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MicroRNA-22 promotes the osteogenic differentiation of valvular interstitial cells by targeting calcium binding protein 39

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Calcific Aortic Valve Disease (CAVD) is a complex pathological process for which no effective therapies currently exist. Transformation of Valvular Interstitial Cells (VICs) to osteoblasts is believed to be one of the most important causes of valve calcification. Recently, emerging evidence suggests that pro-osteogenic MicroRNAs play essential roles in the calcification of the aortic valve. The purpose of this study is to determine whether miR-22 is critically involved in the osteogenic differentiation of VICs and if so, to determine the molecular mechanisms involved. A total of 33 CAVD patients were enrolled in the study. The severity of CAVD was determined by standard echocardiographic methods. To identify the aberrant expression of miRNAs in calcified aortic valve, real-time PCR was performed to detect the expression profiles of osteogenic miRNAs in CAVD patients. Subsequently, we identified miR-22 as one of the most significantly up-regulated miRNAs in calcified aortic valves. Fluorescence *in situ* hybridization assay showed that miR-22 was expressed throughout the regions of the calcified valves and predominantly localized in VICs, as indicated by the co-expression of vimentin. Elevated miR-22 levels were positively correlated with the expression of OPN ($rs=0.820$, $P<0.01$) and Runx2 ($rs=0.563$, $P<0.01$) as well as VIC osteogenic differentiation. Furthermore, we identified calcium binding protein 39 (CAB39) as a novel downstream target of miR-22 in VICs, as determined by dual-luciferase reporter assay, real-time PCR (Polymerase Chain Reaction) and western blot assays. Furthermore, we found that the CAB39 expression was negatively correlated with the calcification severity in clinical CAVD samples, as determined by immunohistochemical staining analysis. Adenovirus-mediated both gain- and loss-of-function analyses demonstrated that miR-22 is critically involved in the osteogenic differentiation of VICs, specifically through regulating the CAB39-AMPK-mTOR signaling pathway. MicroRNA-22 serves as a potential inducer of CAVD through inhibiting the CAB39/AMPK/mTOR signaling pathway. These results suggest that miR-22 may serve as a potential therapeutic target for the calcific aortic valve disease.

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