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Another way to grow blood vessels

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Researchers at Dana-Farber Cancer Institute have found a previously unknown molecular pathway in mice that spurs the growth of new blood vessels when body parts are jeopardized by poor circulation.

At present, their observation adds to the understanding of blood vessel formation. In the future, though, the researchers suggest it is possible that the pathway could be manipulated as a means of treating heart and blood vessel diseases and cancer. The paper appears in the Feb. 21 issue of the journal *Nature*.

Bruce Spiegelman, PhD, and his colleagues at Dana-Farber discovered that PGC-1alpha – a key metabolic regulatory molecule – senses a dangerously low level of oxygen and nutrients when circulation is cut off and then triggers the formation of new blood vessels to re-supply the oxygen-starved area – a process known as angiogenesis.

A similar response to hypoxia, or oxygen deprivation, has been observed before. The response is regulated by a group of proteins known as Hypoxia Inducible Factors (HIF) that detect hypoxia and activate the production of VEGF (vascular endothelial growth factor). VEGF, in turn, stimulates angiogenesis.

The newly discovered pathway provides “an independent way of getting there,” says Spiegelman, who is also a professor of cell biology at Harvard Medical School. Along with lead author Zoltan Arany, MD, PhD, and colleagues, Spiegelman found that HIF was completely left out of the loop when PGC-1alpha accomplished the same feat in single cells

and in live mice using a different regulator, known as ERR-alpha (estrogen-related receptor-alpha).

When the scientists knocked out the activity of PGC-1 alpha (which was first identified in the Spiegelman lab) in cells and live mice, the hypoxia-induced response and angiogenesis were sharply decreased.

“We were surprised to find this novel mechanism,” comments Spiegelman.

“It was apparently there all along,” adds Arany. “That means there is now a second pathway that you need to know about if you are trying to activate or inhibit angiogenesis.”

Angiogenesis occurs in the normal development of the body, but it’s also an on-call service when an injury or an artery blockage – the cause of heart attacks and strokes – leaves normal tissues starved for blood. Generating a new network of small vessels to nourish the area can protect against further injury. Muscle-building exercise also triggers angiogenesis to provide circulation for the enlarging muscle tissue.

On the downside, cancer has evolved the ability to commandeer VEGF and other angiogenic factors to encourage blood vessel growth around tumors that have outgrown their oxygen supplies.

In recent years, companies have developed a number of drugs that manipulate the angiogenic pathway – in both directions. Among them are anti-angiogenic cancer drugs, including thalidomide and Avastin, which are designed to starve tumors by blocking the formation of blood vessels. Avastin is also used to dampen the abnormal growth of small vessels in the retina that causes macular degeneration in the eye.

Conversely, researchers have tried using VEGF and other compounds to

improve the circulation in the legs and feet – and even heart muscle – of patients with poor blood supply.

“We’re still far from having good drugs to modulate angiogenesis through the HIF pathway,” commented Arany. The discovery of a second, alternate pathway, involving PGC-1 alpha and ERR-alpha, leading to angiogenesis may offer new opportunities for therapy “in any situation where angiogenesis is a factor,” he said.

Source: Dana-Farber Cancer Institute