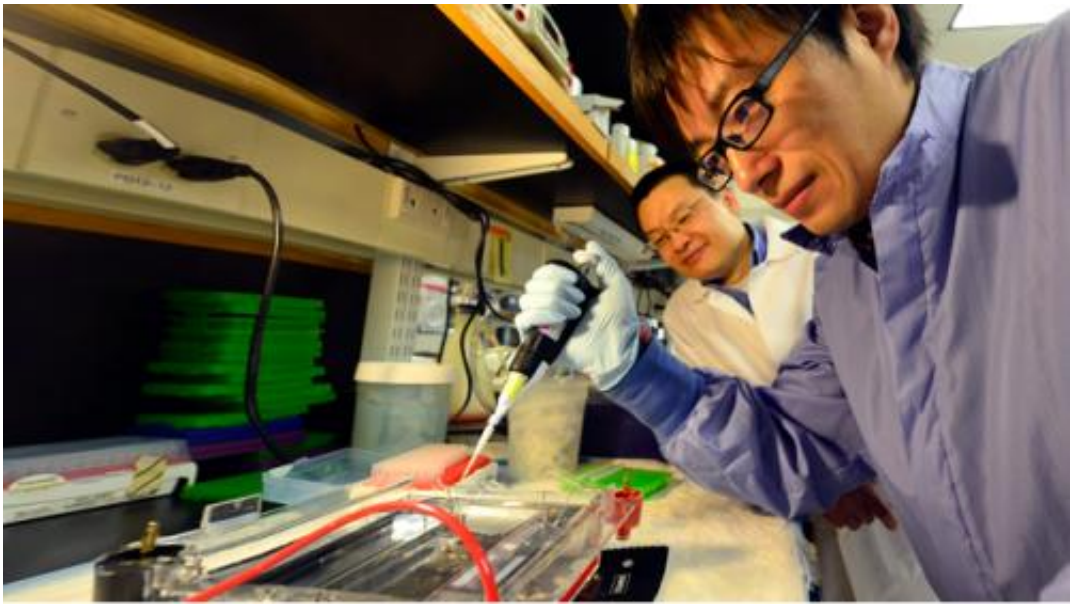
Protein called YAP gives blood vessels strength, shape

March 24 2014



This is a photo of Dr. Jiliang Zhou, vascular biologist at the Medical College of Georgia at Georgia Regents University, with Georgia Regents University postdoctoral fellow Yong Wang. Credit: Phil Jones

A protein known to promote cancer appears to give the blood vessels strength and shape, researchers report. When yes-associated protein, or YAP, is deleted from vascular smooth muscle cells during development, the protein makes thin-walled blood vessels that over-dilate in response to the usual pressure of blood flow, said Dr. Jiliang Zhou, vascular biologist at the Medical College of Georgia at Georgia Regents University.

"The thickness of the arterial wall decreases from three or four layers of smooth muscle cells to one or two layers," said Zhou, corresponding author of the study featured on the cover of the American Heart Association journal, *Circulation Research*.

The researchers also found that YAP appears to manage vascular smooth muscle cells by controlling expression of the cell cycle arrest gene, Gpr132. During growth, YAP suppresses this suppressor then, when blood vessels walls are the right size, YAP expression decreases and Gpr132 expression increases.

"The balance shifts," Zhou said. When the scientists deleted YAP in mice, Gpr132 expression increased and cell proliferation decreased. Conversely, knocking down Gpr132 expression increases vascular smooth muscle cell proliferation.

The study required deleting YAP from both vascular smooth muscle cells and heart cells – technology does not enable more selective removal – so the mice also were born with significant heart defects, confirming the protein's key role in heart formation. YAP's absence has been shown to cause, for example, ventricular septal defects, a common congenital heart defect in which a persistent hole between the right and left ventricle can lead to heart failure.

The mice in this study died shortly after birth from significant heart and vascular defects. Zhou suspects that less severe alterations in YAP may also produce aneurysms, weak points in the vascular system that often go undetected before rupturing, with benign to lethal results depending on their size and location. He and his colleagues are working on a method to selectively manipulate YAP levels in smooth muscle cells to further pursue their role in aneurysms and, ideally, find a way to easily identify and treat them.

"If you completely disrupt YAP function, you are not going to survive," Zhou said. "But you also may experience a dose-dependent defect so your arterial walls are thinner and you can survive development but may be prone to aneurysms as an adult."

showed that YAP plays a role in the re-narrowing, or restenosis, of the carotid artery after treatment to avoid a stroke. Those studies were published in the AHA journal *Arteriosclerosis, Thrombosis, and Vascular Biology*.

They found that physical injury resulting from inserting a catheter to clear the artery then inserting a stent to help keep the artery open led to YAP-mediated creation of new plaque over just two weeks in rats, which likely translates to a couple of years in humans.

"It's a double-edged sword. You remove the plaque but you somehow create the new stress to the tissue and the smooth muscle cells respond by building plaque again," Zhou said. Coating stents with drugs such as rapamycin, an immunosuppressive drug given to kidney transplant patients, appears to reduce or at least delay restenosis.

Zhou is working with Dr. Alvin V. Terry Jr., Chairman of the MCG Department of Pharmacology and Toxicology, to develop an anti-YAP drug that could provide another layer of protection. He's also working with MCG Vascular Surgeon Gautam Agarwal to look at carotid artery plaque removed from patients to see if YAP, along with known culprits such as a high-fat, high-cholesterol diet, also has a role in its initial formation. YAP's role in restenosis prompted Zhou to explore its role in normal blood vessel wall formation.

Zhou noted that YAP likely plays a similar role in blood vessel formation throughout the body and he suspects it also has a role in endothelial cells, which comprise the innermost layer of blood vessels.

YAP is also known to help determine organ size; in fact, when it's overexpressed in, for example, the liver for only a week, the organ can grow five times its usual size.

Because of YAP's varying roles. drugs to control it will require localized delivery, which is another reason Zhou likes the idea of coating stents. YAP was originally identified in the fruit fly.

Provided by Medical College of Georgia