Lonza

The Role of Valvular Interstitial and Endothelial Cells in Aortic Valve Stenosis

by Stephanie Nickles Thielemann B.S., M.Sc.
Director, Marketing Discovery Services

Aortic valve stenosis (AVS) is the most prevalent heart valve disease and the third leading cause of cardiovascular disease (Rutkovskiy, 2017). The main causes of the disease include a congenital heart defect of the valve itself or calcification of the valve. Calcification can be triggered by an initial endothelial injury and dysfunction followed by immune cell infiltration, and myofibroblastic/osteoblastic differentiation of vascular interstitial cells (VICs). As these calcium deposits increase with age, the valve stiffens and narrows leading to reduced blood flow from the heart to the aorta. The progression of the disease over time can be life threatening as the heart weakens from working harder to compensate for the limited functionality of the valve(Goody, 2020). Currently, there are no medications to prevent or cure heart valve disease leaving surgical intervention as the only viable option for patients with late stages of the disease. However, potential therapeutic targets for non-surgical treatment have been identified through the research of resident cells in the valves, including their response to pathological stimulation and the mechanisms that regulate these responses.

This article summarizes the current knowledge of the roles vascular endothelial and interstitial cells play in aortic valve calcification and the research models used to further study these attributes. The cellular and molecular pathogenesis of heart valve disease have been studied in increasing depth as the availability of cultures of VICs and valve endothelial cells (VECs) has improved. VICs are the most prevalent cells in the heart valve and are found in all three layers – the fibrosa, the spongiosa, and the ventricularis – and are thought to be responsible for maintaining the structural integrity of the valve. The entire valve is covered with VECs. During embryogenesis the endothelial cells covering the primordial valve cushions migrate inside the underlying matrix and undergo endothelial– to– mesenchymal transition to become the interstitial cells (Rutkovskiy, 2017). Recent studies revealed that the valvular tissue response to disease is characterized by a marked accumulation of VICs associated with inflammatory cells, neovascularization, increased matrix, and eventually fibrosis and calcification (Liu, 2007). Although no cause-and-effect relationships were determined, these investigations proposed that in healthy valves the VICs maintain normal valve structure and function, and that in diseased valves, VICs become activated to regulate valve repair and remodeling (Liu, 2007)

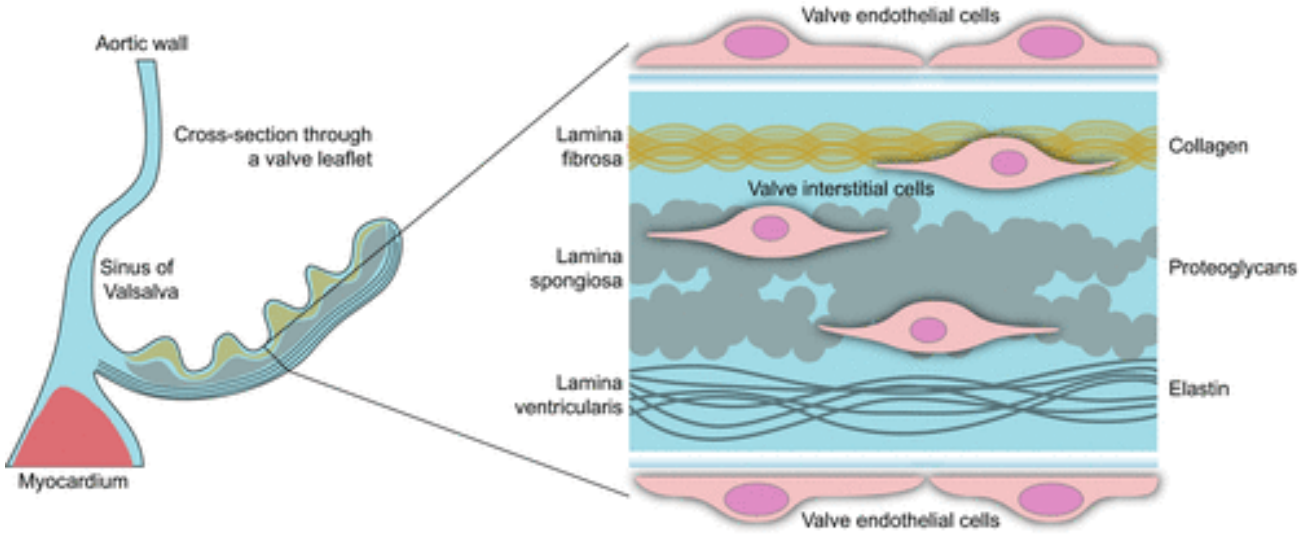

Figure 1.
Illustrated cross section through the noncoronary leaflet of the aortic valve on the left. The right shows the trilayered organization of the extracellular matrix and the localization of the aortic valve endothelial cells and interstitial cells.

Scientists continue to investigate how characteristics of these two major cell types, VECs and VICs, and their mechanical relationships with the valvular extracellular matrix promote structural integrity and age-related remodeling. Further mechanistic studies of VIC regulation of valve structure have reaffirmed the central role of VICs in repair, and have also shown that VICs express a variety of defined phenotypes associated with remodeling and repair. In fact, abnormal changes in VECs, VICs and the extracellular matrix at the molecular level lead to gross tissue malformations and dysfunction (Goody, 2020).

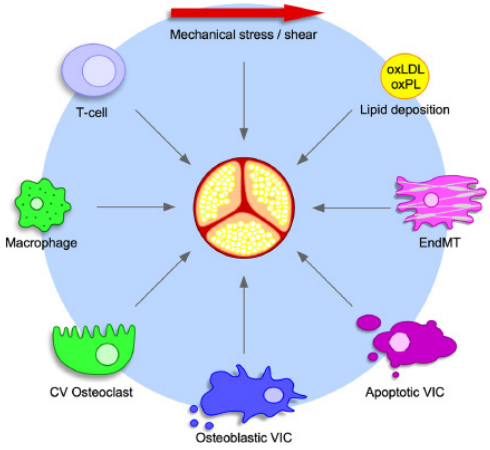

Figure 2.
Pathological progression of calcification in aortic valve stenosis. (Goody, 2020)

As shown in Figure 2, when calcific aortic valve disease (CAVD) occurs, there is a progression of phases that ultimately leads to calcification of the valve. Several studies have shown that initially there is a stimulus, such as mechanical or shear stress, that causes dysfunction in the VECs allowing lipoproteins to infiltrate the valve matrix followed by inflammation resulting from an invasion of immune cells. Altered regulation of eNOS endothelial pathway stimulates oxidation of the lipoproteins which promotes apoptosis of VICs (Mahmut, 2013). This releases apoptotic bodies into the matrix causing diffuse calcification. In the valvular tissue, these oxidized lipoproteins also initiate an inflammatory response through activation of macrophages, CD4+ and CD8+ T lymphocytes, and mast cells (Mathieu, 2015). In turn, monocytes and macrophages stimulate the osteogenic differentiation of VICs and calcification with the release of TNF.

Macrophages and VICs also release extracellular vesicles (EV) that shed calcium and inorganic phosphates that further promote calcification (Goody, 2020). The role of EVs in cardiovascular calcification is well studied, and their lipid content can either promote or inhibit calcification. More research is needed with EVs' role in CAVD to determine if the effects are similar.

Through review of the literature, five phenotypes have been identified that represent the VIC family of cells, each exhibiting specific sets of cellular functions for normal valve physiology and pathological processes. These phenotypes include as embryonic progenitor endothelial/mesenchymal cells, quiescent VICs (qVICs), activated VICs (aVICs), progenitor VICs (pVICs), and osteoblastic VICs (obVICs). These phenotypes can exhibit plasticity and convert from one form to another (Liu, 2007). When pathological or physiological stimulation occurs, aVICs morph themselves into an osteoblastic phenotype (oVICs) which is the main driver of calcium deposition in CAVD (Ma, 2020).

The embryonic progenitor endothelial/mesenchymal cells undergo endothelial-to-mesenchymal transformation (EndMT) that initiates the process of valve formation in the embryo. Several studies indicate that this same process affects adult VECs and the pathogenesis of CAVD (Mahler, 2013), and other cardiovascular diseases such as atherosclerosis, cardiac fibrosis, pulmonary hypertension (Ma, 2020). The EndMT process involves the cellular reprogramming of endothelial cells to gain mesenchymal cell markers and features, and lose some endothelial markers and function (Yu, 2014). Many different cell types are involved and communicate with each other to affect changes in phenotypes in CAVD. Experiments with co-cultures of VICs and VECs demonstrated that VICs inhibit the EndMT process of VECs, and VECs dramatically reduce the activation of VICs (Hjortnaes, 2015). Furthermore, in the diseased state, VECs differentiate into endothelial VICs, which in turn differentiate into obVICs, thus increasing calcification and progressing the disease.

The use of primary cells from large animals and humans is the main source for experimental models of aortic valve calcification. Although there has been significant research advances over recent years to elucidate the causes and treaments for this disease, there is much more to be discovered especially in the area of non-surgical therapeutics. With the various cellular pathways of VICs and VECs being revealed, there are more potential therapeutic targets to investigate.

Lonza CellBio Services has human valvular endothelial and interstial cells readily available upon request. In addition, we can provide custom isolations of these cells from large animals including porcine, bovine, and ovine.

Additional product information including instructions, protocols, and recommended culture media is available on our website:
www.lonza.com/cellbioservices

For details, visit our website, or email us at
cellbioservices@lonza.com

References:

https://www.ahajournals.org/doi/full/10.1161/ATVBAHA.119.313067
Goody, P. R., Philip Rog er Goody Correspondence to: Philip Roger Goody, Hosen, M. R., Mohammed Rabiul Hosen From the Heart Center Bonn, Christmann, D., Dominik Christmann From the Heart Center Bonn, . . . Al., E. (2020, March 12). Aortic Valve Stenosis. Retrieved from https://www.ahajournals.org/doi/full/10.1161/ATVBAHA.119.313067

Hjortnaes J, Shapero K, Goettsch C, et al. Valvular interstitial cells suppress calcification of valvular endothelial cells. *Atherosclerosis*. 2015;242:251–260.

The Emerging Role of Valve Interstitial Cell Phenotypes in Regulating Heart Valve Pathobiology (nih.gov)
Liu, A. C., Joag, V. R., & Gotlieb, A. I. (2007, November). The emerging role of valve interstitial cell phenotypes in regulating heart valve pathobiology. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2043503/#B4-7418

Ma, X., Zhao, D., Yuan, P., Li, J., Yun, Y., Cui, Y., Zhang, T., Ma, J., Sun, L., Ma, H., Zhang, Y., Zhang, H., Zhang, W., Huang, J., Zou, C., & Wang, Z. (2020). Endothelial-to-Mesenchymal Transition in *Calcific Aortic Valve Disease. Acta Cardiologica Sinica, 36(3),* 183–194. https://doi.org/10.6515/ACS.202005_36(3).20200213A

Mahler GJ, Farrar EJ, Butcher JT. Inflammatory cytokines promote mesenchymal transformation in embryonic and adult valve endothelial cells. *Arterioscler Thromb Vasc Biol.* 2013;33:121–130

Mahmut A, Boulanger MC, El Husseini D, Fournier D, Bouchareb R, Després JP, Pibarot P, Bossé Y, Mathieu P. Elevated expression of lipoprotein-associated phospholipase A2 in calcific aortic valve disease: implications for valve mineralization.J Am Coll Cardiol. 2014; 63:460–469. doi: 10.1016/j.jacc.2013.05.105

Mathieu P, Bouchareb R, Boulanger MC. Innate and adaptive immunity in calcific aortic valve disease.J Immunol Res. 2015; 2015:851945. doi: 10.1155/2015/851945

www.ahajournals.org/doi/10.1161/JAHA.117.006339#jah32473-bib-0001
Rutkovskiy, A., Arkady Rutkovskiy Division of Physiology, Malashicheva, A., Anna Malashicheva Almazov National Medical Research Centre, Sullivan, G., Gareth Sullivan Division of Biochemistry, . . . Rutkovskiy, *. T. (2017, September 14). Valve Interstitial Cells: The Key to Understanding the Pathophysiology of Heart Valve Calcification. Retrieved from https://www.ahajournals.org/doi/10.1161/JAHA.117.006339

Yu W, Liu Z, An S, et al. The endothelial-mesenchymal transition (EndMT) and tissue regeneration. *Curr Stem Cell Res Ther*. 2014;9:196–204.

Contact us

North America
Customer Service: + 1 800 638 8174 (toll free)
order.us@lonza.com
Scientific Support: + 1 800 521 0390 (toll free)
scientific.support@lonza.com

Europe
Customer Service: + 32 87 321 611
order.europe@lonza.com
Scientific Support: + 32 87 321 611
scientific.support.eu@lonza.com

International
Contact your local Lonza Distributor
Customer Service: + 1 301 898 7025
Fax: + 1 301 845 8291
scientific.support@lonza.com

Lonza Walkersville, Inc. – Walkersville, MD 21793

CD-SP090 11/21

https://www.lonza.com/cellbioservices