

# Researchers discover new way to reverse poor circulation and heal wounds

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Researchers have solved a longstanding mystery about how flexing muscles “tell” nearby blood vessels that they need more blood to perform, according to a study published Feb. 15 in the journal *Circulation Research*. The study mechanism suggests new ways to treat conditions that involve poor circulation like peripheral artery disease, which comes with aging, affects 10 million Americans and leads to amputation in the worst cases. Furthermore, the same signals that influence circulation in some tissues drive cell growth elsewhere. That could lead to an ointment that would speed healing when spread across chronic wounds.

In the larger picture, the study results reflect the rise of the extracellular matrix (ECM), a network of proteins that surrounds all cells in the body. Differences in the amounts and types of proteins assembled into the ECM gives rise to various forms of matrix, including both hard connective tissues like bone and the soft connective tissues that surround organs. Once thought to be no more than inert scaffolding that anchors cells and lends shape to human tissue, ECM connective tissue has emerged as a vital signaling partner with cells in controlling bodily function.

The results of the study also reflect a growing recognition of physical force as a driver of biochemical reactions that contribute to both health and disease. Force applied to bone by weightlifting, for example, is now known to thicken bone. The force of fast blood flow on blood vessel walls may protect them from atherosclerosis.

The two trends come together in the new study, which explains for the first time how the force of contracting muscle increases blood flow to that muscle by sending biochemical messages through nearby matrix proteins. Flexing skeletal muscle was found to change the shape of the matrix protein fibronectin, which in turn, signaled for the relaxation of smooth muscle surrounding blood vessels. This enabled the vessels to dilate, increasing blood flow through them. The authors have also shown that a key piece of fibronectin, on its own, causes blood vessels to dilate, a first step toward pro-circulatory drug design.

“Along with a fundamental contribution to the understanding of exercise physiology, our data study suggests that engineering fibronectin could provide a simple, elegant way to maintain normal blood vessel function in the aging, and to restore such function in hard-to-heal wounds,” said Ingrid H. Sarelius, Ph.D., professor of Pharmacology and Physiology at the University of Rochester Medical Center, and a study author. “Aging and disease bring changes in matrix structure, and we may be able to reverse them.”

## **Twitching Muscles**

As a physiologist interested in the body’s response to exercise, Sarelius has for many years been studying the responses of surrounding tissue to muscle fiber contraction. Muscles are generally made up of a mix of fast-twitch fibers; which shorten rapidly for delivery of explosive power, say for a 100-yard dash, but then quickly fatigue; and slow-twitch fibers, which produce less power but keep flexing as oxygen supply dwindles during a long-distance run. Fast-twitch fibers should need more fuel to bring about a greater dilation in the vessels supplying them, but her experiments found no difference in initial dilation of vessels between twitch types. Some unknown mechanism was influencing the degree to which blood vessels dilate in response to muscle flex.

Meanwhile, the current study's lead author, Denise C. Hocking, Ph.D., associate professor of Pharmacology and Physiology at the Medical Center, had been studying how the ECM protein fibronectin affects cell signaling and function.

Past studies in her laboratory had found that fibronectin's structure to include a binding site, a place where most of its interactions with other proteins and cells take place, and which is key to its ability to pass on biochemical messages. That binding site, however, is normally buried until certain triggers expose it. How this buried or "cryptic" site in fibronectin becomes exposed and available for signaling had been a mystery.

The Hocking and Sarelius laboratories are next door to each other and it soon became apparent that their research paths might intersect. They began looking into whether flexing skeletal muscle could stretch fibronectin fibrils to expose their cryptic sites and initiate signals that increase blood flow. They reasoned that fibronectin fibrils, which surround blood vessels and interact with skeletal muscle, are perfectly suited to serve as a biochemical switch. They can be turned on quickly when muscles contract and then turned back off when muscles relax.

In their current collaboration, Sarelius and Hocking studied an abdominal muscle type in hamsters similar to some human muscles. Custom applications of imaging technologies were used to record blood vessel behavior under various conditions. The team injected the muscle with a monoclonal antibody, which recognizes the fibronectin cryptic site, attaches to it and shuts it down. They found that vessel dilation was significantly inhibited as the antibody turned off fibronectin signaling. They also captured images for the first time showing that fibronectin is continuously deposited into the matrix between skeletal muscle and nearby blood vessels. Together, these data provide the first proof that fibronectin signaling links flexing muscle to increased blood flow.

In addition, the team was able to pinpoint the portion of the fibronectin cryptic site involved in signaling for dilation. Among the proteins that bind to the site is heparin, first known for its ability to interfere with the building of blood clots. Increasingly, it has come to be regarded as a regulator of the functions of many ECM proteins, including fibronectin. Within the fibronectin cryptic site is a heparin-binding site, an amino acid sequence designed to link up with heparin and heparin-like molecules. Going into the current study, Hocking had already built this heparin-binding fragment separately from its larger parent protein.

The current team injected the heparin-binding fibronectin fragment into anesthetized animals. As expected, the fragment alone triggered a rapid and reversible dilation of nearby, small blood vessels. Furthermore, the effect was blocked by the addition of a nitric oxide inhibitor. This confirmed that the fragment signals for dilation by causing the release of the well-known vasodilator, nitric oxide, and perhaps by binding to heparan sulfate proteoglycan molecules on the surface of smooth muscle cells.

“It takes energy to move fibronectin out of the bloodstream, assemble it into ECM fibrils, and open its cryptic site,” Hocking said. “Injecting recombinant fibronectin fragments, engineered to express an “open” version of the site, directly onto tissues should bypass these energy requirements, and increase blood vessel dilation in patients.

Furthermore, exposing the fibronectin cryptic site is known to increase cell growth and migration, processes that are central to wound healing. Applying topical ointments that contain our engineered fibronectin fragments to chronic wounds should increase nutritive blood flow to accelerate healing.”

Source: University of Rochester

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