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Deficiency of miR-1954 promotes cardiac remodeling

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Cardiac remodeling due to hemodynamic overload is associated with significant morbidity and mortality. In response to stress, cardiomyocyte (CM) become hypertrophied whereas cardiac fibroblasts convert into myofibroblasts. The phenomenon leads to the development of cardiac hypertrophy, fibrosis and impair cardiac function. Previously, we have shown the pivotal role of miRNA (a new class of post-transcriptional regulators) in cardiac remodeling, but, loss of miRNA contributing to the onset of cardiac remodeling remains elusive. Using next generation miRNA sequencing, we discovered a panel of novel dysregulated miRNAs from read-data, secondary structure and miRPara classification score analysis in wild-type mice (WT) infused with Angiotensin II (Ang II). Among them, one was identified as miR-1954, a novel miRNA which was significantly reduced in Ang II-infusion and transverse aortic constriction (TAC). Following an unbiased approach, we confirmed that Sp1-Gata4-Col I-Tsp1-axis is the bona-fide targets. Our hypothesis is that deficiency of miR-1954 exacerbates cardiac remodeling leading to hypertrophy and fibrosis through paracrine mechanism; and overexpression of miR-1954 mitigates the cardiac damage and abrogates remodeling by modulating Sp1-Gata4-Col I-Tsp1-axis. Our data demonstrated that depletion of miR-1954 in CM triggers hypertrophic response by modulating Sp1 and Gata4; releases soluble factors (Tgfb1) that triggers cardiac fibroblasts proliferation; upregulation of thrombospondin 1 (Tsp1) and collagen I (Col I). Overexpression of miR-1954 in CM reverses these processes implicated a cellular cross-talk. Cardiac-specific overexpression of pre-miR-1954 transgenic mice (miR-1954 Tg) showed reduced cardiac mass and improved function compared to WT littermate after Ang II treatment. Inhibition of miR-1954 by locked nucleic acid of anti-miR-1954 exacerbates cardiac hypertrophy and fibrosis. Our findings provide evidence that loss of miR-1954 promotes cardiac remodeling by targeting Sp1-Gata4-Col I-Tsp1-axis and, overexpression of miR-1954 reverses the process. We conclude that miR-1954 could be a triggering factor in cardiac remodeling and providing new mechanistic information for therapeutic benefit.