

Noncanonical Wnts at the Cusp of Fibrocalcific Signaling Processes in Human Calcific Aortic Valve Disease

Cecilia M. Giachelli, Mei Y. Speer

Calcific aortic valve disease (CAVD), the progressive accumulation of fibrocalcific matrices and calcified, bony nodules in aortic valves that results in aortic stenosis, accounts for $\approx 50\%$ of cardiac valve disease.^{1,2} In developed countries, CAVD is the third most common cardiovascular disease behind coronary artery disease and hypertension.³ Although CAVD is often asymptomatic during the first several decades of life, notably, approximately one third of our elderly have early valve disease as indicated by echocardiographic or radiological evidence of aortic sclerosis.^{2,4,5} By age 65, $\approx 2\%$ of individuals develop symptomatic aortic stenosis, characterized by severe valve calcification, impaired leaflet motion, and cardiac outflow, which, if untreated, leads to life-threatening left ventricular dysfunction, angina, syncope, and heart failure.^{6,7}

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CAVD risk factors include congenital malformation, age, male sex, smoking, hypercholesterolemia, hypertension, and diabetes mellitus.⁸ Importantly, level of aortic valve calcification at diagnosis is highly associated with rate of aortic stenosis progression.³ Despite the huge clinical significance of CAVD, there are currently no pharmacological therapies to improve the outcomes of this disease. Furthermore, statins have proven ineffective in blocking calcification and treating CAVD to date,^{9–11} leading to the idea that mechanisms beyond those involved in atherosclerosis need to be considered in CAVD.¹² Clearly, a better understanding of the cause and signaling pathways regulating aortic valve calcification is essential for the development of therapeutics for preventing and treating this debilitating disease.

Wnt proteins are secreted glycoproteins known for their importance in cardiovascular development, playing key roles in cell-type specification, morphogenesis, and cardiac valve formation.¹³ In recent years, the role of the canonical Wnt signaling pathway (β -catenin dependent) in osteochondrogenic differentiation of tunica media cells in diseased, calcified blood vessels has come to the forefront.^{14,15} On binding of paracrine Wnt ligands to the transmembrane Frz and LRP5/6 coreceptor complexes of medial cells,^{16,17} the cytoplasmic degradation complex of axin, APC, and GSK3 β is disassembled, allowing β -catenin to enter the nucleus and induce

Runx2 and/or LEF1-mediated osteogenic differentiation and calcification.¹⁸ Supporting a potential role of canonical Wnts in CAVD, LRP5/Wnt3 was abundantly expressed in calcified human aortic valves.¹⁹ On the other hand, noncanonical Wnts act through β -catenin-independent signaling pathways, and much less is known about their potential roles in cardiovascular calcification.

In this issue of *ATVB*, Albanese et al²⁰ have uncovered the potential importance of noncanonical Wnt signaling in CAVD. The authors capitalized on access to extremely well-characterized normal and diseased human valve tissues and cells to perform an impressive array of immunochemistry, Western blotting, gene expression studies, and in vitro functional studies. They found that Wnt5a, a dual-action noncanonical Wnt that either inhibits Wnt/ β -catenin pathway via direct inhibition of LRP6 or activates Wnt-catenin pathway in the presence of Frz4,²¹ occurred only in or around calcified areas of diseased human aortic valves, whereas Wnt5b and Wnt11 were more ubiquitously distributed throughout the areas of inflammation, fibrosis, lipid core, and calcification. Importantly, recombinant forms of all 3 noncanonical Wnts promoted apoptosis, expression of genes associated with osteochondrogenic differentiation, and calcification of human aortic valve interstitial cells. Finally, a positive correlation of noncanonical Wnt5b and Wnt11 immunoreactivity with aortic valve stenosis parameters, such as aortic jet velocity, P_{max} and P_{mean} , as well as preoperative risk assessment score, was observed.

This study provides strong evidence for the association of noncanonical Wnts with aortic valve calcification and stenosis and determined for the first time their proapoptotic and osteochondrogenic effects on cultured valve cells. Together with previous studies, this work supports the hypothesis that both canonical and noncanonical Wnt signaling pathways may contribute to detrimental calcification processes in CAVD, including apoptosis and osteochondrogenic differentiation. However, none of the studies to date have proven causality of Wnt signaling in CAVD, or which pathways may be most important for valve calcification and subsequent aortic stenosis. Additional gain and loss of function studies in appropriate animal models are critical to determine which Wnt signaling pathways, if any, may indeed serve as therapeutic targets to block valve calcification or biomarkers for disease progression.

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Disclosures

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