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# Commentary: Two clinical solutions and many molecular options for aortic valve stenosis

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**CENTRAL MESSAGE**

Experimental research on epigenetics, such as METTL3-mediated m6A modification, may open a vast field of still-uncovered possibilities to unravel clinically unsolved dilemmas.

ADULT

Aortic valve replacement either with or without cardiopulmonary bypass necessitates much from the patient and the surgical team. Surgical intervention requires technical expertise, hospitalization, and must be tailored according to comorbidities. The current 2 options to treat the patient with severe aortic valve stenosis include implantation of a prosthesis after either radical extraction or crunching of the lesions against the more or less diseased aorta. What if the entire aortic valve stenosis was prevented even from developing?

The current study by Zhou and colleagues[1] demonstrates that methyltransferase-like 3 (METTL3) participates in aortic valve stenosis by inhibiting twist-related protein 1 (TWIST1) while interacting with $N^6$-methyladenosine (m6A). Human interstitial cells from both healthy and calcified aortic valves were investigated for METTL3. METTL3 was upregulated in calcific aortic valves and acted as a positive regulator of osteogenic differentiation of the aortic valve interstitial cells, as shown by increased alkaline phosphatase activity, calcified nodule formation, and the protein levels of 3 osteogenic-specific markers, namely Runx2, osterix, and osteocalcin. Demonstrative figures are presented. The study adheres to power calculation with a representative number of samples.

METTL3-mediated m6A modification has a key role in human cardiovascular diseases, such as cardiac hypertrophy, heart failure, and coronary artery disease.[2-4] The study investigated several important regulators of aortic valve calcification, namely TWIST1, serotonin 2B receptor, klotho, histone deacetylase 6, calponin 2, cyclooxygenase 2, and dipeptidyl peptidase-4; only TWIST1 was decreased at the gene and protein levels upon increased METTL3 expression. The role of TWIST in the differentiation of aortic valve is well-established, but TWIST1 has also been reported to be modulated by other pathways.[5]

What can the clinician learn from this study? Presumably, the METTL3-mediated m6A modification pathway needs to be inhibited before any onset of aortic valve calcification. Maybe the inhibition of the pathway could be done using an Adeno-associated virus vector carrying the METTL3-like inhibitor[1]; gene therapy with Adeno-associated virus vectors has already been successful in a few previous experimental studies.[6,7] The promising results warrant further experimental studies before the theory is safely considered to be applied into a translational protocol aiming to prevent aortic valve stenosis. It is still unknown whether the specific inhibition of the molecular METTL3-mediated m6A modification pathway is sufficient to abolish the osteogenic-like process leading to aortic valve stenosis. The challenge is not to completely abolish METTL3 as this, ironically, may lead to heart failure through acceleration of some altering pathways.[8] There may be a threshold of METTL3 inhibition that should not be reached not to evoke compensatory pathways that could instead lead to undesired outcome.

Aortic valve interstitial cell deterioration is an end-stage phenomenon of a diverse of cellular pathways leading to aortic valve stenosis. Identifying different molecular pathways leading to calcification of the aortic valve interstitial

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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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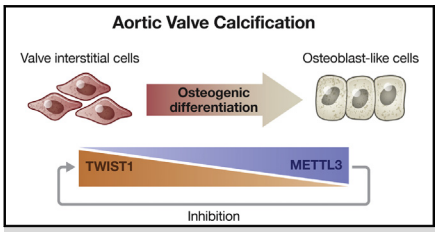
Aortic valve calcification (AVC) is considered a multifactorial disease involving a diverse spectrum of cellular and molecular mechanisms.[1] Recently, it was hypothesized that valvular interstitial cells (VICs), which are prevalent in all layers of the aortic valve, may play an important role in AVC.[2] 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.




Schematic of the TWIST1/MATTL3 pathway in osteogenic differentiation of interstitial cells.

**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 events[4] 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 colleagues[6] 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

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