The C-type Natriuretic peptide: a new player in the development of the Marfan syndrome ?

The Marfan Syndrome (MFS) is an autosomal dominant inherited connective tissue disorder affecting the cardio-vascular system. Aortic dissections and ruptures are the primary cause of morbidity and mortality in these patients. This disease is a rare disease and no treatment really cures patients.

The C-type natriuretic peptide (CNP) is a local regulator of skeletal growth and of vascular homeostasis, remodeling and angiogenesis. CNP is constitutively released by endothelial cells, whereas TGF-β stimulates its secretion by smooth muscle cells. CNP modulates endothelial cell proliferation and smooth muscle cell proliferation, phenotype and survival.

The aim of our project is to determine whether altered CNP signaling pathway contributes to the development and progression of the vascular phenotype in patients suffering from MFS.

For this purpose, studies on human plasma and vessel biopsies taken from Marfan patients (RAVAD registery, CHUV Lausanne) will be conducted in parallel, with experiments on the Fbn1 C1039G/+ mouse model which recapitulates several features of the human MFS phenotype, including the aortic wall degeneration and the development of aneurysms.

The objectives of the project are to

A) Determine how the CNP signaling pathway is modified during the progression of aortic aneurysm in Marfan patients and in Fbn1 +/- mice. The involvement of the endothelial (ECs) and smooth muscle cells (SMCs) will be studied using Fbn1 +/- mice carrying a CNP deletion specifically in endothelial or smooth muscle cells.

B) Determine the normal function of CNP in "healthy" aortas (i.e. its responding cells, signaling pathways and cellular mechanisms). Furthermore, RNA seq experiments will help to identify new targets linked to altered CNP level during the MFS development. In vitro experiments on ECs and SMCs isolated from "healthy" aortas will also allow to understand the interactions between the CNP and the TGF-β and Angiotensin II, both molecules contributing to the MFS pathology.

C) Rescue the phenotype in vivo in Fbn1 +/- mice by modulating the CNP signaling pathway.

All these experiments will be performed in male and female mice. Whereas it was admitted since several decades that the Marfan disease is more serious in men than in women, this assumption is currently contreversial. We will thus compare the progression and severity of the MFS in both sex and relate the differences to the CNP signaling pathway modifications.

The current therapeutically treatment based on prevention of aortic dilation, dissection and rupture are not very specific and don't prevent aortic dissections in some Marfan patients. The results generated in this project will help to understand the role of the CNP-mediated signaling pathway in the development of MFS and will mainly open the door to new therapeutical options aimed to prevent the development of aneurysms and their progression to rupture.