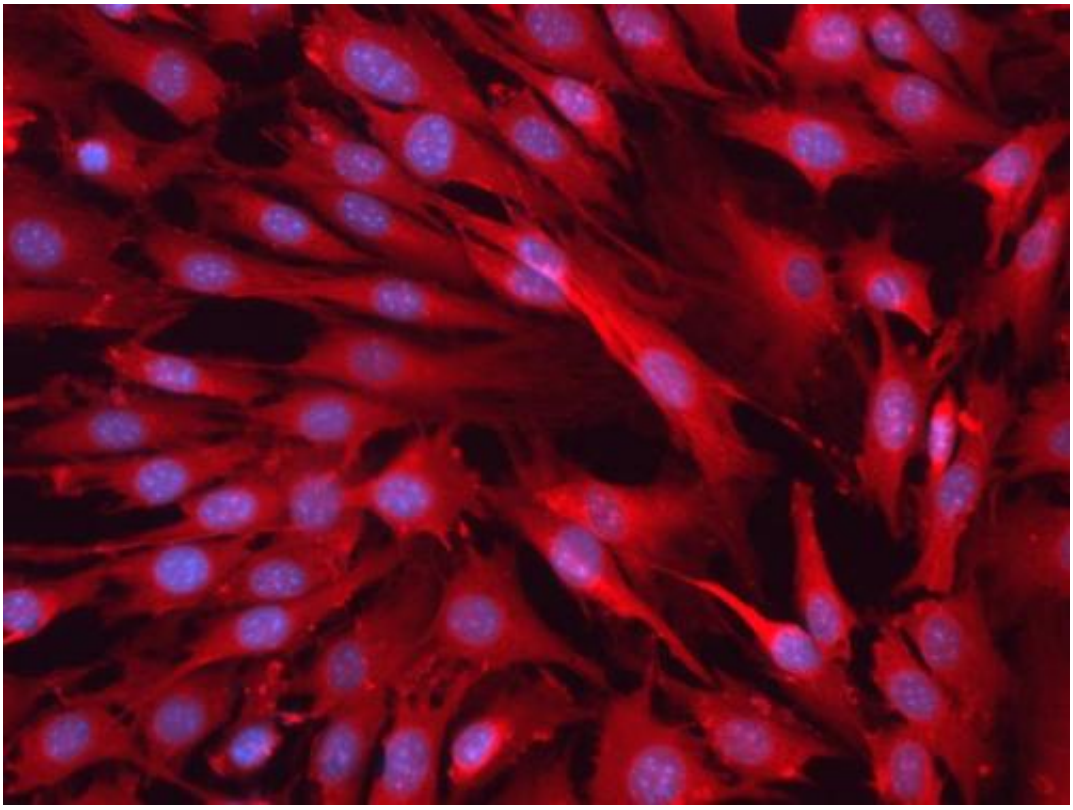

This image shows collagen production (stained red) in aortic smooth muscle cells. The cell nuclei are stained blue. Credit: Richard K. Assoian, Ph.D., Perelman School of Medicine, Univeristy of Pennsylvania; *Cell Reports*

(Medical Xpress)—Arterial stiffening has long been considered a major risk factor for cardiovascular disease. Keeping arteries soft and supple might reduce disease risk, but the mechanisms of how arteries stave off

hardening has remained elusive.

Researchers from the Perelman School of Medicine, University of Pennsylvania, Wistar Institute, and The Children's Hospital of Philadelphia have discovered that the protein apolipoprotein E (apoE) plays a major role in maintaining arterial softness by suppressing production of the extracellular matrix, a network of connective tissue in the body. Their research appeared in the most recent issue of *Cell Reports*.

ApoE is a component of several lipoproteins, including HDL, the "good" cholesterol, and is generally believed to forestall atherosclerosis. But several recent major studies have questioned the link between HDL and cardiovascular protection. Meanwhile, other research involving cultured cells has indicated that apoE has effects beyond its role in regulating lipid levels as a component of HDL. The present work suggests that it may be the apoE-containing HDL that confers the main benefit of HDL by promoting arterial softness.

Analyzing genetic datasets of regular mice and mutant mice without apoE, the researchers showed definite differences in gene expression, with the apoE-null mice displaying marked increase in indicators of stiffening – the proteins collagen, fibronectin, and lysyl oxidase in response to stiffening in the aorta, which led to severe atherosclerosis. To attempt to mitigate the atherosclerosis seen in the apoE-null mice, the researchers fed them a high-fat diet and treated them with a lysyl oxidase inhibitor, which softened their arteries.

Despite highly elevated cholesterol, the mice showed a marked improvement in their atherosclerosis. The results suggest that the lack of apoE results in arterial stiffness, and that even with high cholesterol, increasing arterial elasticity by pharmacologic means can greatly reduce atherosclerotic disease.

"HDL can't be looked at as just one compound, because it is a mixture of different molecular components," explains senior author Richard K. Assoian, PhD, professor of Pharmacology. "The component that has these effects on arterial stiffening is a minor part of total HDL." Assoian notes that this could help to reconcile the conflicting clinical evidence regarding the link between HDL and reduced cardiovascular disease. "It might be the apoE HDL fraction that you need to keep high and not worry about the total HDL," he suggests. Because apoE is only about 6 percent of total HDL, "it could go up sky high or not at all, and you probably wouldn't detect it in these studies that try to raise total HDL."

The possibility of preventing or treating atherosclerosis by promoting arterial elasticity independent of cholesterol could be a boon for the many people unable to tolerate the statin drugs that are the usual treatment.

"Perhaps there are other routes that you could use, independent of cholesterol and statins, that could help keep atherosclerosis at bay," says co-first author Devashish Kothapalli, PhD. "We think controlling stiffening is one of those. We showed in the paper that even when cholesterol is remarkably high, if you soften tissues back to a healthy level, atherosclerosis is inhibited."

Targeting arterial stiffening could also provide added benefit for patients already on statins. "Ultimately we would hope that controlling stiffening could be used in conjunction with a statin for the large percentage of people who are already on statins but need extra help," says co-first author Shu-Lin Liu, PhD.

Although the current study demonstrates how apoE and apoE-containing HDL promote cardiovascular health by maintaining arterial softness, Assoian notes that a practical treatment would likely not target apoE, because it "does a lot of other things that you don't want to interfere

with. So the goal in my mind would be to develop something that is really targeting stiffness but not affecting any of the lipid aspects of atherosclerosis that apoE and HDL control. The lysyl oxidase inhibitor drug we used in this study, BAPN, is good for proof of principle, but not useful on a practical level, because there are too many side effects."

More information: download.cell.com/cell-reports …2211124712003221.pdf

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