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INVITED EDITORIAL

When cell mechanics meets epitranscriptomics: reduction of m^{6}A in Piezo2 RNA ameliorates cardiac fibrosis

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This editorial refers to 'Epitranscriptomic regulation of cardiac fibrosis via YTHDF1-dependent *PIEZO2* mRNA m^{6}A modification', by J.-F. Ding *et al.*, https://doi.org/10.1093/cvr/cvae239.

Cardiac fibrosis is one of the conditions predisposing to heart failure, involving the activation of cardiac fibroblasts (CFs) with a consequent maladaptive remodelling of the myocardium. While in healthy conditions, CFs are responsible for renewal of extracellular matrix (ECM) proteins, under pathological conditions like ischaemia or pressure overload, they become activated, proliferate, and differentiate into myofibroblasts.[1] These cells respond to hypoxia signalling and inflammatory cues, causing matrix degradation and collagen deposition, leading to significant increase in myocardial stiffness. Interestingly, CFs also respond to mechanical cues with activation of mechanosensitive signal transduction pathways (e.g. the YAP/TAZ signalling[2]) making them central effectors of convergent molecular pathological activation.[3]

Epitranscriptomics is the term describing the summary of RNA modifications that have potential to regulate downstream gene expression with fine-tuned readouts on cellular phenotypes.[4] Among the various RNA modifications, the transfer of a methyl group onto the N6-methyladenosine (m^{6}A) is the most abundant in coding and non-coding RNAs with a complex regulatory significance in various transcriptional processes.[4] RNA methylation is reversible and dynamically regulated by 'writers' and 'erasers' that catalyze, respectively, the addition and the removal of the methylation marks and by 'readers' that bind to mRNAs affecting their heir 3D conformation, stability, and translation.[5] Aberrant gene expression regulations by epitranscriptomics could represent the trigger to prompt quiescent fibroblasts towards pathologic phenotype. Recently, for example it has been found that post-transcriptional modifications of RNA, including RNA editing and methylation, affect the expression of fibrosis-related genes and ECM components.[6]

In this issue of *Cardiovascular Research*, Ding *et al.*[7] show that expression of the pro-fibrotic mechanosensitive channel Piezo2 is subjected to m^{6}A control. In particular, the authors identified a substantial number of m^{6}A modifications in the coding sequence and the 3′UTR regions of Piezo2 in mice subjected to ISO/Ang-II/TAC pressure overload and in CFs treated with the pro-fibrotic factor TGF-β1.[8] Authors validated the relevance of the m^{6}A modification for Piezo2 expression by using m^{6}A methylation inhibitor. Results showed a significant reduction in both RNA and protein levels of Piezo2, and this was correlated with a significant reduction of myofibroblast markers, suggesting that interfering with the epitranscriptomic regulation of Piezo2 could be an efficient way to blunt CF activation. The authors then identified YTHDF1 as the most closely RNA reader candidate to be active in Piezo2 m^{6}A methylation. YTHDF1 is a m^{6}A RNA-binding protein, located in the cytoplasm, which promotes translation of mRNA.[9] YTHDF1 knockdown significantly decreased Piezo2 mRNA levels, the expression of key CF activation markers, and reduce the migratory and the proliferative abilities of CFs. Site-directed mutagenesis of the m^{6}A modification sites reduced the binding capacity of YTHDF1 to Piezo2 mRNA, and treating ISO/Ang-II/TAC mice with AAV9-based vectors to *in vivo* knockdown YTHDF1 ameliorated cardiac fibrosis by reducing CF autophagy and collagen deposition and by improving cardiac function.

While these findings highlight the close relationship between m^{6}A modification and the pro-fibrotic role of Piezo2 and open the way to novel therapeutic approaches to reduce cardiac fibrosis, they also suggest an intriguing cooperation between CF activation and cell mechanosensation. Piezo2 is, in fact, a mechanosensitive non-selective cation channel, regulating calcium efflux to mediate cellular responses such as proliferation, differentiation, and migration,[10] whose regulation could be also subjected to alterations in mechanical properties of the myocardium (e.g. the stiffness) or to cellular stretch. The data contained in the study by Ding *et al.* support this hypothesis by showing that exposure of cells to cyclic strain increased Piezo2 expression in keeping with fibrosis markers COL1A1 and POSTN, suggesting that the expression/activity of the m^{6}A writers may also be under mechanical control (*Figure 1*).

In summary, the study by Ding *et al.* has described a novel epitranscriptomic regulation of the mechanosensor Piezo2 in CF activation that involves the m^{6}A reader protein YTHDF1. The interaction between Piezo channels and RNA modifications raises intriguing questions about how cells integrate mechanical cues with RNA regulatory mechanisms. On the basis of their data, it is possible to speculate that mechanical stimulation could alter m^{6}A methylation, thus promoting the mRNA translation and stability of genes associated with fibrosis and matrix remodelling. Understanding how Piezo channels and epitranscriptomic mechanisms converge may thus unveil new more general RNA therapeutic strategies for intervention in the failing heart.

The opinions expressed in this article are not necessarily those of the Editors of *Cardiovascular Research* or of the European Society of Cardiology.

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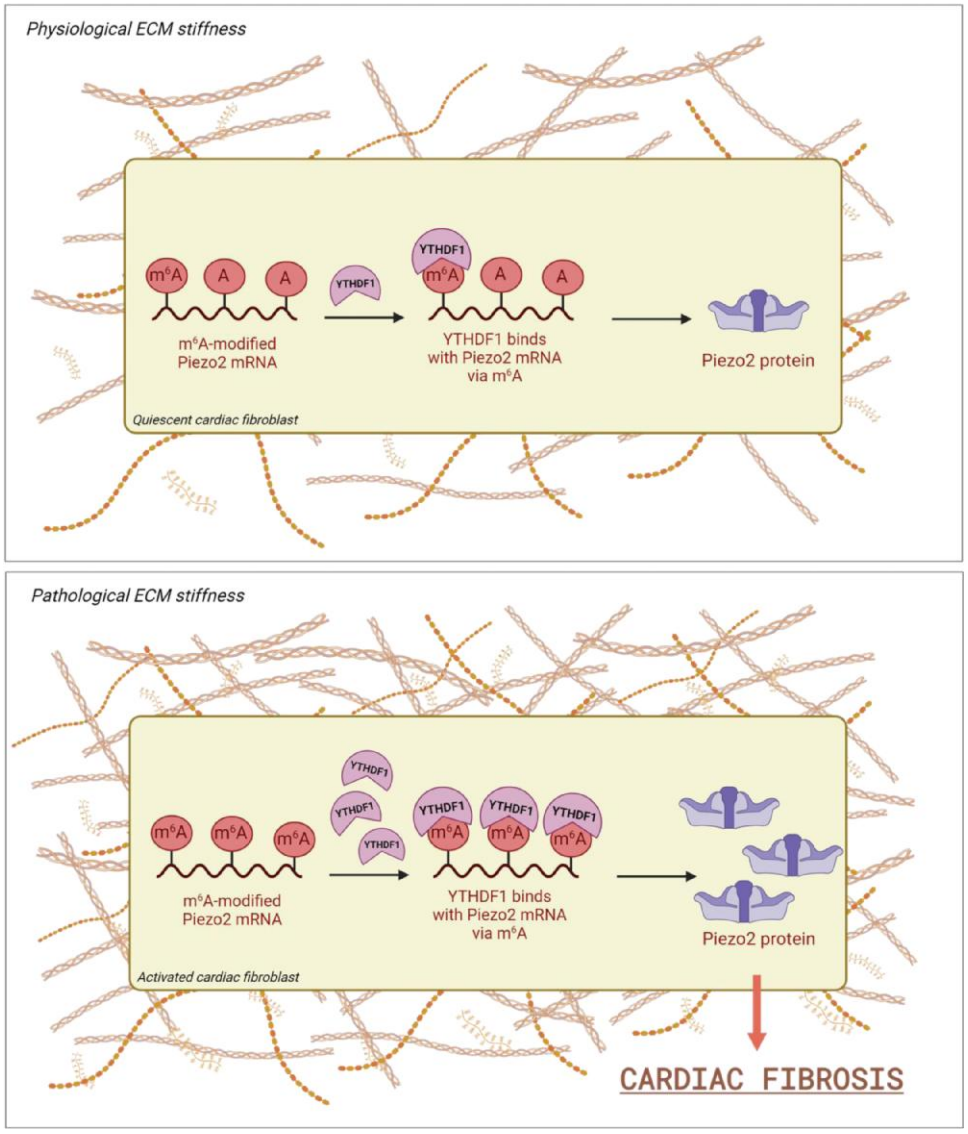

Figure 1 In the absence of myocardial insult, the level of m^{6}A modification of Piezo2 RNA is low and this limits RNA stability and efficient Piezo2 translation (top). In the presence of pressure overload, the elevation of stiffness and the increased response to strain may determine an increase in m^{6}A modification and in YTHDF1 epigenetic reader expression, leading to increased Piezo2 protein expression, favouring cardiac fibrosis.

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Data availability

No new data were generated or analysed in support of this research.

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