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Regulation of LTBP expression as a modulator of TGFβ availability in patients with BAV

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Introduction: Bicuspid aortic valve (BAV) is the most common cardiac defect in human, estimated to affect 1-2% of the general population. However, surprisingly, more than 50% of patients undergoing aortic valve and/or ascending aortic surgery display a BAV, rather than a normal tricuspid aortic valve (TAV). People with BAV are consequently 50-70% more likely to develop ascending aortic aneurysm later in life, with no forewarning symptoms.

The association between BAV and ascending aortic aneurysm is believed to be two-fold. Firstly, the valve malformation disturbs the normal blood flow within the system, generating stress to the endothelial cells lining the interior of the aortic tissue, which might in turn modify signalling pathways. Secondly, it is likely that the genetic changes responsible for the development of a BAV also interfere with the structure of the ascending aorta, which has a common embryologic origin with the aortic valve, rendering it less resilient and more susceptible to dilatation and rupture.

Purpose: The aim of this project is to understand the extent to which cells issued from patients with BAV and TAV differ, and how these differences explain the aetiology of BAV-associated aortopathy. Specifically, the present work focuses on latent TGF-β-binding proteins (LTBPs) as regulators of TGF-β activity, which is of crucial importance in ascending aortic aneurysm development.

Methods: Although the exact role of TGF-β in aneurysm initiation and development is still unclear, it seems to differ between BAV-related and otherwise occurring aneurysms. Previous work demonstrated a difference in TGF-β availability between BAV and TAV patients, possibly due to differential sequestering of TGF-β in the extracellular matrix by latent TGF-β-binding proteins (LTBPs). Using electrophoretic mobility shift assay (EMSA) and luciferase reporter assays, the regulation of LTBP expression is studied in BAV and TAV systems, and compared.

Results: We have revealed the presence of protein binding regions in the promoter sequence of LTBP1. Further work is required to confirm whether these interactions are responsible for the regulation of LTBP1 transcription, which could explain the difference in LTBP level observed during aneurysm between BAV and TAV patients.

Conclusion: Differential regulation of LTBP expression in BAV and TAV, through the variation of transcription factors activity or other regulatory elements could explain, at least in part, the differences observed during aneurysm development between BAV and TAV patients.