Abrahimi et al perform CRISPR/Cas9 gene editing in primary human endothelial cells for the first time.

Endothelial cells play a critical role in numerous physiological and pathological processes, such as inflammation, wound healing, vascularization, and atherosclerosis. Cultured human umbilical vein endothelial cells (HUVECs) are a valuable resource for studying endothelial cell biology. However, these cells have a limited replicative lifespan and are difficult to genetically manipulate. Recently, endothelial colony forming cells (ECFCs), also derived from umbilical cords, have been identified as having far longer replicative lives. Furthermore, gene editing using CRISPR/Cas9 technology has revolutionized genetic manipulations. Abrahimi and colleagues have therefore now performed CRISPR/Cas9-mediated gene disruption in ECFCs. They targeted the gene encoding CIITA—the master regulator of expression of the immune protein MHC Class II and are therefore now performing CRISPR/Cas9-mediated gene disruption in ECFCs. The team went on to show that an MMP17 target—osteopontin—failed to be cleaved in the mutant mice. And that expression of the correctly cleaved osteopontin protein could rescue the animals’ defective aortic structure. Screening for MMP17 mutations in patients with a family history of aneurysms has now been associated with predisposition for aortic aneurysm, but up to 75 percent of patients with family histories of aneurysms have no known genetic cause. Martin-Alonso and colleagues have now performed whole exome sequencing of a number of individuals with such inherited predisposition and have identified a new mutation in the ECM enzyme MMP17. When expressed in mice, the mutant version of the protein caused the animals’ aortas to become dilated with altered VSMC morphology and aberrant ECM structure. Moreover, the mice had an increased susceptibility to aortic aneurysm. Certain increased susceptibility of matrix metalloproteinase 17 (MMP17) can increase one’s risk of developing aortic aneurysm.

Aortic aneurysms caused by weakening of the aortic wall can lead to dissection or rupturing of the aorta and are the underlying cause of 1 to 2 percent of deaths in the developed world. Genetic mutations affecting either the extracellular matrix (ECM) or vascular smooth muscle cells (VSMCs) have been associated with predisposition for aortic aneurysm, but up to 75 percent of patients with family histories of aneurysms have no known genetic cause. Martin-Alonso and colleagues have now performed whole exome sequencing of a number of individuals with such inherited predisposition and have identified a new mutation in the ECM enzyme MMP17. When expressed in mice, the mutant version of the protein caused the animals’ aortas to become dilated with altered VSMC morphology and aberrant ECM structure. Moreover, the mice had an increased susceptibility to aortic aneurysm. The team went on to show that an MMP17 target—osteopontin—failed to be cleaved in the mutant mice. And that expression of the correctly cleaved osteopontin protein could rescue the animals’ defective aortic structure. Screening for MMP17 mutations in patients with a family history of aneurysms may lead to early identification of the defect and ultimately to tailored therapies for these patients, the authors suggest.

Although in most patients, hypertension can be controlled with current anti-hypertensive drugs, up to 30 percent of patients remain resistant to current therapy. Reasons for such resistance are not known, but may relate to difference in drug metabolism, genetic predisposition and severity of disease. In addition, the multi-factorial nature of hypertension makes it difficult to control. Hyperension has both neurogenic and inflammatory components and has been linked to increased sympathetic nervous stimulation of bone marrow, which increases inflammatory cell activation. Moreover hypertension is exacerbated by both peripheral and neurological inflammation. To examine the complex relationship between hypertension, inflammation and the brain, Santisteban and colleagues transferred bone marrow from hypertensive rats into those with normal blood pressure and found that the recipient animals’ blood pressure increased. Conversely, hypertensive rats whose bone marrow was replaced with that of normotensive animals exhibited a fall in blood pressure. Peripheral and brain inflammation was also reduced in these animals. Using an anti-inflammatory drug called minocycline that crosses the blood brain barrier, the team was able to inhibit activation of microglia—the brain’s immune cells—and reduce blood pressure in hypertensive rats. These results suggest that reducing peripheral and brain inflammation might be an effective treatment for hypertensive patients resistant to current medications.

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