Researchers solve mystery of how statins improve blood vessel health

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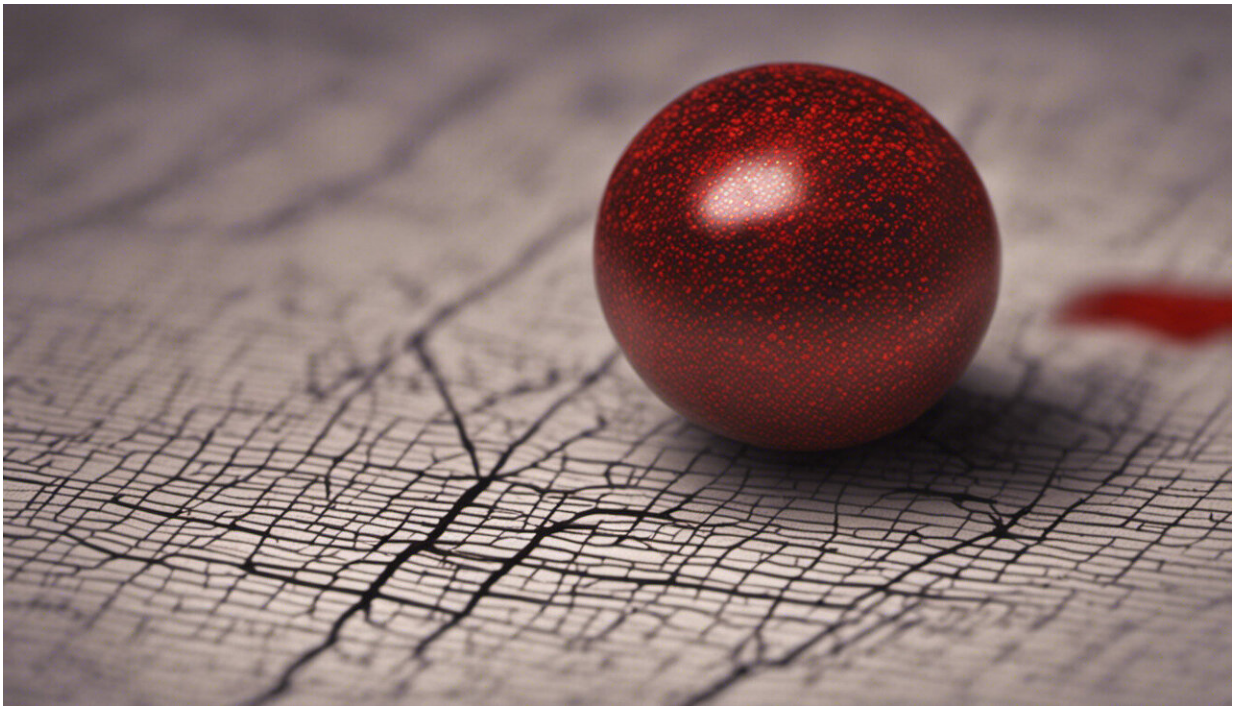

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Using new genetic tools to study statins in human cells and mice, Stanford Medicine researchers and collaborators have uncovered how the cholesterol-lowering drugs protect the cells that line blood vessels.

The findings provide new insight into statins' curiously wide-ranging

benefits, for conditions ranging from arteriosclerosis to diabetes, that have long been observed in the clinic.

"The study gives us an understanding, at a very deep mechanistic level, of why statins have such a positive effect outside of reducing LDL," said professor of medicine Joseph Wu, MD, Ph.D., referring to low-density lipoprotein, or "bad" cholesterol. "Given how many people take statins, I think the implications are pretty profound."

Statins are the most prescribed medications in the country, with more than 40 million Americans taking them. Developed in the 1980s from compounds found in mold and fungi, statins target an enzyme that regulates cholesterol production in the liver. But clinical trials have shown that they also seem to safeguard against cardiovascular disease beyond their ability to lower cholesterol.

Heart failure patients who take statins, for example, are less likely to suffer a second heart attack. They have also been shown to prevent the clogging of arteries, reduce inflammation and even lower cancer risk. Yet these underlying mechanisms are poorly understood.

"Statins were invented to lower cholesterol by targeting the liver. But we didn't know the targets or the pathways in the cardiovascular system," said Chun Liu, Ph.D., an instructor at the Stanford Cardiovascular Institute and co-lead author of the study published May 8 in *Nature Cardiovascular Research*. Mengcheng Shen, Ph.D., and Wilson Tan, Ph.D., postdoctoral scholars at the Stanford Cardiovascular Institute, are the other co-lead authors, and Wu is the senior author.

Hints from a dish

To take a closer look at statins' effect on blood vessels, Liu and colleagues tested a common statin, simvastatin, on lab-grown human

endothelial cells derived from induced pluripotent stem cells. Endothelial cells make up the lining of blood vessels, but in many diseases they transform into a different cell type, known as mesenchymal cells, which are poor substitutes.

"Mesenchymal cells are less functional and make tissues stiffer so they cannot relax or contract correctly," Liu said.

The researchers suspected that statins could reduce this harmful transition. Indeed, endothelial cells treated with simvastatin in a dish formed more capillary-like tubes, a sign of their enhanced ability to grow into new blood vessels.

RNA sequencing of the treated cells offered few clues. The researchers saw some changes in gene expression, but they "didn't find anything interesting," Liu said.

It was not until they employed a newer technique called ATAC-seq that the role of statins became apparent. ATAC-seq reveals what happens at the epigenetic level, meaning the changes to gene expression that do not involve changes to the genetic sequence.

They found that the changes in gene expression stemmed from the way strings of DNA are packaged inside the cell nucleus. DNA exists in our cells not as loose strands but as a series of tight spools around proteins, together known as chromatin. Whether particular DNA sequences are exposed or hidden in these spools determines how much they are expressed.

"When we adopted the ATAC-seq technology, we were quite surprised to find a really robust epigenetic change of the chromatin," Liu said.

ATAC-seq revealed that simvastatin-treated cells had closed chromatin

structures that reduced the expression of genes that cause the endothelial-to-mesenchymal transition. Working backward, the researchers found that simvastatin prevents a protein known as YAP from entering the nucleus and opening chromatin.

The YAP protein is known to play important roles in development, such as regulating the size of our organs, but also has been implicated in the abnormal cell growth seen in cancer.

A look at diabetes

To see the drug in context, the researchers tested simvastatin on diabetic mice. Diabetes causes subtle changes to blood vessels that mimic the damage commonly seen in people who are prescribed statins—older patients who do not have a cardiovascular condition, Liu said.

They found that after eight weeks on simvastatin, the diabetic mice had significantly improved vascular function, with arteries that more easily relaxed and contracted.

"If we can understand the mechanism, we can fine-tune this drug to be more specific to rescuing vascular function," Liu said.

The findings also provide a more detailed picture of the vascular disease process, which could help doctors identify and treat early signs of vascular damage.

"I've been taking statins for the past 10 years to keep my cholesterol down. I also knew it has good vascular effects. I just didn't know how it does it," said Wu, the Simon H. Stertzer, MD, Professor who is also the director of the Stanford Cardiovascular Institute. "This study explains how."

More information: Chun Liu et al, Statins improve endothelial function via suppression of epigenetic-driven EndMT, *Nature Cardiovascular Research* (2023). DOI: 10.1038/s44161-023-00267-1