'Big data' approach helps pinpoint possible new stent drug to prevent heart attacks

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Euan Ashley and his colleagues have identified what they believe would be a better drug for use on stents that prop open clogged heart arteries. Credit: Mark Tuschman

(Medical Xpress)—Stanford University School of Medicine researchers hunting for a better drug coating for coronary stents, the small mesh tubes used to prop open plaque-filled arteries, have pinpointed a cancer drug as a possible candidate.

In mice, crizotinib helped to prevent stent disease, the often-serious

medical problem caused by stents themselves, without affecting the blood vessel lining. The medication has already been approved by the U.S. Food and Drug Administration for chemotherapy.

A paper describing the findings was published online Nov. 17 in The *Journal of Clinical Investigation*.

"This could have major clinical impact," said Euan Ashley, MD, senior author of the study and associate professor of cardiovascular medicine and of genetics. "We found the agent crizotinib not only reduced stent disease but also protected the endothelium of the blood vessels. The implications are that, down the road, patients who receive drug-eluting stents with this new drug may no longer be required to take blood thinners after their procedure."

The power of big data

The study is also an example of scientists harnessing vast quantities of data to understand genetically complex diseases. By combining text analysis of the whole medical literature with data from large-scale genetic studies in humans, the researchers built a theory that they then tested in the laboratory.

"We used human tissue to identify novel mediators of disease using the computational biology approach—the 'big data' approach," said Ziad Ali, MD, PhD, lead author of the paper. Ali was a cardiovascular fellow at Stanford during the first years of the study and now is associate director of translational medicine at Columbia University Medical Center.

"The computational biology approach can give you a good hypothesis, but then you need to prove it in the lab," he added. "The marriage of the two is what makes this study really special."

In order to find a more effective drug to use on stents, the researchers first wanted to better understand the genetic pathways of coronary artery disease, also known as coronary atherosclerosis. The disease is caused by the buildup of plaque along the inner walls of heart vessels. The buildup can eventually lead to chest pain and potentially lethal heart attacks. It is the leading cause of death worldwide.

Balloon angioplasty is a common treatment for atherosclerosis. It's used to open up a clogged artery, often in combination with the placement of a stent that helps keep the artery open. But stent disease, or in-stent stenosis, is the major limitation to this treatment. This occurs when the stents themselves damage the artery lining, causing the growth of scarlike tissue that narrows the vessels. Such narrowing can lead to recurrence of symptoms and even heart attacks.

The risks of drug-eluting stents

To solve this problem, drug-eluting stents are used to block such growth. These stents can help but also can inhibit the regrowth of the lining of the blood vessel, the endothelium, leading to delayed arterial healing and increasing the risk of blood clots and heart attacks. Thus, patients treated with drug-eluting stents, a total of 1 million each year nationwide, according to the American Heart Association, require longer treatment with blood thinners to prevent sudden stent blockage from a blood clot. This makes drug-eluting stents less desirable for people with bleeding problems or those who will need some type of surgery within a year after the stent is put in.

"Even though we've made drug-eluting stents, still 10 percent of stents block up," Ali said. "Patients have to take a blood thinner for about a year. A lot of our patient population is on the elderly side with bad hips or diabetes. Once you get a drug-coated stent, you can't have surgery for a year. And if you stop the blood thinners for any reason, you're at risk

of a stent clotting off. And that actually causes a heart attack. Stent thrombosis has a high mortality rate.

"Our idea was to find a novel therapeutic that would stop the regrowth while not affecting the endothelium of the vessels," Ali said.

Zeroing in on genes

To study the genetic pathways involved in coronary artery disease, researchers started with a gene network analysis of coronary artery samples collected from 89 patients in Germany. Their analysis identified the gene GPX1 as associated with cardiovascular events. GPX1 is one of the body's strongest natural antioxidant defense mechanisms. They further tested this by studying mice with atherosclerosis in which the gene had been knocked out. Plaque increased significantly in the arteries of mice with knocked-out GPX1.

Conducting further analyses of gene interactions in two studies—one from Japan, the other a meta-analysis of genome-wide data for stent disease done in the United States—researchers found that there was an increased risk of the disease from regulatory interplay between two genes, GPX1 and ROS1.

"We didn't know anything about ROS1," Ashley said. "It hadn't been studied in cardiovascular diseases. We knew it was an important gene in cancer. We thought, that's odd, since the growth caused by stents is almost like a tumor. It's odd that it was a cancer gene."

To test whether inactivation of ROS1 could help modulate the damage to blood vessels, researchers applied the chemotherapy drug crizotinib—which is used as a personalized medicine treatment for certain ROS1-positive lung cancers—to mice with coronary artery disease and surgically implanted stents. They found that the drug stopped

stent disease and didn't damage the endothelial growth.

"The major finding of the study is that artery stent disease acts surprisingly like a tumor in the blood vessel wall," Ashley said. "Inhibiting it with nonspecific pharmaceutical agents, as we do now, leads to heart attacks from clots caused by lack of endothelial lining on the stent, whereas targeting it with the drug we use here, crizotinib, acts much more specifically and inhibits the disease without affecting the endothelium."

These results also highlight the need for targeted rather than broad-spectrum therapies, the study says.

Provided by Stanford University Medical Center