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Researchers discover a new pathway in blood vessel inflammation and disease

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Case Western Reserve researchers have identified a genetic factor that blocks the blood vessel inflammation that can lead to heart attacks, strokes and other potentially life-threatening events.

The breakthrough involving Kruppel-like factor (KLF) 15 is the latest in a string of discoveries from the laboratory of professor of medicine Mukesh K. Jain that involves a remarkable genetic family. Kruppel-like factors appear to play prominent roles in everything from cardiac health and obesity to metabolism and childhood muscular dystrophy.

School of Medicine instructor Yuan Lu, MD, a member of Jain's team, led the study involving KLF-15 and its role in inflammation, which appears online this week in the *Journal of Clinical Investigation*. Lu and colleagues observed that KLF-15 blocks the function of a molecule called NF-kB, a dominant factor responsible for triggering inflammation.

This finding reveals a new understanding of the origins of inflammation in vascular diseases, and may eventually lead to new, targeted treatment options.

"It had been suspected that smooth muscle cells were related to inflammation, but it hadn't been pinpointed and specifically linked to disease," said Jain, Ellery Sedgwick Jr. Chair and director, Case Cardiovascular Research Institute at Case Western Reserve School of Medicine. Jain also is chief research officer for the Harrington Heart &

Vascular Institute at University Hospitals Case Medical Center. "This work provides cogent evidence that smooth muscle cells can initiate inflammation and thereby promote the development of vascular disease."

Smooth muscle cells are only one of two major cell types within blood vessels walls. The other cell type, endothelium, has traditionally taken the blame for inflammation, but Jain's study suggests that both cells are critically important in the development of vascular disease.

The researchers learned that expression of this factor appeared mainly in smooth muscle cells and that levels were markedly reduced in atherosclerotic human blood vessels. To establish causality, the team generated genetically-modified mice where they deleted KLF-15 gene in smooth muscle cells.

"We expected to see more proliferation of the smooth muscle cells as this is a common response of this cell type in disease," Lu said, first author on the paper. "Instead, we were surprised to see rampant vascular inflammation and hyper activated NF-kB, the master regulator of inflammation."

The results offer hope for the development of specific anti-inflammatory therapies for vascular disease. Cholesterol-lowering drugs such as statins have some anti-inflammatory effects, but despite their widespread use, the burden of vascular disease remains high. As statins' primary role is to lower cholesterol levels, developing additional or more potent anti-inflammatory therapies are needed to compliment statins' important function.

Jain's previous research of the KLF family of genetic factors revealed regulator functions in blood vessels. KLF4 was shown to potently inhibit inflammation in the endothelium, the other major cell type in vessels. The current work is first to establish a role for these factors in smooth

muscle inflammation.

"Collectively, these studies establish KLFs as a central hub regulating vascular health," Jain said. "Boosting levels of these factors may be a particularly effective way to reduce inflammation and the development or progression of vascular diseases such as atherosclerosis."

Provided by Case Western Reserve University