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Mini molecules could help fight battle of aortic bulge

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When aortic walls buckle, the body's main blood pipe forms an ever-growing bulge. To thwart a deadly rupture, a team of Stanford University School of Medicine researchers has found two tiny molecules that may be able to orchestrate an aortic defense.

A team led by cardiovascular scientists Philip Tsao, PhD, and Joshua Spin, MD, PhD, identified two microRNAs — small molecules that usually block proteins from being made — that work to strengthen the aorta during bulge growth. By tweaking the activity of each molecule, they could reduce abdominal aortic aneurysms in mice, which they believe is a promising step toward a new treatment for the disease.

Their findings will be published Feb. 22 in *Science Translational Medicine* and are a continuation of work the researchers published Feb. 1 in the *Journal of Clinical Investigation*.

Abdominal aortic aneurysms affect thousands of people in the United States each year. The ballooning blood vessel — which looks more like a snake digesting a bowling ball than a central thoroughfare for oxygenated blood — is most likely to occur in people over age 65. For smokers, the chances are even greater.

"Ninety percent of people who get one of these are smokers," said Spin, an instructor in cardiovascular medicine and a co-author of both papers.

These types of aortic aneurysms usually form below the kidneys, before

the aorta branches into the legs. When they rupture, blood spills out into the abdomen, causing death in up to 90 percent of cases. Knowing you have an aortic aneurysm can be nerve-wracking.

"There are no approved therapies, so the recommendation for many patients is just watchful waiting," said Tsao, professor of cardiovascular medicine and the senior author of both papers. "When they reach a certain size, the risk of rupture outweighs the risks of surgical intervention."

To repair the weak blood channel, doctors can either surgically replace the aneurysm with a graft, or use catheters to insert a self-expanding, cloth-covered tube that blocks off the ballooned region and restores blood flow to a straight path.

With such high stakes, Tsao and Spin set out to better understand why aneurysms form. All they knew was what happened in the aorta when they did: dissolution of muscle cells, inflammation, and thinning of supportive collagen and other fibers.

To understand the causes, the team compared cells in the vessel wall at the site of the aneurysm to unaffected cells nearby and to aortas without aneurysms. When they looked at genes that cells were turning on or off, they found differences in two microRNAs: miR-21and miR-29b.

MicroRNA is a special type of RNA, which usually functions as an intermediate step in the decoding of DNA into proteins for the cell to use. MicroRNAs, which get their names from being smaller than typical RNA, specifically clamp onto other RNA molecules and block the cell from making proteins.

From previous studies, the team knew that miR-21 — which the cells turned on during blood vessel ballooning — works to keep cells alive and

dividing. MiR-29b, which works to keep collagen and other fibers from being made, was reduced.

"When you see something go up or down as disease is getting worse, you assume that what it's doing is causing the disease," Spin said. But appearances can be deceiving.

The team used human tissue, and mice that develop aortic aneurysms, to understand what these microRNA changes meant for aneurysm development. In each of the studies, they injected the mice with molecular mimics of the microRNAs, or other molecules that would specifically block either miR-21 or miR-29.

Because smoking is a large risk factor for the deadly aorta expansions, they also gave the mice nicotine injections to test whether it played a role.

Surprisingly, they found that when they gave the mice more miR-21, their aortas didn't balloon as much or burst open. In contrast, knocking down the level of miR-21 in the cells had the opposite effect. Since the cells at the site of the aneurysm already had elevated levels of miR-21 compared to other cells, the team thinks the change is an attempt by the body to protect itself.

"This looks like a response of the body to the process; it's trying to limit how fast the aneurysm is growing," Spin said.

Interestingly, in the mice given nicotine, aneurysms grew even faster, suggesting that smoking, and more specifically nicotine, was a direct factor in aneurysm development. Additional miR-21 was also beneficial in this model of accelerated disease.

"Often one of the things that people try to use to stop smoking is

nicotine therapy," Spin said. "That may not be the best way to prevent an aneurysm from getting worse."

When they looked at miR-29b, which the cells naturally turn down in aneurysms, they found that artificially knocking it down further slowed aneurysm development and prevented rupture. It too seems to be responding protectively to aneurysm development, rather than contributing.

While insights from the discoveries about the two microRNAs may lead to therapies for aortic aneurysms, the path is not without complications.

"Unfortunately, treatments that benefited aneurysms in the mice came with negative consequences on the heart and the liver," Tsao said. "So one of the pressing matters would then be, 'how can we get it only in that area or concentrated in the area?'"

They already have a collection of ideas of how to deliver the mini molecules, including using a balloon-like device at the location of the aneurysm that would directly inject microRNA mimics or inhibitors onto the cells.

It might be the case, Tsao said, that miR-29b or miR-21 might not be the best microRNAs to target. "Perhaps there are others that could work better," he said. "But we hope this will establish a new way to approach the disease."

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