Novel insights into the molecular basis of calcific aortic valve disease

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Calcific aortic valve disease (CAVD) is the most common valvular heart disease in the elderly. CAVD is a slowly progressive disorder that ranges from mild valve thickening without obstruction of blood flow, termed aortic sclerosis, to severe calcification with impaired leaflet motion, termed aortic stenosis (AS). CAVD is in one of the most important contributors to cardiovascular morbidity and mortality (1,2). AS occurs in 2% of people above 65 years old, and its prevalence is likely to increase due to the aging of the population (3). Although many studies have been made to understand the factors driving progression of CAVD, the molecular mechanisms and signalling pathways underlying the pathophysiological responses of this disease are still obscure.

Pathogenesis of CAVD

CAVD is recognized as an actively regulated disease (4). In the initiation phase, risk factors it shares with atherosclerosis and mechanical strain contribute to the endothelial damage on the aortic valve, leading to infiltration of oxidized phospholipids (OxPL) into the valve (*Figure 1*). Both the endothelial dysfunction and the retention of OxPL promote inflammatory infiltrates to accumulate into the valve (5) that in turn promote profibrotic processes, stimulating myofibroblastic differentiation of valve interstitial cells (VICs) and extracellular matrix (ECM) modelling. Eventually, cellular pathways that promote calcification are activated, and calcification starts to accumulate leading to progressive aortic valve obstruction (6).

Relevance of omics studies in CAVD

Generation of "omics data" via high-throughput technologies such as DNA microarrays and proteomics have provided a deeper understanding of biological processes, molecular pathways, and interaction networks involved in cardiovascular diseases (7). As the pathobiology of CAVD is the sum of several contributing processes, omics-analyses have been used to understand the complexity of the disease progression. Several studies have compared transcriptomic (8-10) and proteomic (11-13) profiles of human calcified and normal aortic valves. However, the studies have often a small sample size, and also different technology platforms and data processing techniques have been used in producing altogether inconsistent results. In their study, Zhang and Ma (in 2020) used an integrated bioinformatics analysis to overcome this problem of heterogenicity (14). They combined gene expression profiling datasets, performed functional and pathway enrichment analysis and constructed the protein-protein interaction (PP1) networks to reveal key genes and molecular mechanisms that contribute to the progression of CAVD.

Key genes and pathways in CAVD

The study of Zhang and Ma (in 2020) identified altogether 53 up- and 54 down-regulated genes in CAVD by integrated analysis of two datasets (8,10). Since individual genes are often involved in multiple cellular processes, the authors identify also the molecular processes associated to dysregulated genes highlighting the importance on
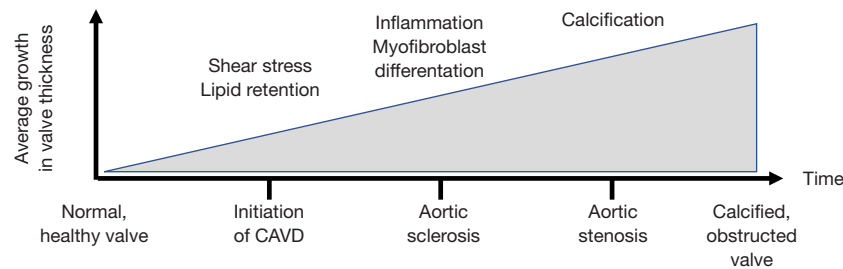
Figure 1 Different pathobiological processes over the time course of CAVD development. CAVD, calcific aortic valve disease.

ECM modelling and immune response related processes in CAVD.

They further identified hub of six genes in protein-protein interaction (PPI) network analysis. These genes, VCAM1, MMP9, ITGB2, RAC2, vWF and ALDH2, were mainly enriched in cell adhesion and leukocyte transendothelial migration pathways. The potential significance of key genes for disease progression of CAVD is discussed by the authors, but it is notable that so many of them is contributing to inflammatory response. Confirming validity of their study, the roles of vascular cell adhesion molecule 1 (VCAM1) and matrix metalloproteinase 9 (MMP9) are well defined in CAVD (15,16). VCAM1 is expressed in the endothelial cells and facilitates inflammatory cell infiltration into the valvular tissue whereas MMP9 along with the other MMPs and tissue inhibitors of metalloproteinases (TIMPs) promote ECM remodelling even in an early phase of CAVD and the fibrotic process continues also in the advanced stages of the disease (6,17). von Willebrand factor (VWF) is a glycoprotein that interacts with several factors that are associated with AS including ADAMTS13, Factor VIII, collagens and integrins (18). VWF has an important role in platelet adhesion and hemostasis and it might contribute to the regulation of angiogenesis (18). The intriguing finding of the study of Zhang and Ma (2020) is that among the key genes are integrin beta 2 (ITGB2), Rac family small GTPase 2 (Rac2) and aldehyde dehydrogenase (ALDH2) but no previous research has investigated their role in CAVD. Integrins have been shown to enhance migration of leukocytes into the tissues and they could act also as mechanosensor on the cell surface of VICs in response to increased shear stress (19). The future studies will show whether Rac2 and ALDH2 play a role in CAVD.

Lastly, the authors generated a PPI network that is based on previously known interactions among the identified genes. It is important to note that this is a putative network,

and these interactions have not been confirmed to happen in aortic valves. In fact, based on transcriptomics we might have a complete picture on what RNAs are produced within aortic valve, but it is not known if these genes are translated to functional proteins. However, since the impact of individual gene on the disease phenotype is often modest in complex diseased like CAVD, these interaction networks may shed some light on the complicated disease process. Concequently, the next step will be to confirm the expression of these genes with other quantitative gene expression platform and to perform additional experiments elucidate the interactions between dysregulated genes.

In conclusion, the progression from normal valve to aortic sclerosis and further to AS is slow. Progressive stenosis occurs in almost all patients, even though there is large variation in the speed of disease progression in individual patients. The present study expands the overall data on CAVD transcriptomics by performing integrated data analysis of gene expression changes in order to better understand molecular drivers contributing to the progression of CAVD. Consequently, this data may be useful in developing therapeutic strategies to treat this disease.

Footnote

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