Researchers find potential link between fat in blood and blood vessel recovery in ischemia

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The buildup of fat in the blood makes a bad situation worse - it not only raises a person's risk for heart attack or stroke but also impairs the growth of new blood vessels. How excess fat in the blood - a condition known as hyperlipidemia - blocks vessel growth was unclear, but new work by researchers at Temple University School of Medicine (TUSM) shows that a molecule known as caspase-1 plays a central role and that preventing its activity could be the key to building new blood vessels and restoring blood supply to oxygen-starved tissues.

"Caspase-1 acts as a lipid sensor in endothelial cells, which are abundant in the inner lumen of blood vessels," explained Xiao-Feng Yang, MD, PhD, FAHA, Professor of Pharmacology, Professor of Microbiology and Immunology in the Center for Metabolic Disease Research, Professor in the Cardiovascular Research Center and Professor in the Sol Sherry Thrombosis Research Center at TUSM, and senior investigator on the new study, which appears in print in the July 10 issue of the *Journal of Biological Chemistry*. "When lipids reach dangerously high levels in the circulation, the caspase-1-inflammasome complex initiates inflammation in the blood vessel," notes, Dr. Yang. "It turns out that caspase-1 signaling also inhibits endothelial cell growth, undermining the ability of the vasculature to recover from ischemic disease."

Ischemic diseases, which include heart attack, stroke, and peripheral artery disease, are a leading cause of illness and death in the United States. Ischemia starves tissues of blood and oxygen, resulting in severe

damage to the blood vessels in affected tissues. Finding ways to therapeutically restore blood flow after ischemia without causing further tissue injury is a major goal in metabolic cardiovascular research.

Caspase-1 inhibition could prove to be hugely important in the treatment of ischemic disease. In their new report, Dr. Yang and colleagues show that the caspase-1 distress signals triggered by hyperlipidemia produce different effects in endothelial cells of differing size. In small endothelial cells, it triggers cell death, but in larger cells, it is involved in endothelial cell activation, in which the inner lining of the blood vessel undergoes a series of changes that ultimately contribute to the high lipid-induced inflammatory response.

"The growth status of endothelial cells is important to the inflammatory process," according to Dr. Yang. The major growth signaling pathway in endothelial cells is mediated by vascular endothelial growth factor receptor-2 (VEGFR-2), which also happens to be necessary for angiogenesis - the formation of new blood vessels.

In a series of experiments in human endothelial cells, Dr. Yang's team— in collaboration with Hong Wang, MD, PhD, FAHA, EMBA, Associate Dean of Research, Director of the Center for Metabolic Disease Research, Professor of Pharmacology, Professor in the Cardiovascular Research Center and Professor in the Sol Sherry Thrombosis Research Center at TUSM, and Eric T. Choi, MD, Chief of Vascular and Endovascular Surgery at Temple University Hospital, and Associate Professor of Surgery at TUSM— demonstrated that when caspase-1 was inhibited, VEGFR-2 activity was enhanced and the cells' angiogenic function restored. The cells successfully organized themselves into capillary-like structures in a tube-formation assay designed to measure angiogenic potential.

Similar effects on angiogenesis were seen in caspase-1-deficient mice

with hyperlipidemia and hind-limb ischemia. Compared to hyperlipidemic mice with normal caspase-1 expression, mice lacking the sensor molecule had better blood flow and vessel growth in their ischemic limb.

"The findings describe the significance of the caspase-1 pathway to post-ischemia revascularization," Dr. Yang said. "From a therapeutic point of view, we want to try to trigger revascularization and make existing vessels recover as soon as possible. The novel caspase-1 signaling pathway could have therapeutic potential in this area."

Dr. Yang next intends to figure out how caspase-1 modulates the activities of endothelial cells and of bone marrow-derived stem cells, which function in vascular repair. In research published earlier in 2015, he and colleagues discovered that caspase-1 activation weakened the vascular repair activity of stem cells in hyperlipidemic mice. Those findings could have implications for stem cell-based therapies for ischemia.

Provided by Temple University

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