Canadian Journal of Cardiology 30 (2014) 982–993

Review

Basic Mechanisms of Calcific Aortic Valve Disease

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ABSTRACT

Calcific aortic valve disease (CAVD) is the most common heart valve disorder. There is no medical treatment to prevent and/or promote the regression of CAVD. Hence, it is of foremost importance to delineate and understand the key basic underlying mechanisms involved in CAVD. In the past decade our comprehension of the underpinning processes leading to CAVD has expanded at a fast pace. Hence, our understanding of the basic pathobiological processes implicated in CAVD might lead eventually to the development of novel pharmaceutical therapies for CAVD. In this review, we discuss molecular processes that are implicated in fibrosis and mineralization of the aortic valve. Specifically, we address the role of lipid retention, inflammation, phosphate signalling and osteogenic transition in the development of CAVD. Interplays between these different processes and the key regulation pathways are discussed along with their clinical relevance.

RÉSUMÉ

La calcification de la valve aortique (CVA) est le trouble des valves cardiaques le plus fréquent. Aucun traitement médical ne peut prévenir ou favoriser la régression de la CVA. Par conséquent, il est particulièrement important de définir et de comprendre les principaux mécanismes de base sous-jacents qui sont impliqués dans la CVA. Au cours de la dernière décennie, notre compréhension des fondements des processus menant à la CVA a progressé très rapidement. Par conséquent, notre compréhension des processus biopathologiques fondamentaux impliqués dans la CVA mènerait éventuellement à l'élaboration de nouveaux traitements pharmacologiques de la CAV. Dans cette revue, nous discutons des processus moléculaires qui sont impliqués dans la fibrose et la minéralisation de la valve aortique. Particulièrement, nous traitons du rôle de la rétention lipidique, de l'inflammation, de la signalisation du phosphate et de la transition ostéogène dans le développement de la CVA. Nous discutons des interactions entre ces différents processus et les voies de régulation principales ainsi que leur pertinence clinique.

Calcific aortic valve disease (CAVD) encompasses a wide spectrum of clinical entities, from aortic sclerosis to severe aortic stenosis (AS). However, there is a general agreement that aortic sclerosis and AS are part of a same pathobiological process whereby the aortic leaflets undergo a progressive mineralization and fibrotic process. Hence, a group of leading experts, convened by the National Heart, Lung and Blood Institute, have developed a consensus statement and have recommended that the different clinical entities, aortic sclerosis and AS, should be termed CAVD.[1] For many years, CAVD has been described as a "passive" process related to aging. However, in the past 15 years there has been a growing interest to decipher the cellular and molecular processes involved in CAVD. Studies underscored that CAVD shared many clinical risk factors with atherosclerosis. In addition, histopathological examination of surgically explanted stenotic aortic valves indicated that several features such as lipid infiltration, inflammation, and calcification were commonly observed in CAVD.[2] Moreover, several animal models of atherosclerosis also developed some degree of CAVD.[3] Taken together, these findings suggested that CAVD was only another manifestation of an atherosclerotic process. However, 3 randomized trials with statins failed to demonstrate any benefit from a lipid-lowering approach in patients with a moderate-to-severe AS.[4] These studies suggested that although CAVD has possibly some overlapping processes in common with atherosclerosis it has underlying specific mechanisms that lead to the mineralization of the aortic valve. To this effect, a growing number of studies have since shed more light on the underpinning processes at play in CAVD, which might open new therapeutic avenues. In this article, we review the latest discoveries related to CAVD, its basic molecular processes, and whenever possible we have tried to tie these basic discoveries with clinical observations, keeping in mind a translational approach.

Histopathology of CAVD and Basic Mechanism of Mineralization

CAVD is characterized by the presence of mineralized nodules and fibrosis.[5] Histological sections of explanted CAVD during surgeries revealed that mineralization starts in

Received for publication January 7, 2014. Accepted March 19, 2014.

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See page 990 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2014.03.029

the fibrosa layer and then extend through the tissue in distorting the normal architecture of the aortic valve. It is noteworthy that oxidized lipid species are present in the vicinity of mineralized nodules.[2,6] Simple microscopic observations indicate that inflammatory cells, predominantly composed of macrophages, infiltrate the mineralized aortic valve and tend to form clusters.[7] In these clusters of inflammatory cells an active process of neovascularization takes place. It has been reported that endothelial progenitor cells, which incidentally infiltrate the aortic valve, promote neoangiogenesis.[8] Also, neovascularization of the aortic valve has been shown to be associated with the expression of heat shock protein 60.[9] Hence, it suggests that inflammation and neovascularization are intimately linked to aortic valve mineralization and remodelling. To this effect, we recently reported in 285 stenotic aortic valves that the presence of inflammatory infiltrates is associated with a greater remodelling score of tissues.[10] In some stenotic aortic valves, chondro-osteogenic metaplasia is observed.[11] Dense inflammatory infiltrates often accompany these metaplastic changes (Fig. 1). Thus, it is likely that, at least in a subgroup of valves, active transformation of resident cells into osteoblast-like cells occurs and might therefore participate in the mineralization of the aortic valve. Valve interstitial cells (VICs), the main cellular component of the aortic valve, are actively involved in the production of extracellular matrix and mineralization during CAVD. It should be pointed out that VICs represent a heterogeneous population of cells, which might thus exhibit different phenotypes. Li et al. proposed that VICs should be regrouped into 5 distinct phenotypes: (1) embryonic progenitor endothelial/mesenchymal cells; (2) quiescent VICs; (3) activated VICs; (4) progenitor VICs; and (5) osteoblastic VICs.[12] VICs represent a cell population with a high plasticity, that might change phenotype interchangeably depending on cell context and cues delivered to the cells. As such, different VIC populations are present at different degrees from embryogenesis to later in life in the adult. For instance, although embryonic progenitor endothelial/mesenchymal cells are involved in endothelial-mesenchymal transition (EndoMT) during valve formation from endocardial cushion, in adulthood the quiescent VICs ensure a normal valve function by promoting the maintenance of the extracellular matrix components.[13] Activated VICs and progenitor VICs, which are involved in tissue repair, might also play a major role during different pathobiological processes, including CAVD. On this score, signals delivered to VICs play a key role in the development and progression of CAVD. For instance, VICs with a strong osteogenic potential have been identified in the aortic valve and therefore with appropriate cues this population might be activated and promote mineralization.[14] It should be pointed out that, because of intensive research effort, several molecular cues and signalling cascades involved in pathologic mineralization and fibrosis have been brought to light in the recent years.

Lipid Retention Process

Small, dense, low-density lipoprotein

Epidemiological studies emphasized that low-density lipoprotein (LDL) cholesterol is a risk factor for the development of CAVD.[15] Also, as previously highlighted when retrospective study results indicated that statins were associated with a slower hemodynamic progression rate of stenosis, 3 randomized controlled studies reported in contrast, that a lipid-lowering strategy neither resulted in lower aortic valve-related events nor in a slower progression rate of stenosis.[4] Hence, considering that different active lipid species are present in the aortic valve, why did statins fail at preventing valve-related events? It has been argued that statins might have been started too late in the disease process when it was too advanced. Also, part of the answer might lie in the specific processes related to lipid retention and modification that occurs during CAVD. Oxidized LDL (ox-LDL) and their derived reactive lipid species are strong promoters of mineralization when assessed in isolated VICs.[16] Studies indicate that circulating levels of ox-LDL are associated with the remodelling score of mineralized aortic valves.[6] Moreover, Mohty et al. showed that the amount of ox-LDL within explanted CAVD tissues was associated with aortic valve inflammation (Fig. 2).[17] In this study, the only lipid variable associated with the accumulation of tissue ox-LDL was the proportion of small, dense LDL. Small, dense LDLs have greater ability to infiltrate tissues and are prone to the oxidation process. The high proportion of small, dense LDL in patients with the metabolic syndrome might explain the faster progression rate of AS documented in this group of patients.[18,19] In addition, it should be pointed out that although statins are efficient at lowering LDL-cholesterol they have, however, no or at best a modest effect on the proportion of circulating small, dense LDL.

Lipoprotein-associated phospholipase A2 mediates mineralization of the aortic valve

Uncoupling of nitric oxide (NO) activity in CAVD has been documented and it has been shown that it promotes the generation of reactive oxygen species, which might, in turn, promote the production of highly reactive lipid-derived oxidized species.[20] We recently identified that lipoprotein-associated phospholipase A2 (Lp-PLA2) is overexpressed in tissues of CAVD. Lp-PLA2 converts ox-LDL into lysophosphatidylcholine (LPC), which is incidentally present in CAVD tissues.[21] Moreover, LPC is a strong promoter of mineralization in isolated VICs through a cyclic adenosine monophosphate (cAMP)/protein kinase A pathway. Therefore, it is likely that Lp-PLA2 is produced locally, within the aortic valve, by macrophages and/or is transported in the aortic valve by LDL, particularly by small, dense LDL, and enhances lipid retention/modification. Recently, a single nucleotide polymorphism in the lipoprotein (a) locus (rs10455872) has been associated with aortic valve calcification.[22] Moreover, the blood plasma level of lipoprotein (a) has also been associated with an increased risk of aortic valve stenosis.[23] These findings are of interest considering that lipoprotein (a) transports oxidized-phospholipids, which are transformed by Lp-PLA2 into LPC.[24] It should also be highlighted that other enzymes, expressed in stenotic aortic valve, might promote lipid retention/modification. In this regard, lipoprotein lipase is expressed in CAVD tissues where it colocalizes with oxidized lipids.[25] Also, phospholipid transfer protein (PLTP) is overexpressed in CAVD tissues. Derbali et al. found that stimulation of