Commentary: When a histone deacetylase fails, the aortic valve gets stressed into old age

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One of the most common diseases affecting the aortic valve (AV) is the calcification of its leaflets leading to stenosis. The gold standard treatment is surgery, whether open with valve replacement using a mechanical or a bioprosthetic valve or endovascular with deployment of a bioprosthetic valve stent through the original valve.¹ However, these techniques have their limitations. In the case of mechanical valves, although they may last a lifetime, the patients must be perpetually anticoagulated, which carries significant bleeding risks. On the other hand, bioprosthetic valves obviate the need for anticoagulation; however, this comes at the price of diminished valve longevity, making reintervention an almost unavoidable reality if the patient survives long enough.²

As such, understanding the mechanism of how this calcification occurs may help develop medical therapy, which could potentially halt if not at the very minimum slow down the disease process. Therefore, this has been an active field of investigation.

Histone deacetylases (HDACs) act on both histones and nonhistone proteins.³ Their inhibition has been linked with vascular calcification.⁴ The endoplasmic reticulum (ER) compartment of a cell is responsible for ridding the cells from abnormally folded proteins.⁵ The dysfunction of the ER has been implicated in the pathogenesis of AV calcification, a process termed “ER stress.”⁶ It has also been shown that disruption to the HDAC pathway may lead to ER stress.⁷ As such, Fu and colleagues⁸ set out to investigate the potential link among HDAC, ER stress, and AV calcification.

With the use of Western blotting and immunohistochemistry, Fu and colleagues⁸ first demonstrate that HDAC6 levels are significantly diminished in the cusps of diseased human AVs compared with controls. They further go on to show that inhibition of HDAC6 using the specific inhibitor Tubacin promotes the activation of the osteogenic pathway in the valvular interstitial cells as measured by

Central Message

The current article neatly demonstrates that HDAC6 plays a crucial role in protecting aortic valves from becoming calcified and consequently stenosed by preventing ER stress.

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the increased expression of the protein Runx2. Similar observations were also obtained via RNA silencing of HDAC6. Next, the authors show that inhibition or silencing of HDAC6 promotes the expression of ER stress marker proteins in interstitial cells. Of note, the effects of HDAC6 blockade are more pronounced in interstitial cells from diseased AVs compared with controls presumably because of the former being already sensitized to HDAC6 dysfunction.

On the flip side, inhibition of ER stress using taurour-sodeoxycholic acid prevented the activation of the osteogenic pathway induced by the inhibition or silencing of HDAC6. Similar results were obtained via the knockdown of the activating transcription factor 4, a protein that directly links ER stress with activation of the Runx2 osteogenic pathway.

Finally, the promotion of osteogenesis by the blockade of HDAC6 in interstitial cells was ascertained using Alizarin red staining, which highlights calcium deposits. This effect was reversed via the inhibition of ER stress.

In all, Fu and colleagues⁸ have elegantly shown that HDACs play a crucial role in preventing ER stress and the subsequent activation of the osteogenic pathway in interstitial cells of AVs. This discovery may lead to the development of novel medical therapies against calcified AV disease.

However, the study is limited by its small sample size and the lack of in vivo experiments. Furthermore, the control

tissue had been taken from patients with aortic insufficiency. As such, the comparison of the calcified samples was not exactly against normal AVs. Further studies will have to be conducted to address these issues. Nonetheless, this study provides a platform upon which medical therapies may be developed against the accelerated calcification and aging of AVs.

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