Calcific Aortic Valve Disease: Cellular Origins of Valve Calcification

Nalini M. Rajamannan

CALCIFIC aortic valve disease is the most common indication for surgical valve replacement in the world. For years this disease was thought to be a passive degenerative phenomenon. Understanding of the cellular mechanisms of this valve lesion will present new cellular therapeutic options to slow disease progression. In this study by Egan et al, they identify for the first time in human calcifying aortic valves a population of circulating osteogenic precursor cells (COP) in calcified human aortic valves. Their finding of these CD45+ OCN+ COP cells in areas of calcification and not in the unaffected calcified tissues provides another level of evidence that mesenchymal derived cell populations are responsible for the development of osteogenesis in the calcified aortic valve. Specifically, the study demonstrated that these cells were localized to areas of confirmed endochondral ossification and bone formation. Within the regions of interest there were areas of mature bone with the characteristic architecture including osteocytes and bone lining cells. However, within the limits of the study there was no consistent involvement of the valve leaflet layers as the areas of endochondral ossification were found to extend to variable depths. The conclusions from this study provide the first evidence in human calcifying aortic valve tissue that a novel cellular origin is found on the calcific aortic valve and that these COP cells play a role in the cellular mechanisms of osteogenesis.

Previously, we and Mohler et al have demonstrated that aortic valve calcification is associated with endochondral bone formation and an osteoblast bone-like phenotype. This bone phenotype is regulated by canonical Wnt pathway in experimental cardiovascular calcification. We have also shown that the canonical Wnt/Lrp5 pathway is upregulated in diseased human valves from patients with valvular heart disease. Bone and cartilage are major tissues in the vertebrate skeletal system, which is primarily composed of 3 cell types: osteoblasts, chondrocytes, and osteoclasts. In the developing embryo, osteoblast and chondrocytes both differentiate from common mesenchymal progenitors in situ, whereas osteoclasts are of hematopoietic origin and brought in later by invading blood vessels. Osteoblast differentiation and maturation lead to bone formation controlled by 2 distinct mechanisms: intramembranous and endochondral ossification, both starting from mesenchymal condensations.

Two osteoblast-specific transcripts have been identified: (1) Cbfa1 and (2) osteocalcin. The transcription factor Cbfa1 has all the attributes of a “master gene” differentiation factor for the osteoblast lineage and bone matrix gene expression. During embryonic development, Cbfa1 expression precedes osteoblast differentiation and is restricted to mesenchymal cells destined to become osteoblast. In addition to its critical role in osteoblast commitment and differentiation, Cbfa1 appears to control osteoblast activity, ie, the rate of bone formation by differentiated osteoblasts. The regulatory mechanism of osteoblast differentiation from osteoblast progenitor cells as shown in Figure A into terminally differentiated cells is via a well-orchestrated and well-studied pathway that involves initial cellular proliferation events and then synthesis of bone matrix proteins, which requires the actions of specific paracrine/hormonal factors/BMP and the activation of the canonical Wnt pathway. In a previous study by Suda et al, they have shown that these isolated COP cells can express BMP and can form bone in vivo. Confirming the hypothesis that these COP cells are capable of homing to sites of valve calcification and neovascularization and form bone.

The studies to date indicate that the cellular origins of bone forming cells in the calcifying aortic valve have 2 distinct pathways as shown in Figure B. The cells can either be the COP cell capable of differentiating to bone at the site of calcification and disease, or the interstitial aortic valve cell that is capable of differentiating to bone in vivo, as described in the most recent National Heart and Lung and Blood Institute Working Group paper on calcific aortic valve disease. Further evidence for the circulating stem cell was published in a study by Tanaka et al, which demonstrated using transplanted bone marrow cells composed of 17% of the population of calcifying cells in the native atherosclerotic valve. The presence of variable depths of the COP cell in the calcific valve is consistent with the hypothesis that these cells can home to the diseased valve but are not responsible for the entire bone formation process. The native interstitial cells also have the potential to differentiate to bone in situ and contribute to the calcifying cells in the native valve. The contribution of these 2 cell types toward the development of calcification in the aortic valve requires further ongoing investigation. In summary, this study provides incremental understanding into the role of calcific aortic valve disease. In the future, these studies will provide the roadmap for targeted cellular therapies for the treatment of this disease process to

© 2011 American Heart Association, Inc.


DOI: 10.1161/ATVBAHA.111.237610
slow the progression of this disease and delay surgery in this patient population.

Acknowledgments
Dr Rajamannan is the inventor on a patent for methods to slow progression of valvular heart disease. This patent is owned by the Mayo Clinic and the author does not receive any royalties from this patent. This work is supported by NIH grant funding: 5R01HL085591 and 3R01HL085591S1.

References

Key Words: calcification ■ heart valves ■ stem cells
Calcific Aortic Valve Disease: Cellular Origins of Valve Calcification
Nalini M. Rajamannan

Arterioscler Thromb Vasc Biol. 2011;31:2777-2778
doi: 10.1161/ATVBAHA.111.237610
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/31/12/2777

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/