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Dipeptidyl Peptidase-4 Induces Aortic Valve Calcification by Inhibiting Insulin-Like Growth Factor-1 Signaling in Valvular Interstitial Cells

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Calcification of the aortic valve leads to increased leaflet stiffness and consequently to the development of calcific aortic valve disease. However, the underlying molecular and cellular mechanisms of calcification remain unclear. Here, we identified that dipeptidyl peptidase-4 (DPP-4, also known as CD26) increases valvular calcification and promotes calcific aortic valve disease progression. We obtained the aortic valve tissues from humans and murine models (wild-type and endothelial nitric oxide synthase-deficient-mice) and cultured the valvular interstitial cells (VICs) and valvular endothelial cells from the cusps. We induced osteogenic differentiation in the primary cultured VICs and examined the effects of the DPP-4 inhibitor on the osteogenic changes in vitro and aortic valve calcification in endothelial nitric oxide synthase-deficientmice. We also induced calcific aortic stenosis in male New Zealand rabbits (weight, 2.5–3.0 kg) by a cholesterol-enriched diet+vitamin D2 (25 000 IU, daily). Echocardiography was performed to assess the aortic valve area and the maximal and mean transaortic pressure gradients at baseline and 3-week intervals thereafter. After 12 weeks, we harvested the heart and evaluated the aortic valve tissue using immunohistochemistry. We found that nitric oxide depletion in human valvular endothelial cells activates NF-κB in human VICs. Consequently, the NF-κB promotes DPP-4 expression, which then induces the osteogenic differentiation of VICs by limiting autocrine insulin-like growth factor-1 signaling. The inhibition of DPP-4 enzymatic activity blocked the osteogenic changes in VICs in vitro and reduced the aortic valve calcification in vivo in a mouse model. Sitagliptin administration in a rabbit calcific aortic valve disease model led to significant improvements in the rate of change in aortic valve area, transaortic peak velocity, and maximal and mean pressure gradients over 12 weeks. Immunohistochemistry staining confirmed the therapeutic effect of Sitagliptin in terms of reducing the calcium deposits in the rabbit aortic valve cusps. In rabbits receiving Sitagliptin, the plasma insulin-like growth factor-1 levels were significantly increased, in line with DPP-4 inhibition. DPP-4-dependent insulin-like growth factor-1 inhibition in VICs contributes to aortic valve calcification, suggesting that DPP-4 could serve as a potential therapeutic target to inhibit calcific aortic valve disease progression.