Discovery points way to new treatments for painful circulation problem

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(Medical Xpress)—A discovery at the University of Virginia School of Medicine is opening up new avenues for treating peripheral arterial disease, a common circulation problem that afflicts millions of Americans. Researchers have pinpointed a key genetic regulator that appears to control the ability to adapt to blockages in blood vessels – and it turns out to be a tiny RNA molecule.

The finding gives researchers a new target for potential therapies to treat patients with peripheral arterial disease, as well as allowing them to better understand the progression of the disease in patients.

"Why does one person with peripheral arterial disease remain stable and do well while another person has a much worse clinical course? We need to begin to unravel these types of questions," said Dr. Brian Annex, division chief of cardiovascular medicine at U.Va. "When we see a patient with peripheral arterial disease, the reality is that information we get out of their age, gender, risk factors and basic clinical measures doesn't tell us how the patient is going to do. We're often left with uncertainty. I think as we begin to understand the [implications of the discovery], we will better understand PAD and open up entirely new treatment approaches."

Peripheral arterial disease is caused by atherosclerosis that builds up inside the arteries and impedes blood flow, most often to the legs. Treatments to date have been ineffective at improving blood flow in PAD.

U.Va.'s discovery may help change that. The researchers determined that a specific "microRNA" molecule, microRNA-93, appears to control the expression of several related genes in mouse models of PAD.

"This microRNA had profound effects on both endothelial and muscle cells," Annex said. "Whether we used a gain of function or loss of function, in pretty much every situation, whenever we got a gain of function or a therapeutic benefit, the microRNA was present at a higher level and suppressed three genes. Whenever you had less miR-93, you had more expression of these and a poorer response to injury/repair."

Scientists once thought that microRNAs were effectively junk with no ability to generate proteins. But recently microRNAs have emerged as major regulators of how genes respond to injury. In the case of PAD, the U.Va. researchers found, microRNA-93 directs how genes react to the restriction in blood supply.

"The central dogma of molecular biology – that DNA makes RNA and RNA makes protein – is probably wrong more often than it's right," Annex said.

U.Va.'s discovery presents an exciting new possibility of treating PAD by boosting the effects of microRNA-93, Annex said.

"To date, drugs used to treat patients with PAD have always tried to target a single gene, whereas it's very clear this microRNA has significant effects on multiple related genes," Annex said. "This opens up an entirely new paradigm for treating and understanding peripheral arterial disease."

While more research needs to be done, Annex foresees several potential ways doctors could manipulate microRNA-93 to target PAD and avoid problems that plague other efforts to develop new treatments.

"One can imagine a direct strategy of delivering the microRNA, one can imagine a strategy to change the body's own expression of the microRNA, one can try to figure out ways to prevent the breakdown of the microRNA," he said. "Many of the strategies that are being set up to treat patients with peripheral arterial disease try to grow new blood vessels. Our microRNA will grow blood vessels, but what's absolutely fascinating is that … it not only makes new blood vessels, but the blood vessels have structure and architecture and may very well get around the prior problems where drugs cause the development of leaky, malformed blood vessels."

The new findings have been detailed in a paper published online by the journal *Circulation*.

Provided by University of Virginia