Non-canonical Wnt signaling and aortic valve stenosis

Even with the countless drugs we have to treat cardiovascular diseases, the majority of these diseases remain without a cure. Aortic valve stenosis (AVS) is one of these diseases, characterized by the narrowing of the aortic valve opening with significant deposition of calcium on the valve leaflets. Patients with this disease experience an array of symptoms such as shortness of breath, chest pain and heart failure ultimately leading to death. Currently, the only viable treatment for AVS is surgical valve replacement using minimally invasive approach or open heart surgery. If left untreated, the disease is associated with significant mortality. To combat this limitation, our lab is dedicated to understanding the pathogenesis of the disease in hopes of providing better insight to develop novel treatments for AVS.

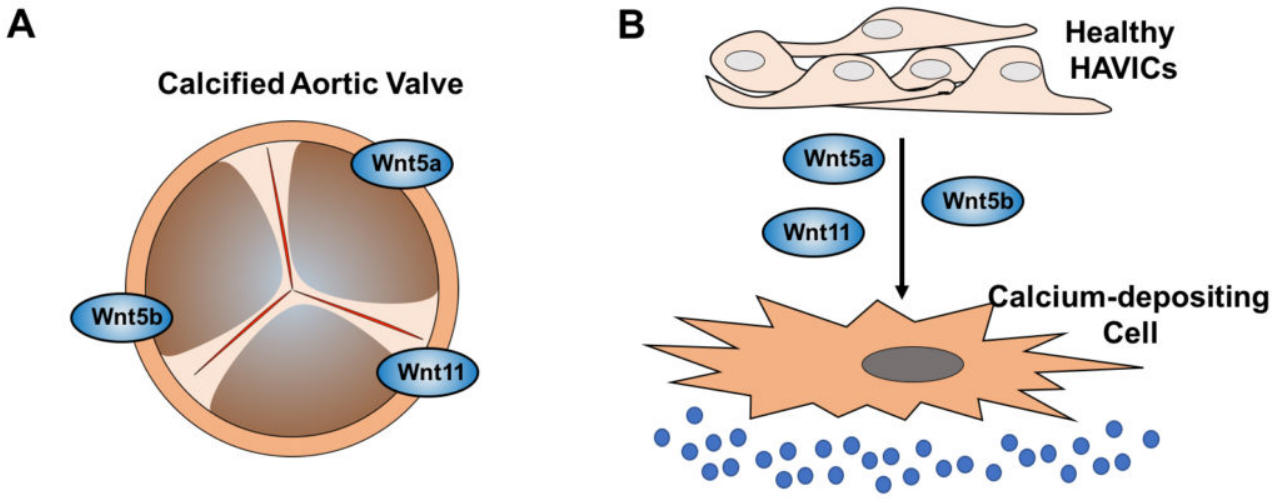

Fig. 1. Increased gene expression of Wnt5a, Wnt5b and Wnt11 was found in calcified aortic valves (A). Proposed mechanism of aortic valve calcification: treating healthy HAVICs with non-canonical Wnt ligands converts healthy cells to calcium-depositing cells, leading to disease onset (B).

Wnts are a group of ligands that activate multiple pathways and as of late have gained a lot of interest in AVS pathogenesis. Wnts play an important role in fetal development and bone formation. The two main Wnt signaling pathways are the canonical and non-canonical pathways. Previously, the canonical Wnt signaling pathway has been implicated in AVS pathogenesis. However, the role of non-canonical Wnts in AVS are currently unknown. With this in mind, we decided to investigate the presence of non-canonical Wnts in AVS, hypothesizing that non-canonical Wnt ligands are upregulated in AVS and contribute to aortic valve calcification.

To do this, we obtained healthy and calcified aortic valves from patients undergoing heart transplantation or aortic valve replacement, and assessed the tissue expression of three non-

canonical Wnt ligands: Wnt5a, Wnt5b, and Wnt11. We observed increased gene expression of all three non-canonical Wnt ligands in diseased human aortic valves compared to healthy ones. We also found significant correlations between the presence of Wnt5b and Wnt11 in areas with calcification, lipid score, fibrosis, and new vessels formation. To aid in our investigation, we isolated human aortic valve interstitial cells (HAVICs) from the explanted valves. Protein expression analysis found increased expression of Wnt5b and Wnt11 proteins in calcified HAVICs. Healthy HAVICs treated with the three non-canonical Wnts resulted in significant cell death and calcification. To explore the possible mechanisms of action, we assessed the expression of alkaline phosphatase (ALP), a protein involved in calcium deposition, after treatment with non-canonical Wnts. We found no significant effect on ALP activity, suggesting that calcification in AVS may be due to other mechanisms. Instead, it is likely that these non-canonical Wnts increase calcification by converting particular valvular cells into calcium-releasing cells.

Learning that patients with AVS have increased levels of non-canonical Wnts is novel and striking. We now know that both canonical and non-canonical Wnts pathways are involved in the pathogenesis of AVS, yet the exact mechanisms for how these pathways are related to the disease are still unknown. This new understanding paves the way for developing new drug targets to reduce calcification in the aortic valve. With further research, we anticipate a novel role for non-canonical Wnt signaling in AVS.

Kashif Khan, Adel Schwertani
Divisions of Cardiology and Cardiac Surgery,
McGill University Health Centre, Montreal, Quebec, Canada

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