cells aids to perceive a comprehensive molecular network explaining the mosaic-like pathogenesis of the aortic valve disease; experimental research on epigenetics, such as METTL3-mediated m6A modification, may open a vast field of still-uncovered possibilities to unravel clinically unsolved dilemmas.

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Commentary: Aortic valve calcification: A new story with a twist?

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Aortic valve calcification (AVC) is considered a multifactorial disease involving a diverse spectrum of cellular and molecular mechanisms.¹ Recently, it was hypothesized that valvular interstitial cells (VICs), which are prevalent in all layers of the aortic valve, may play an important role in AVC.² In particular, their differentiation into the osteoblast phenotype is a key pathogenetic mechanism of aortic valve osseous metaplasia with subsequent mineralization. Although many factors could contribute to the development of AVC, including but not limited to abnormal biomechanical forces, hypercholesterolemia and inflammation,³ factors triggering the osteoblastic differentiation of VICs have not been completely identified.

CENTRAL MESSAGE

A novel therapeutic target using the TWIST pathway and valvular interstitial cells may prevent aortic valve calcification.

The methylation of N⁶-methyladenosine (m6A), an abundant nucleotide modification in eukaryotic RNA, is essential for multiple RNA processing events⁴ and, as was recently discovered, plays an important role in cardiomyocyte homeostasis.⁵ This process is accomplished via the methyltransferase complex, in which methyltransferase-like 3 (METTL3) plays a key role.

The interesting report by Zhou and colleagues⁶ in this issue of the *Journal* confirms that METTL3 is a positive regulator of VIC osteogenic differentiation in the setting of AVC. The osteogenic differentiation occurs via suppression of twist-related protein 1 (TWIST1) (Figure 1), which is in turn a negative regulator of VIC osteogenic differentiation.⁷ Importantly, although the role of TWIST 1 in the process of osteogenic differentiation of

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Disclosures: Authors have nothing to disclose with regard to commercial support. Received for publication Oct 29, 2019; revisions received Oct 29, 2019; accepted for publication Nov 4, 2019; available ahead of print Nov 27, 2019.

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J Thorac Cardiovasc Surg 2021;161:e188-9
0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2019.11.025>

FIGURE 1. Schematic of the TWIST1/METTL3 pathway in osteogenic differentiation of interstitial cells.

VIC has been established,⁷ the role of METTL3 has not been yet elucidated. Thus, this study contributes to our understanding of fundamental molecular mechanisms of the AVC and potentially may lead to the development of novel diagnostic and therapeutic strategies. On the other hand, considering the versatile functions of m6A in various physiological processes,⁴ it would not be surprising to find links between m6A and AVC.

Virtually any interstitial cell could be differentiated into an osteoblast when appropriate stimuli are applied.⁸ This reflects the versatility of ectopic calcification as a consequence of injury or inflammation, for example. It would also be tempting to use the atherosclerotic process as a model for studying osteogenic differentiation of interstitial cells, given that the end-stage of atherosclerotic process is calcification.⁹ However, although it has been shown in vitro that statins inhibit the osteogenic differentiation of VICs, randomized clinical trials using statins to treat AVC failed to demonstrate any benefits.⁸

The interest in AVC research is increasing exponentially during the last decade,¹ and several osteogenic pathways

leading to aortic valve calcification have been identified.¹⁰ Most of these studies were conducted in vitro or using an animal model. Although the possible clinical implications of such molecular research are not entirely clear, with the rapid advancement of modern technology, it might be possible to apply regenerative strategy using novel molecular pathways to prevent the calcification and degeneration of valvular tissue.

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