Study unravels biological pathway that controls the leakiness of blood vessels

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(Medical Xpress)—A research team led by scientists at Mayo Clinic in Florida have decoded the entire pathway that regulates leakiness of blood vessels—a condition that promotes a wide number of disorders, such as heart disease, cancer growth and spread, inflammation and respiratory distress.

They say their findings, published online Dec. 17 in the Journal of Cell Biology, suggest that several agents already being tested for other conditions might reverse vessel leakiness.

"Now that we understand a lot more about the pathway that leads to leaky blood vessels, we can begin to try to target it in an efficient way, and that is very exciting," says the study's lead investigator, Panos Z. Anastasiadis, Ph.D., chair of the Department of Cancer Biology at Mayo Clinic in Florida.

Physicians have attempted to regulate that pathway in cancer through use of VEGF inhibitors, such as Bevacizumab, but these drugs are not as effective as they might be if other parts of the pathway were also inhibited, Dr. Anastasiadis says.

The research team, led by Dr. Anastasiadis and Arie Horowitz, Ph.D., at Cleveland Clinic Foundation, found that VEGF is one of two different molecules that affect a key downstream protein, Syx, to regulate the permeability of blood vessels.

Blood vessels are made up of endothelial cells that have to fit tightly together to form a solid tubular structure that blood can flow through. The researchers discovered that VEGF turns off Syx, which normally ensures the junctions between endothelial cells are strong. Without Syx, adhesion between the cells is loose, and the blood vessels are leaky. When new blood vessels are needed—such as to feed a growing tumor—VEGF loosens up endothelial cells so new vessels can sprout.

Then, after new vessels are formed, a second molecule, angiopoietin-1 (Ang1) works to glue the cells back together, Dr. Anastasiadis says. "These molecules have opposing, yin and yang effects. VEGF kicks Syx out of the junctions between cells, promoting leakiness, and Ang1 brings it back in to stabilize the vessel," he says.

The issue in cancer, however, is that VEGF overwhelms the system. "There isn't enough Ang1 to glue the vessels back together, and this leakiness allows cancer cells to escape the tumor and travel to other parts of the body," Dr. Anastasiadis says. "In late stages of the cancer, it also promotes the leaking of liquids into organs, such as the lungs. This results in profound effects that are often lethal."

Other disorders, such as inflammation and sepsis, a deadly bacterial infection that can result from excess liquid in lungs, are also induced by a leaky vascular system, he says.

Based on a detailed analysis of molecules involved in the VEGF/Ang1/Syx pathway, Dr. Anastasiadis believes that several experimental agents might help reverse vascular leakiness. One of them inhibits protein kinase D1 (PKD1), which might prevent endothelial cells from coming apart from loss of adhesion, and the other is a Rho-kinase inhibitor that prevents endothelial cells from contracting—which they must do to loosen up and become leaky.

"We now have new directions for both further basic research into leaky blood vessels and for potential clinical treatment," Dr. Anastasiadis says.

Investigators from Johns Hopkins University, Dartmouth Medical School, and Case Western Reserve University also contributed to the study.

Provided by Mayo Clinic