Research Theme
Metabolic Disorders

Research Project Title
The Role of RLC in Age-Related Heart Failure Progression

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Project Description

**AIM:** understand the molecular mechanism by which contractile dysfunction occurs during age-related heart failure progression. Specifically, we aim to characterize the role of phosphorylation of the regulatory light chain of myosin (RLC) as a modulator of heart failure progression and to test its potential as a therapeutic strategy.

**SIGNIFICANCE:** Data from the Singapore Ministry of Health (MOH) and Singapore Heart Foundation (SHF) shows that 15 people die of cardiovascular diseases every day comprising ~30% of all deaths. About 25% of hospital stays in Singapore are for cardiovascular reasons with HF being the major cardiac cause of hospitalization that increased by ~40% over the last decade, at great cost to individuals, their family and the Country. We have shown that RLC phosphorylation can improve muscle performance in vitro. But it is not known if RLC phosphorylation is an efficient strategy for therapy to improve or revert primary contractile defects during HF progression. Moreover, performing gene-targeted therapy for missense mutations that cause cardiac hypertrophy revealed that therapy at early stages of hypertrophy or younger age is crucial (60). This further suggests importance of understanding changes that occur during the progression of HF, especially at earlier stages, as we have proposed here to test from 48hrs to 16 weeks post-MI.

**APPROACH:**
Major methods include:

1. Mice expressing human beta-cardiac myosin heavy chain (Humanized mice);
2. Surgical induction of heart failure in humanized mice;
3. Testing the contractility of cardiac muscle fibers from humanized MYH7 mice and MyBPC3 knock-out mice;
4. Testing the effect of kinase intervention on cardiac trabeculae and the effect of exchanging optimally phosphorylated RLC into the trabeculae;
5. Quantification of RLC phosphorylation during heart failure progression;

This proposal connects molecules to physiology of heart failure progression towards mechanistic understanding and to discover improved strategies of therapeutic interventions. To our knowledge, this is the first opportunity to combine these approaches to explore progressive HF at molecular and physiological levels.

**Contact Us**

If you have questions regarding this project, please email the Principal Investigator.

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