JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 4, 2022

EDITORIAL COMMENT

DCBL2 Deficiency Contributes to Aortic Stenosis via Increased BMP2 Signaling*

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The emergence of medical therapy to treat and prevent human disease was a sweeping technologic development of the 20th century. Despite these revolutionary innovations, aortic stenosis (AS) remains a disease with no effective medical therapy. This privation of medical therapy for AS partly reflects a central facet of basic and translational research in AS that requires consideration: animal models that recapitulate the key features of human AS are lacking. In more than a dozen animal models of AS, remarkably few develop hemodynamically significant stenosis.[1] The use of preclinical animal models is an essential tool in translation endeavors seeking to identify mechanisms of disease, and to establish new therapeutic targets. Therefore, new animal models of AS are required to overturn the prevalent notion that AS is a disease without medical therapy.[2]

In this issue of *JACC: Basic to Translational Science,* Jung et al[3] identify the role of DCBL2 in AS and introduce the *Dcbl2*$^{-/-}$ mouse model, both of which have important implications for basic and translation research in AS. DCBL2 is a transmembrane protein implicated in regulating growth factor signaling, vascular remodeling, and angiogenesis. *DCBL2* gene expression was previously found to be decreased in human aortic valve (AV) tissue in patients with severe AS, thus motivating studies to determine the role of DCBL2 in AS.

There are 4 key findings of the present study: 1) DCBL2 gene and protein expression is decreased in AV tissue from humans with severe AS; 2) *Dcbld2*$^{-/-}$ mice develop hemodynamically significant AS with increased valve calcification and fibrosis; 3) *Dcbld2*$^{-/-}$ mice have a high prevalence (~50%) of bicuspid AV (BAV), which is associated with more severe AV calcification, fibrosis, and stenosis; and 4) bone morphogenetic protein (Bmp) 2 signaling is higher in *Dcbl2*$^{-/-}$ mice with BAV than tricuspid aortic valve (TAV).

The present study clearly demonstrates for the first time both reduced gene and protein expression of DCBL2 in human AS and that *Dcbl2*$^{-/-}$ mice develop AS that recapitulates some of the features of human AS. However, the absolute amount of calcification in *Dcbl2*$^{-/-}$ mice was relatively small, which implicates fibrosis as a potential culprit process responsible for the development of AS in *Dcbl2*$^{-/-}$ mice. Future studies are required to determine the contribution of AV fibrosis in the development of AS in *Dcbl2*$^{-/-}$ mice. Nonetheless, Jung et al[3] show that DCBL2 is a novel mediator of AS and represents a heretofore unrecognized therapeutic target in AS. The severity and prevalence of AS in *Dcbl2*$^{-/-}$ mice are without precedent.[1] The prevalence of BAV of ~50% in *Dcbl2*$^{-/-}$ mice is also remarkably high. In comparison, the prevalence of BAV in the *Npr2*$^{+/-}$ mouse model of AS is only 10%.[4] The *Dbcl2*$^{-/-}$ mouse model represents a critical new tool to further understanding of AS, and to identify and test new therapeutics with the potential to alter the natural history of AS in humans.

The mechanism of AS in the *Dcbl2*$^{-/-}$ requires further investigation. Jung et al[3] demonstrate increased BMP2 in human AS, and enhanced Bmp2 signaling in vitro and in vivo is responsible for the enhanced AV calcification in *Dcbl2*$^{-/-}$ mice. Targeting

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2022.01.015

Bmp2 signaling with the Bmp2 receptor inhibitor LDN-193189in vivo attenuates Smad1/5/9 phosphorylation and osteocalcin expression. However, future studies are required to demonstrate if targeting Bmp2 signaling can prevent AV calcification, fibrosis, and stenosis in vivo.

It is proposed that increased Bmp2 signaling is a mechanism that integrates increased valve calcification and stenosis and *Dcbl2*$^{-/-}$ mice with BAV. However, in vitro studies show that siRNA-induced reduction in *DCBL2* increases BMP2 in porcine valve interstitial cells. These data suggest that BMP2 contributes to AS independent of leaflet anatomy. The mechanism of augmented Bmp2 signaling in *Dcbl2*$^{-/-}$ mice requires further clarification. It is possible that biomechanical alterations contribute to earlier-onset AS in BAV. A previous report of RNA sequencing in human AVs suggests that common pathways lead to AS in both BAV and TAV.[5] The *Dcbl2*$^{-/-}$ mouse model may parallel the common genetic architecture in BAV and TAV in humans. Overall, these data strengthen the position of the *Dcbl2*$^{-/-}$ mouse as a model to identify novel mechanisms and therapeutic targets in AS.

The relatively slow progression of AS in humans challenges the conduct of randomized trials with sufficient statistical power to prove clinical efficacy. It has been proposed that enriching clinical trials with patients at a high risk of rapid progression will improve efficiency and reduce cost. Enriching trials with patients with BAV is one proposed strategy.[2] The common mechanisms of AS in BAV and TAV provide an incentive for this approach. The presence of BAV and TAV make the *Dcbl2*$^{-/-}$ mouse an ideal candidate model for translation studies to establish preclinical efficacy of novel therapeutics.

Jung et al[3] should be commended for pioneering a new tool in basic and translational research in AS. Future studies are required to further characterize mechanisms of AS in *Dcbl2*$^{-/-}$ mice and test innovative approaches to lay the foundation for medical therapy for AS.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Merryman is supported by the National Institutes of Health (HL135790) and the Leducq Foundation. Dr. Armstrong has reported that he has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS aortic stenosis, aortic valve, bicuspid aortic valve, calcification