GW23-e2696 **MICRORNAS CONTROL CARDIAC FIBROSIS**

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Hongli Shan, Haihai Liang, Yanjie Lu, Baofeng Yang, Hongli Shan. *Harbin Medical University, Harbin, Heilongjiang*

Objectives Cardiac fibrosis is characterised by aberrant proliferation of cardiac fibroblasts and exaggerated deposition of extracellular matrix (ECM) in the myocardial interstitium, and eventually leads to heart failure. Therefore, revealing the mechanism of cardiac fibrosis is of great value for clinical therapy. microRNAs (miRNAs) are a class of endogenous, non-coding small RNAs, 22nd in length. Mature miRNAs negatively modulate gene expression by repressing translation of target genes or inducing degradation of target mRNAs by binding to the 3′-UTR of target genes. Increasing evidence supports that miRNAs play indispensable roles in the process of cardiac diseases, such as arrhythmia, atrial fibrillation, cardiac hypertrophy and so on.

Methods The model of AF was established by nicotine administration. The atrial fibroblasts isolated from healthy dogs were treated with nicotine. microRNAs level was quantified by Real-time PCR. The role of miRNAs on the expression and regulation of target genes were detected by Western blot and Luciferase assay. Collagen production was evaluated in vivo and in vitro.

Results Some miRNAs related to cardiac fibrosis have been reported. Eva van Rooij et al. firstly confirmed that microRNAs play an important role in cardiac fibrosis by revealing miR-29 as a regulator of cardiac fibrosis. Connective tissue growth factor (CTGF), a potent inducer of cardiac fibrosis, is reported to be regulated by two major cardiac microRNAs, miR-133 and miR-30. Other studies found that miR-24 attenuates cardiac fibrosis and improves heart function after myocardial infarction. Some evidence

showed that miR-21 contributes to cardiac fibrosis by regulating Spry1 and PTEN. Silencing of miR-21 in a mouse pressure-overload-induced disease model inhibits interstitial fibrosis. However, another group showed that miR-21 knockout and inhibition by 8-nucleotide antagomirs fails to prevent ventricular hypertrophic and fibrotic responses in mice subjected to pressure overload. In our study, we found that miR-133 and miR-590 were down-regulated in the canine model of atrial fibrosis induced by administrating nicotine for 30 days. Transfection of miR-133 or miR-590 into cultured atrial fibroblasts decreased TGF-β1 and TGF-βRII levels and collagen content. Further experiments confirmed that miR-133 and miR-590 showed their protective roles on cardiac fibrosis by targeting TGF-β1 and TGFβRII respectively. These effects were abolished by the antisense oligonucleotides against miR-133 or miR-590.

Conclusions The results uncover a novel molecular mechanism for myocardial fibrosis and provide a new strategy for the prevention and treatment of cardiac fibrosis.