Inhibition of proteins activated by nitric oxide reverses aortic aneurysm in Marfan syndrome

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Scientists at the Centro Nacional de Investigaciones Cardiovasculares Centro de Biología Molecular Severo Ochoa (CBM-CSIC-UAM) have discovered that the nitric oxide (NO) pathway is overactivated in the aortas of mice and patients with Marfan Syndrome and that the activity of this pathway causes the aortic aneurysms that characterize this disease.

The results of the study, published today in Nature Communications, reveal the essential role played by NO in Marfan Syndrome aortic disease. "We previously detected high expression of a protein with a high capacity for NO production in the aortas of Marfan Syndrome patients and an animal model of the disease, and we therefore undertook an in depth investigation of the role of NO in the associated aortic disease," explained Dr. Campanero.

Aortic aneurysm (AA) is a progressive dilatation and weakening of the aortic wall. AA can be harmless, but in some patients can lead to dissection (rupture) of the aorta, resulting in death.

Marfan Syndrome is a hereditary disease that affects connective tissues, which are the fibrous structures that bind and anchor all the organs and tissues in the body. Marfan Syndrome principally affects the skeleton, the eyes, the heart, and the blood vessels. A particularly common disease manifestation is thoracic aortic aneurysm and dissection (TAAD). "Aortic dissection accounts for more than 90% of deaths associated with Marfan Syndrome," explained CNIC investigator Dr. Juan Miguel Redondo, study co-director together with CBM-CSIC-UAM investigator Dr. Miguel Campanero.

Current treatments for Marfan Syndrome are aimed at reducing blood pressure on the artery wall, but do not prevent its deterioration. The only effective intervention for the aortic disease in Marfan Syndrome is surgery.

The researchers therefore recognize "the urgent need to identify new targets for the development of pharmacological treatments for TAAD in Marfan Syndrome."

Staining showing pVASP-S239 (red), elastic fibers (green) and nuclei (blue) in the aortic wall of a healthy donor (Healthy Aorta) and a patient with Marfan Syndrome (Diseased Aorta from Marfan Patient). The images show how the NO-sGC-PRKGI pathway is over-activated in the aortic wall from Marfan patients. Credit: CNIC/ CSIC
The research team also explored possible “footprints” left by high NO levels in the blood. "Working with the CNIC Proteomics Unit and clinical groups at Vall D´Hebron, Puerta de Hierro, Marqués de Valdecilla, and Ghent University hospitals, we found that the high NO levels in Marfan Syndrome lead to increases in protein nitration and cGMP in the blood of mice and patients with this disease," said Dr. Campanero.

"This discovery has important implications for patients with this syndrome, because these molecules could be used as biomarkers for disease monitoring, and we are now studying their potential as prognostic indicators," explained Dr. Redondo.

The researcher conclude that their results are therefore good news.


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