



MiR-29 family: another “cogwheel” in myocardial remodeling

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MicroRNA (miRNA) and cardiac remodeling

In recent years small non-coding RNAs such as miRNAs have been identified as important molecular players in the process of pathological cardiac remodeling (1). Cardiac remodeling is one of the major alterations in the heart structure that causes a hemodynamic imbalance leading to change in the dimension, mass, shape and function of the heart. The rearrangement leads to pathological remodeling resulting in cardiac hypertrophy, cardiac fibrosis and eventually cardiac failure. Interestingly, dysregulation of miRNA(s) expression *in vivo* suggest an involvement of those miRNAs in cardiac remodeling. Determining the function of these miRNAs may provide a valuable therapeutic approach in cardiac remodeling. A growing number of miRNAs has been implicated in many cardiac diseases and primarily rely upon both functional and observational data. In the past decade, we have observed several miRNAs that contribute significant role in cardiac remodeling (hypertrophy) (2-4). Among them, the well-studied miRNAs include miR-21, miR-23, miR-133, miR-378 and miR-208 and, contribute to the development cardiac hypertrophy. However, miR-21 and miR-133 are implicated in both hypertrophy and fibrosis. In this study, miR-29, previously known as a preferentially abundant miRNA in cardiac fibroblasts (5) and belong to a “fibro” miR family; now take a seat in cardiac remodeling (hypertrophy) board.

MiR-29 family: a “new” take home message (so far)

The miR-29 family was first reported by Olson research team in 2008, as pro-fibrotic miRNA which was shown to be significantly reduced in various organ fibrosis models including lungs, kidney, liver and heart (5). The gene encoding the precursors of miR-29b-1 and miR-29a are located on chromosome 7q32.3 in human, while the gene encoding miR-29b-2 and miR-29c are on chromosome 1q32.2 (6). The sequences encoding each cluster are separated by <1 kb and are transcribed together (6). The molecular mechanism underlying transcriptional and post-transcriptional regulation of miR-29 family members remains to be further investigated as several factors including a wide variety of *cis* elements may contribute to the observed differential regulation (7). The miR-29 family was first demonstrated as a family of downregulated miRNAs under stress condition like myocardial infarction along with other disease models and also in explanted human hearts (8). As a result of downregulation of miR-29 family members, the target genes (such as collagens, CTGF, *etc.*) have been shown to be elevated. Intriguingly, inhibition of miR-29 (mostly miR-29b) promotes cardiac fibrosis illustrates a sense of belief in the setting of miRNA/mRNA stoichiometric balance (5,9). Interestingly, when a cardioprotective drug, Tanshinone IIA, which also has an anti-fibrotic effect, was used; miR-29b was found back to

normal levels (9).

In this article, Sassi *et al.* demonstrated for the first time evidence of miR-29's role in cardiac remodeling thereby elucidating a critical but "contentious" finding. Using state-of-the-art technology, authors have used organ-specific knock-out of miR-29b (miR-29ab1^{-/-}) and cardiotropic expression of exogenous miR-29, AAV9-miR-29a mice along with chemically synthesized anti-miR-29 to deplete miR-29b expression *in vivo*. Using TAC model as a comparative bet, authors have shown separately the protective effect of miR-29 both ablation and inhibition *in vivo* models. Targeted deletion and inhibition of miR-29b prevents cardiac hypertrophy and fibrosis. Furthermore, overexpression of miR-29a promotes cardiac hypertrophy (supplemental data). Finally, to determine the mechanism, authors took a proteomic approach to identify the target(s) and came into a conclusion of both canonical and non-canonical pathway molecules of Wnt signaling are involved. The design of the study is elegant, data are impressive and convincing.

For the first time, miR-29 family (a-c) is upregulated in TAC model; age-dependent increase of miR-29 (a-c) expression, myocyte-specific deletion or chemical inhibition of miR-29 prevents cardiac remodeling and targeted overexpression of miR-29 promotes hypertrophy by modulation of canonical and non-canonical Wnt signaling pathway.

It is of note that the TAC and myocardial prevention data contradicted with their previous publication by Abonnenc *et al.* (10). All members of miR-29 were significantly reduced in TAC model and inhibition of miR-29b showed excessive perivascular fibrosis whereas in this report, we observed the opposite effect. The same group previously reported using a synthetic screening library of miRNAs and revealed a panel of pro- or anti-hypertrophic miRNAs. However, the role of miR-29 families was not investigated at that time (11). Due to lack of plausible explanation, I leave the clarification for further investigation in the future. The study primarily employed *in vivo* inhibition by three different approaches to establish the fact that suppression of miR-29b is cardio-protective. While overexpression data using AAV9-miR-29a is supportive, but, cardiac-specific overexpression of pre-miR-29a/b would provide more detailed insight in the future. Importantly, the clinical data in the article seems to be unmatched as miR-29 family members are reportedly downregulated in human disease conditions (aortic valve stenosis) raised a critical translational outcome. While aortic stenosis samples may consider a relevant

clinical model to compare for cardiac remodeling, it would be worth taking other human samples like dilated cardiomyopathy and fibrotic hearts to attest their findings. These diseases also occur due to cardiac remodeling. Aortic stenosis restricts the blood flow from ventricle to the artery/aorta and may also affect the pressure in the left atrium. It is unclear whether patients are suffering from hypertrophy or not, making it harder to reconcile the animal data with human data.

For target prediction, authors have used an innovative approach, however, which was previously used by the group (8). The only difference stems from transfection of the miR-29 in cardiomyocytes. The readout provided a new array of targets primarily denoting the Wnt signaling pathways. This is a novel observation where Wnt were targeted by miR-29 in myocytes. However, it is unclear which particular candidate is appropriately modulated by miR-29. Furthermore, a speculation exists whether any paracrine function operates that may influence cardiac fibrosis. Interestingly, it is observed that miR-29 transfection both in myocyte and fibroblast elicit two different signaling patterns providing a new insight of dynamicity of miR-29 in cardiac cells (8). This is particularly intriguing as two different cell types respond and promote two different signaling cascades. We need to stay in tune for the next article for underlying reasons.

Accomplish two goals with one effort!

The original concept of anti-fibrotic effect of miR-29 fits the observation that miR-29 expression is reduced by TGF- β 1, a key pro-fibrotic factor. This, however, does not rule out the involvement of other pathological pathways. The current article is the perfect example and in fact, members of the miR-29 family exhibit diverse characteristics suggesting complex functions of miR-29. This could largely be due to isoform and tissue-specific nature. Overall, the study may provide a new platform for novel therapeutic opportunities to understand and define precise contribution of miR-29 in cardiac remodeling process: hypertrophy and fibrosis. It seems like "we achieve two goals in one effort". However, we are still in a process to unwind the therapeutic benefit of using this critical molecule. It is a strange twist at this juncture to evaluate the fate of an evolutionary conserved sequence molecule for the treatment of cardiac disease. Nonetheless, there is strong preclinical evidence in this study that miR-based therapy may be an effective strategy, but firmly challenging our concept. Several

important questions relevance to miR-29 family should be addressed in future studies. It will be critical to further investigate the mechanisms underlying the differential regulation and subcellular localization of miR-29 family members, as well as physiological and disease implications of such differential regulation. Finally, potential diagnostic and therapeutic values of miR-29 remain to be established.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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