Exhaustive research to improve prevention and treatment of aneurysms

The Loeys-cardiogenomics lab aims to contribute to the further elucidation of the genetic and mechanistic landscape of thoracic aortic aneurysm, with the ultimate goal of improving patient management.

Research and Discoveries

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Its ongoing research lines are contrived in a way its results should increase the molecular diagnostic yield, improve genetic counseling, and identify predictive markers and develop curative therapies. Together with an American colleague, Bart Loeys discovered a previously unknown form of aortic aneurysm, which now bears their name: the Loeys-Dietz syndrome. This discovery framed his research into Marfan syndrome – a specific weakening of the aorta – and related diseases, which contributed greatly to a better understanding of the genetic mechanisms that cause aortic damage.

The lab has a longstanding tradition in the use of DNA sequencing technologies to find novel thoracic aortic aneurysm genes. Besides traditional molecular biology approaches, the current research projects involve the use of state-of-the-art techniques such as whole genome sequencing, transcriptomics and interactomics/proteomics in patient samples, induced pluripotent stem cell-derived vascular smooth muscle cells and/or mouse models. “By profoundly mapping the downstream functional consequences of gene mutations, we aim to identify genetic modifiers and pinpoint novel drug targets,” says team leader Prof. Dr. Bart Loeys.

Aorta-on-a-chip

In an aneurysm, part of a blood vessel is abnormally dilated. Such a dilation occurs unnoticed and usually causes no symptoms. As the aneurysm grows, the aortic wall becomes increasingly weak and can rupture even at normal blood pressure, resulting in

life-threatening bleeding. “We are looking for innovative solutions to test better treatments faster in aortic models. One obstacle is that we do not yet have a good human model. We now use mouse models, but drugs that seem safe and effective for mice may be ineffective or even harmful for humans. As an intermediate step, we want to develop a human aorta on a chip – a 3D complex of cells that mimics the real aorta. From the patient’s white blood cells, we make stem cells, which we differentiate into the various cell types in the aortic wall. We are now trying to bring those cell types together on a chip containing mini-channels so that we can irrigate the cells to mimic blood flow or to test candidate drugs.”

Nano-particles

In mice, it was shown that a high dose of losartan can stop aortic dilation. “But in humans, oral administration of such a high dose of losartan results in side effects that are too severe. Therefore, a method is needed to administer losartan very specifically, so that it acts specifically on the diseased parts of the aorta. Therefore, we are now testing in mice first the use of nano-particles loaded with losartan. By chemically ‘labelling’ these particles, we send them specifically to the diseased spot in the aorta and investigate whether they can better prevent aneurysm formation there. We also want to test this later in the aorta-on-a-chip, before setting up clinical trials with patients. Importantly, the use of nanoparticles in humans has already been approved. Once we succeed in developing an effective ‘address label,’ we can start using them on humans.”

GEMS

Together with patient organisation F101G-foundation, Bart Loeys is leading the international GEMS project (Genome-wide Epistasis for cardiovascular severity in Marfan Study). “We identified one specific genetic FBN1 variant that causes a very variable clinical picture in Marfan patients worldwide: from aortic dissection at a young age to completely normal aorta in later life. Based on whole genome sequencing and study of the stem cells of patients with these extreme presentations, we hope to identify the genetic modifier(s). Its discovery may lead to new therapeutic pathways to prevent aneurysms.”

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