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Screening for Excitation-Contraction related proteins in heart failure

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Background and aims: Hypertrophic cardiomyopathy, one of the major human health problems, is associated with severe consequences of heart failure and malignant arrhythmia. The remarkable architecture of the t-tubule/sarcoplasmic reticulum association of the cardiac excitation-contraction (E-C) apparatus experiences an extensive pathological remodeling during hypertrophy, thus leading to cardiac dysfunction and sudden death. We and others have previously reported that cardiac striatin (STRN) is a partner of the E-C coupling proteins yet its role in hypertrophy/heart failure remains undefined. The aim of this study was to investigate the effects of STRN on cardiomyocyte hypertrophy and cardiomyocyte contraction.

Methods: Experiments were performed on cultured neonatal rat cardiomyocytes with altered expression of STRN (knockdown & overexpression) by adenoviral transduction, followed by protein-protein interaction, contraction measurement, and pharmacological induction of hypertrophy (isoproterenol: ISO, 10 µM).

Results: The results showed that STRN and caveolin-3 competitively interact with calmodulin in a calcium depending fashion (both caveolin-3 and calmodulin are being associated with heart failure). Silencing the STRN gene in neonatal rat cardiomyocytes showed significant increase in cardiomyocyte surface area. In contrast, overexpression of STRN in cardiomyocytes reduced the hypertrophic effect of ISO on these cells. In parallel, while the overexpression of STRN was associated with increased contraction rate of cardiomyocytes, the knockdown of STRN resulted in lower contraction rate. Interestingly, ISO treatment failed to restore the contraction rate of cardiomyocytes with lower levels of STRN, thus phenotypically mimicking cardiac failure in humans. On the other hand, the overexpression of STRN promoted the ISO-induced chronotropic effect. Similar data were recorded using the direct activator of adenylyl cyclase, forskolin.

Conclusions: Collectively, we provide new evidence showing that STRN is a novel regulator of cardiomyocyte contraction rate, and that it regulates their size and response to adrenergic stimuli. These data further support the notion that STRN may be a potential therapeutic target for hypertrophic cardiomyopathy and cardiac failure. Further screening for new proteins involved in E-C coupling and human heart failure is imperative to understand the etiology of this disease.

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