NRSF-GNAO1-CaMK2 axis exacerbates cardiac remodeling and progresses heart failure by impairing Ca2+ homeostasis

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Background: In the development of heart failure, pathological intracellular signaling reactivates fetal cardiac genes, which leads to maladaptive remodeling and cardiac dysfunction. We previously reported that a transcriptional repressor, neuron restrictive silencer factor (NRSF) represses fetal cardiac genes and maintains normal cardiac function under normal conditions, while hypertrophic stimuli de-repress this NRSF mediated repression via activation of CaMKII. Molecular mechanisms by which NRSF maintains cardiac systolic function remains to be determined, however.

Purpose: To elucidate how NRSF maintains normal cardiac homeostasis and identify the novel therapeutic targets for heart failure.

Methods and results: We generated cardiac-specific NRSF knockout mice (NRSF cKO), and found that these NRSF cKO showed cardiac dysfunction and premature deaths accompanied with lethal arrhythmias, as was observed in our previously reported cardiac-specific dominant-negative mutant of NRSF transgenic mice (dnNRSF-Tg).

By cDNA microarray analysis of dnNRSF-Tg and NRSF-cKO, we identified that expression of Gnao1 gene encoding Gαo, a member of inhibitory G proteins, was commonly increased in ventricles of both types of mice.

ChIP-seq analysis, reporter assay and electrophoretic mobility shift assay identified that NRSF transcriptionally regulates Gnao1 gene expression.

Genetic Knockdown of Gαo in dnNRSF-Tg and NRSF-cKO by crossing these mice with Gnao1 knockout mice ameliorated the reduced systolic function, increased arrhythmogenicity and reduced survival rates.

Transgenic mice expressing a human GNAO1 in their hearts (GNAO1-Tg) showed progressive cardiac dysfunction with cardiac dilation. Ventricles obtained from GNAO1-Tg have increased phosphorylation level of CaMKII and increased expression level of endogenous mouse Gnao1 gene. These data suggest that increased cardiac expression of Gαo is sufficient to induce pathological Ca2+-dependent signaling and cardiac dysfunction, and that Gαo forms a positive regulatory circuit with CaMKII and NRSF.

Electrophysiological analysis in ventricular myocytes of dnNRSF-Tg revealed that impaired Ca2+ handling via alterations in localized L-type calcium channel (LTCC) activities; decreased T-tubular and increased surface sarcolemmal LTCC activities, underlies Gαo-mediated cardiac dysfunction. Furthermore, we also identified increased expression of Gαo in ventricles of two different heart failure mice models, mice with transverse aortic constriction and mice carrying a mutant cardiac troponin T, and confirmed that genetic reduction of Gαo prevented the progression of cardiac dysfunction in both types of mice.

Conclusions: Increased expression of Gαo, induced by attenuation of NRSF-mediated repression forms a pathological circuit via activation of CaMKII. This circuit exacerbates cardiac remodeling and progresses heart failure by impairing Ca2+ homeostasis. Gαo is a potential therapeutic target for heart failure.

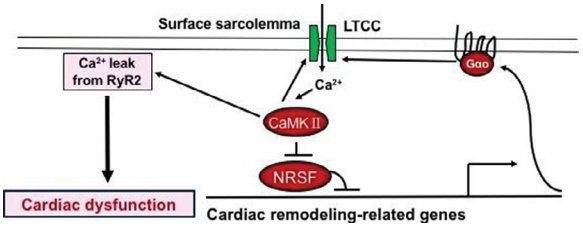

Figure 1