Gene linked to inflammation in the aorta may contribute to abdominal aortic aneurysm

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A gene known to be involved in cancer and cardiovascular development may be the cause of inflammation in the most common form of aortic aneurysm and may be a key to treatment, according to research from Nationwide Children's Hospital. The study, appearing online in Arteriosclerosis, Thrombosis, and Vascular Biology on October 18, 2012, is the first to show that Notch 1 signaling is activated in abdominal aortic aneurysmal tissue in mice and humans.

The aorta is the largest blood vessel in the body. Abdominal aortic aneurysm (AAA) occurs when the weakened aortic wall dilates in the abdominal portion of the vessel; they are the most common form of aortic aneurysms. AAA is a leading cause of death in the United States, especially among men over the age 65, and the disease is linked to smoking, high blood pressure and high cholesterol. AAA is extremely rare in children, but can occur in those who experience a blunt trauma or who have connective tissue diseases. Surgery is currently the only treatment for AAA and less than 20 percent of patients will survive a ruptured aneurysm.

"There is critical need to develop pharmacologic interventions that can selectively target one or more features of AAA to prevent the progression or stimulate regression in already diagnosed patients," says the study's senior author, Vidu Garg, MD a cardiologist in The Heart Center at Nationwide Children's Hospital and a principal investigator in

the Center for Cardiovascular and Pulmonary Research.

Inflammation is a hallmark of AAA. The Notch 1 gene is involved in many developmental processes in humans and studies have shown its signaling pathway to be active in several inflammatory diseases.

"Notch 1 signaling is a significant regulator of the inflammatory response," says the study's lead author, Chetan Hans, PhD, principal investigator in the Center for Cardiovascular and Pulmonary Research at Nationwide Children's Hospital. "However, its role in AAA is unknown."

To examine the role of Notch 1 signaling in AAA development, Dr. Hans and colleagues first inspected tissue specimens from the abdominal aorta of patients undergoing AAA repair and a mouse model of the disease. They provide the first evidence that Notch 1 signaling is activated in these models and in human patients. They then closely examined the role Notch 1 signaling plays in the Angiotensin II-induced mouse model of AAA, when Notch 1 signaling is inhibited.

Findings showed that mice that had a genetic deficiency of Notch1 or received a chemical Notch inhibitor had less inflammation in the aorta and had a reduced incidence of AAA.

"Our data suggest that Notch 1 is an important player in the inflammatory process in the setting of AAA," says Dr. Hans. "Treatment with Notch 1-specific inhibitors may be a potentially promising strategy for slowing aneurysm development."

Dr. Hans says further studies are needed to understand the specific role of these inflammatory factors in AAA.