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Systems Modeling of Cardiomyocyte Mechanobiology

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Abstract: In this article, we summarize our systems model of cardiomyocyte mechano-signaling published in *PLoS Computational Biology* and discuss new approaches to extending these models to predict cardiac myocyte gene expression in response to stretch.

Keywords: Network regulators, mechanotransduction, cardiac muscle.

1 Introduction

Cardiac muscle cells can sense and respond to mechanical cues, and this ability is a fundamental feature of cardiac hypertrophy and remodeling in response to altered hemodynamic loads [Omens, McCulloch and Lorenzen-Schmidt (2007)]. Many mechano-sensitive proteins and signaling molecules have been identified in cardiac myocytes [Zou, Akazawa, Qin et al. (2004)]. However, it remains poorly understood how the downstream signaling pathways integrated into hypertrophy and remodeling responses [Zablocki and Sadoshima (2013)]. Computational systems models can quantify cell signaling and elucidate mechanisms, but they had not previously been developed for cardiac myocyte mechanosignaling. In our published paper, we reconstructed and tested the first computational model of the cardiac mechanosignaling network and used it to identify regulators if the stretch-induced hypertrophic response [Tan, Buchholz, Omens et al. (2017)].

2 Methods

We formulated the model as a system of ordinary differential equations in which every state variable followed a sigmoidal Hill-type activation curve. The network was reconstructed from information in 172 published papers and contained 94 nodes connected by 125 reactions. Experimental data from isolated cardiac myocytes in a separate group of 54 papers, not used to formulate the model, was used to validate model predictions.

The model correctly predicted 78% of these independent observations including 9/9 input-output predictions, 43/43 input-intermediate predictions, and 82/120 results of inhibition experiments. A sensitivity analysis showed that calcium, actin, Ras, Raf1,

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PI3K, and JAK were the dominant regulators in the network and the main mediators of expression stimulated by angiotensin receptors, integrins, and calcium channels.

3 Results

Using the model to analyze the effects of pairwise inhibition, the model identified combinations of targets with additive or synergistic effects on mechanosignaling, including valsartan/sacubitril, a combination angiotensin receptor-neprilysin inhibitor recently approved for treating heart failure marketed as Entresto. This prediction was subsequently confirmed in a later publication [Lu, Tong, Chen et al. (2018)]

4 Discussion

In as yet unpublished work, we have extended this model to include the expression of 645 target genes of the 11 transcription factors in the model. Of those genes, 16 were nodes in the mechano-signaling network itself, and therefore fed back into the network *via* translation reactions. The model has been validated using RNA-seq measurements in micropatterned mouse neonatal ventricular myocytes subjected to 14:3% primarily transverse or longitudinal non-equibiaxial stretch for 30 minutes to 4 hours resulting in the significant up- or downregulation of 843 genes (Benjamini-Hochberg False Discovery Rate<0.05). In preliminary results, the model accurately predicted 51% of differentially expressed genes that were also in the model with an up-down prediction accuracy of 74%.

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