

ABSTRACT

Thoracic aortic aneurysms (TAAs) account for 1-2% of all deaths in Western countries. Aneurysms are characterized by the dilation of arteries, where the affected vessel's diameter exceeds 1.5 times the normal size, often leading to complications such as dissections or ruptures. Currently, there is no definitive treatment, and the precise underlying mechanisms remain partially unidentified.

Approximately 30% of TAA cases are genetically influenced, associated with over 15 penetrant genes. Thus, Marfan syndrome, a rare vascular disease characterized by aneurysm development, is caused by mutations in the Fibrillin 1 gene. The discovery of these mutations, alongside single-cell analysis of aneurysmal tissue, has underscored the crucial role of vascular smooth muscle cells (vSMCs) in maintaining aorta structure throughout life. It suggests that a malfunction in "mechanosensing," resulting in altered vSMC contractility, contributes to TAA development.

C-type natriuretic peptide (CNP) is a local regulator influencing skeletal growth, vascular homeostasis, remodeling, and angiogenesis. CNP interacts with two receptors, NPR-B and NPR-C. Mutations in CNP or its NPR-C receptor genes, observed in both humans and mice, are associated with aneurysm development.

In our preliminary research, we observed decreased CNP levels in the plasma of TAA patients. Additionally, CNP and NPR-C protein levels were reduced in the aortae of these patients. A similar pattern emerged in our mouse model, the *Fbn1*^{+/-} mice, where decreased NPR-C levels in the aortae correlated inversely with ascending aorta dilation.

This project aims to investigate whether the altered CNP signaling pathway contributes to TAA development and/or progression to rupture.

This project is divided into two primary components:

1. Assess whether CNP supplementation can delay or mitigate TAA development in *Fbn1*^{+/-} mice.
2. Investigate the direct impact of CNP stimulation on vascular smooth muscle cells isolated from aneurysmal and non-aneurysmal aortae in both mice and humans.

We will conduct parallel research, utilizing the well-established TAA mouse model with the Fibrillin 1 (*Fbn1*) C1039G/+ mutation and analyzing blood samples and aorta biopsies from patients who developed TAA following an *Fbn1* gene mutation (Marfan patients). Distinctions between males and females will also be considered.

The outcomes of this project may have significant implications, including the enhancement of TAA severity detection (through CNP measurement as biomarker), the advancement of TAA treatments, the improvement of patient follow-up and management, and the accounting for gender differences.