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A tissue stem cell niche regulates calcific aortic valve disease via Wnt/LRP5

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Calcific aortic valve disease is the most common indication for valvular surgery in the United States. Cellular mechanisms are under intense investigation. This study hypothesizes that this disease develops secondary to a tissue stem cell niche. The niche is regulated by Wnt secretion from the endothelial layer to activate LRP5 receptor on the adjacent myofibroblast cell to form bone.

Methods: Human ex vivo calcified valves versus control aortic valves were tested for Lrp5/Wnt3a expression by RTPCR, Western Blot and Immunohistochemistry. eNOS null mice: control (n=20), cholesterol (n=20), cholesterol + Atorvastatin (n=20), were tested for the development of aortic stenosis by Visual Sonics Echo, Immunohistochemistry for Wnt, Lrp5, Osteocalcin, PCNA and RTPCR for Lrp5 and Cbfa1. In vitro studies were performed to isolate Wnt3a from aortic valve endothelial cells in the presence of lipids with and without Atorvastatin using Anion exchange chromatography. Oxidative stress levels were tested via eNOS expression. Treated endothelial cell conditioned media with lipids with and without Atorvastatin was added to myofibroblast cells. Gene expression for Cbfa1, Lp5 and osteocalcin from the valve myofibroblast cells with the various treatments was measured by semi-quantitative RTPCR.

Results: Secretion of Wnt3a(>300-fold,$p<0.0001$) from aortic valve endothelium in the presence of abnormal oxidative stress as measured by nitric oxide regulation and lipids as measured by eNOS enzymatic activity and tissue nitrite levels. Osteoblastogenesis in the adjacent myofibroblast cell treated with conditioned media by LRP5 receptor signaling. Human ex vivo calcified valves express LRP5 as compared to normal valves ($p<0.0001$).Cholesterol treated eNOS mice develop severe stenosis with an increase in Lrp5, Cbfa1, (3-fold increase($p<0.0001$).

Conclusion: Targeting the Wnt3a/Lrp5 pathway in valvular calcification presents a novel approach towards treating this disease. The Wnt3a/LRP5 cross talk mechanism is demonstrated in three models. These findings demonstrate important implications for the therapeutic regeneration of a normal valve.

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