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Increased Gao expression underlies cardiac dysfunction and lethal arrhythmias accompanied with abnormal Ca2+ handling

H. Inazumi[1], K. Kuwahara[2], Y. Kuwabara[3], Y. Nakagawa[1], H. Kinoshita[1], K. Moriuchi[1], H. Yanagisawa[1], T. Nishikimi[1], M. Oya[2], M. Yamada[2], T. Kashihara[2], N. Kurebayashi[4], M. Sugihara[4], K. Nakao[1], T. Kimura[1]

[1]Kyoto University Graduate School of Medicine, Kyoto, Japan; [2]Shinsyu University School of Medicine, matsumoto, Japan; [3]Kyoto University Hospital, Kyoto, Japan; [4]Juntendo University Graduate School of Medicine, tokyo, Japan

Background: We previously demonstrated that a transcriptional repressor, neuron restrictive silencer factor (NRSF), maintains normal cardiac function and electrical stability. Transgenic mice expressing a dominant-negative mutant of NRSF in their hearts (dnNRSF-Tg) exhibit systolic dysfunction with cardiac dilation and premature death due to lethal arrhythmias like human dilated cardiomyopathy (DCM). Underlining mechanisms remain to be elucidated, however.

Purpose: We studied underling mechanisms by which NRSF maintains normal cardiac function to identify novel therapeutic targets for heart failure.

Methods and results: We generated cardiac-specific NRSF knockout mice (NRSFcKO) and confirmed that cardiac phenotypes of NRSFcKO are similar to those of dnNRSF-Tg.

cDNA microarray analysis revealed that cardiac gene expression of GNAO1 that encodes Gαo, a member of inhibitory G protein Gαi family, is increased in both dnNRSF-Tg and NRSFcKO ventricles.

We confirmed that GNAO1 is a direct target of NRSF through ChIP-seq analysis, reporter assay and electrophoretic mobility shift assay.

In dnNRSF-Tg, pharmacological inhibition of Gαo with pertussis toxin improved systolic dysfunction and knockdown of Gαo by crossing with GNAO1 knockout mice improved not only systolic function but also frequency of ventricular arrhythmias and survival rates.

Electrophysiological and biochemical analysis in ventricular myocytes obtained from dnNRSF-Tg demonstrated that genetic reduction of Gαo ameliorated abnormalities in Ca2+ handling, which include increased current density in surface sarcolemmal L-type Ca2+ channel, reduced content of sarcoplasmic reticulum Ca2+ and lowered peak of Ca2+ transient. Furthermore, genetic reduction of Gαo attenuated increased phosphorylation levels of CAMKII in dnNRSF-Tg ventricles, which presumably underlies the improvement in Ca2+ handling. In addition, we identified increased Gαo expression in ventricles of heart failure model mice induced by transverse aortic constriction and cardiac troponin T mutant DCM model mice, in both of which, genetic reduction of Gαo ameliorated cardiac dysfunction.

Conclusions: We found that increased expression of Gαo, induced by attenuation of NRSF-mediated repression, plays a crucial role in the progression of cardiac dysfunction and lethal arrhythmias by evoking Ca2+ handling abnormality. These data demonstrate that Gαo is a potential therapeutic target for heart failure.

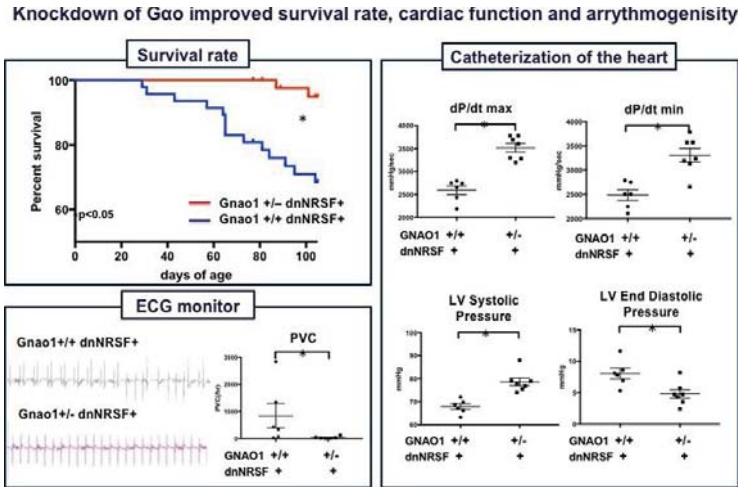

Figure 1