Natural compound library screening identifies new molecules for the treatment of cardiac fibrosis and diastolic dysfunction

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Abstract

Myocardial fibrosis is the hallmark of cardiac remodeling found in hypertensive heart disease, contributing to abnormalities of myocardial relaxation properties and further development of diastolic dysfunction. Therefore, novel experimental approaches targeting fibrosis, especially with cardiac fibroblasts are promising potential therapies for heart disease including hypertension. Here, we aimed at the development of novel anti-fibrotic therapeutics based on natural-derived substance library screens for the treatment of cardiac fibrosis.

Anti-fibrotic drug candidates were identified by functional screening of 480 chemically diverse natural compounds in primary human cardiac fibroblasts (HCFs). Further in vitro fibrosis assay identified 2 lead compounds, steroid bufalin (from Chinese toad venom) and the alkaloid lycorine (from Amaryllidaceae species) to be most effective anti-fibrotic molecules. To validate therapeutic approaches of the compounds in hypertensive in vivo model, bufalin and lycorine were administered upon systemic delivery to angiotensin II (Ang II)-mediated mouse model as well as Dahl salt sensitive rat model. Administration of bufalin and lycorine strongly prevent cardiac fibrosis as well as preserve cardiac function, evidenced by increased myocardial performance index (MPI), decreased end diastolic pressure volume relationship (EDPVR) in two rodent models of hypertension. While both compounds show no effect on the morphology of kidney and liver, providing first promising data of toxicological assessment.

We further performed transcriptomic analysis of HCFs to elucidate of a potential effector of anti-fibrotic natural compounds. Interestingly, we identified interaction between miR-671-5p and it's target SEPP1 is mechanistically involved in anti-fibrotic effect of the lead natural compounds. MiR-671-5p plays key role in both fibrosis and inflammatory pathways by suppressing SEPP1 expression in HCFs. However, treatment with bufalin and lycorine restored SEPP1 expression by repression of miR-671-5p, leading to reduced fibrosis, evidenced by decline of α-SMA expression. These results suggest that SEPP1 might be the anti-fibrotic target of miR-671-5p that explains the mechanistic involvement of this miRNA in the anti-fibrotic efficacy of the lead natural compounds.

Combined, we identified the molecules bufalin and lycorine as drug candidates for therapeutic applications in cardiac fibrosis and diastolic dysfunction. Moreover, we determined a novel underlying mechanism involving the downstream interaction of miR-671-5p with SEPP1.

Keywords: *diastolic dysfunction, cardiac fibrosis, hypertension, bufalin, lycorine, miR-671-5p, selenoprotein P1*

Biography

MiraJung, Biologist and PhD in Genetic technology, is post-doctoral researcher at IMTTS, investigating the role of non-coding RNAs (ncRNAs)in the cardiovascular disease and accordingly studying development of ncRNA based therapy for heart failure. Extensive research experience in in vivo study, molecular biology, pharmaceutical study of natural compounds.