Cellular and molecular mechanisms involved in the development of thoracic aortic aneurysms in order to develop therapeutic options.

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Thoracic aortic aneurysms (TAAs) are responsible for 1-2% of all deaths in Western countries. Aneurysms are defined as dilatations of arteries when the diameter of the affected vessel exceeds 1.5 times the normal diameter. Dissections or ruptures occur as complications. There is no treatment and all mechanisms have not yet been identified.

30% of the cases are genetically triggered and linked to more than 15 penetrant genes. The identification of these mutations as well as the single cell analysis of aneurysmal tissue highlighted the essential role of vSMCs in maintaining the aorta structure through life and suggested that defective "mechanosensing" leading to altered vSMC contractility is one of the cause of TAA development.

The C-type natriuretic peptide (CNP) is a local regulator of skeletal growth, of vascular homeostasis, remodeling and angiogenesis. CNP binds to two receptors, NPR-B and NPR-C. Mutations in the CNP or in its NPR-C receptor genes in humans and in mice lead to development of aneurysm.

In our preliminary works, we measured decreased CNP level in the plasma of patients with TAA. Furthermore, the CNP and NPR-C protein levels are decreased in the aortae of these patients. This is also the case in our mouse model, the Fbn1+/- mice, in which the decreased level of NPR-C in the aortae inversely correlates with the dilation of the ascending aorta.

Our project aimed to determine whether altered CNP signaling pathway contributes to the TAA development and/or progression to rupture.

For this purpose, we plan to :

1) Determine whether CNP supplementation or activation of the NPR-C receptor is able to delay or limit TAA development in Fbn1 +/- mice.
2) Understand the direct effect of CNP stimulation on vascular smooth muscle cells isolated from mouse and human aneurysmal and non-aneurysmal aortae.

We will work in parallel with a recognized mouse model of TAA, the fibrillin 1 (Fbn1) C1039G/+ mutated mice, and blood samples and aorta biopsies taken from patients developing TAA after a mutation in the Fbn1 gene (Marfan patients). Males and females will be differentiated.

The results generated may help to improve 1) the detection of the severity of the TAA development (by CNP or NPR-C measurement) in patients, 2) the treatment of TAA and 3) the follow-up and management of patients by gender.