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EDITORIAL COMMENT

Valvular Endothelium

A Genetically Susceptible Predilection Site for Calcific Aortic Valve Stenosis*

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The quest toward a medical alternative to the current interventional and surgical treatments for calcific aortic valve stenosis (CAVS) is advancing. Among pathophysiological key players in CAVS, the cytoskeletal regulator PALMD was identified and replicated in genome-wide association studies as a protective factor for CAVS development.[1] Importantly, PALMD expression in the aortic valve endothelium regulates nucleocytoplasmic transport through complexes with RANGAP1.[2] This affects cytoskeletal arrangements in the endothelium, such as the formation of the nucleus-protecting actin cap,[2] which is required for nuclear resilience of endothelial cells under mechanical stress.

In this issue of *JACC: Basic to Translational Science*, Han et al[3] found dominant endothelial PALMD expression in aortic valves with markedly higher PALMD expression levels in valvular endothelial cells (VECs) compared with valvular interstitial cells (VICs), which confirm the findings previously reported by Sáinz-Jaspeado et al.[2] The observations in this issue extend the current knowledge by pathophysiologically coupling PALMD to an affected aortic valve function.[3] Palmd-deficient old and hyperlipidemic mice displayed increased peak aortic valve velocities and thicker aortic valve leaflets compared with Palmd-expressing control mice.[3] Endothelial PALMD overexpression induced the opposite beneficial effects,[3] supporting endothelial PALMD as a key protective factor against CAVS development.

The aortic valve endothelium is crucial for valvular sensing and adapting to biochemical and biomechanical stimuli in the process to retain valvular homeostasis.[4] The improved valve function as a result of endothelium-specific PALMD expression[3] in addition provides important support to the concept of valvular endothelium as a flow-dependent predilection site for CAVS development.[4] Endothelial activation leading to immune cell recruitment is the initiating event for turning the valve into a site of chronic inflammatory circuits. In addition, a valvular endothelial dysfunction leads to a diminution of protective nitric oxide signaling pathways.[4] Han et al[3] associated endothelial PALMD deficiency with an endothelial-to-mesenchymal transformation (EndMT), in which VECs will acquire VIC characteristics. Among the consequences of a valvular EndMT, disruption of the endothelial barrier integrity will expose VICs, infiltrating leukocytes, and the extracellular matrix to circulating factors, which stimulate valvular remodeling, inflammation, fibrosis, and calcification toward the development of CAVS.[4] Proteoglycan deposition in aortic valve leaflets was increased in Palmd-deficient mice and decreased by endothelial Palmd overexpression,[3] further reinforcing that endothelial dysfunction and disruption contribute to valvular extracellular matrix remodeling and fibrosis. Finally, a direct relation between Palmd and inflammation was supported by effects on ubiquitination to regulate nuclear factor-κB activation.[3]

Although the observed significant effects on aortic valve peak flow by altered PALMD expression

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provides a link to valvular function,[3] those velocities were lower than expected in a diseased state. The decreased systolic function in Palmd-deficient mice[3] was hence an intriguing observation at a degree of valve stenosis that did not cause a significant obstruction. This allows for further exploration of possible direct myocardial effects of endothelial PALMD expression. Likewise, although PALMD is dominantly expressed by VECs, VICs are not completely devoid of PALMD expression,[2,3] which may reflect the degree of EndMT in the donor valve. The possible contribution of nonendothelial PALMD expression after an EndMT remains to be established. However, in support of mainly endothelial effects behind the genetic association of PALMD with CAVS,[1] the downstream PALMD effects in human VECs on perinuclear RANGAP1 and nuclear p53 and p21 depend on the PALMD genotype.[2] The latter findings raise the notion that donor genotype should be considered in valvular cell biology, because key pathways genetically linked to CAVD may be reflected in the in vitro cellular behavior.

Stenotic aortic valves have a distinct sex-specific phenotype, with a less calcific and more fibrotic valve phenotype in women compared men. Transcriptomic analysis of stenotic aortic valves has revealed enriched fibrotic pathways in valves obtained from women undergoing aortic valve replacement for severe CAVS,[5] providing a possible molecular rationale for the observed sex differences. Likewise, the latter study detected valvular transcripts from genes located on the sex chromosomes, which predicted valvular calcification.[5] The future areas of exploration hence also include to consider underlying sex-specific endothelial susceptibility to CAVS.

In summary, the key role of PALMD in CAVS, which was identified by genome-wide association studies[1] and mechanistically linked to actin-dependent endothelial nuclear resilience,[2] exerted beneficial effects on valvular function.[3] The latter novel findings in this issue of *JACC: Basic to Translational Science* extend the mechanistic insights for endothelial PALMD, point to the valvular endothelium as a key predilection site for CAVS development, and underline the importance of endothelial homeostasis to protect the aortic valve against CAVS.

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