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Letter to the Editor

Novel microRNAs involved in regulation of cardiac fibrosis

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We read Wang's Review [1] with great interest and would like to discuss some novel microRNAs (miRs) involved in regulation of cardiac fibrosis which not mentioned in this Review [1].

It was shown that miR-24 was down-regulated in infarcted mouse hearts, and the change in miR-24 expression was closely related to extracellular matrix remodeling [2]. Overexpression in vitro of miR-24 by synthetic miR-24 precursors could decrease the differentiation and migration of cardiac fibroblasts. Furthermore, they demonstrated that the protease furin, which is involved in TGF-β maturation, was identified as the direct miR-24 target [2]. In vivo, myocardial injection with a lentivirus expressing miR-24 can attenuate infarct size and fibrosis in the infarct border zone and slightly improve cardiac function after coronary occlusion [2]. These findings suggest that miR-24 has a critical role in cardiac fibrosis after myocardial infarction (MI) through a furin-TGF-β pathway. However, miR-24 was also found to be expressed in both endothelial cells and cardiomyocytes [3]. Fiedler et al. found that up-regulation of miR-24 was associated with endothelial cell apoptosis after MI [4]. Unfortunately, neither the lentiviral nor anti-miR approaches is specific for any cardiac cell type. Moreover, it is difficult to distinguish effects on cardiomyocytes, fibroblasts, and endothelial cells [3].

More recently, Tijsen et al. showed that miR-15 family was up-regulated in the overloaded heart in multiple species and inhibited the TGF-β pathway by targeting of TGF-β receptor 1 and several other genes within this pathway, including p38, SMAD3, SMAD7, and endoglin. Inhibition of miR-15b by subcutaneous injections of LNA-based anti-miRs in C57BL/6 mice subjected to transverse aorta constriction aggravated fibrosis and hypertrophy. This study identified that miR-15 family as a novel regulator of cardiac hypertrophy and fibrosis acting by inhibition of the TGF-β pathway [5]. Of note, Hullinger et al. found that systemic delivery of anti-miRs of miR-15 family in an ischemia–reperfusion model can protect cardiomyocytes against apoptosis and decreased the infarct size [6]. Porrello et al. showed that treatment with anti-miRs to inhibit miR-15 resulted in increased regeneration of myocardium in infarct area due to proliferation of cardiomyocytes [7]. These studies indicated that miRNA-15 family also affects pathological processes with beneficial effects in the heart.

Several other novel miRs may also be involved in regulation of cardiac fibrosis. It had been reported that miR-206 is upregulated upon high mobility group box 1 protein treatment in a murine MI model and associated with decreased cardiac fibrosis [8]. More recently, Nagalingam et al. showed that miR-378 is a negative regulator of TGF-β and cardiac fibrosis [9]. In a mouse model of transverse aortic constriction, inhibition of miR-652 is associated with improved cardiac function and reduced cardiac fibrosis [10]. However, effects of these miRs on endothelial cells and cardiomyocytes are still unknown.

Taken together, more and more evidences showed that microRNAs maybe a new targets in cardiac fibrosis. However, as seen in miR-24 and miR-15, possibilities of off-target effects or opposing effects of miRNAs in different tissues/cells may exits, which could affect beneficial and pathological processes. The development of new cardiovascular therapy delivery systems with orientating to target specific cell populations are needed to optimize miRNA therapy strategies in cardiac repair.

Conflict of interest

None.

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