Orchestrated regulation of energy supply and energy expenditure: Transcriptional coexpression of metabolism, ion homeostasis, and sarcomeric genes in mammalian myocardium

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BACKGROUND During the development of heart failure, the myocardium undergoes profound electrical remodeling, characterized by prolongation of action potential duration, changes in Ca^{2+} homeostasis, and slowing of conduction.

OBJECTIVE We tested the hypothesis that the electrical remodeling, indexed by the expression of ion channel and transporter genes, occurs in the context of a coordinated regulation of metabolism and signaling processes observed in heart failure.

METHODS A meta-analysis of myocardial murine and human microarray data sets was performed.

RESULTS We identified transcripts that were coordinately expressed with 132 myocardial ion channel and transporter genes in 18 murine and human myocardial microarray data sets. The genes coexpressed with ion channels were subsequently grouped into Gene Ontology (GO) categories, revealing 4 major, mutually exclusive GO clusters: 55 ion channel and transporter genes were coexpressed with major bioenergetic pathways (oxidative phosphorylation, citric acid cycle, glycolysis, and fatty acid metabolism) and contractile processes (muscle contraction, sarcomere, and Z disc), while 36, 16, and 25 ion channel transcripts were associated with the GO clusters of signal transduction, transcription/translation, and a nonspecified cluster, respectively. Myocardial expression of ion channel genes coexpressed with metabolic processes was >10-fold higher than that of ion channels associated with the other 3 clusters. In addition to transcriptional coexpression, major myocardial ion channels were found to physically interact with metabolic pathways based on protein-protein interaction data.

CONCLUSION Electromechanical and metabolic remodeling processes are intricately linked at the transcriptional level, suggesting an orchestrated regulation of energy supply (metabolism) and energy expenditure (muscle contraction and ion homeostasis) in mammalian myocardium.

KEYWORDS Ion channels; Gene expression; Metabolism; Heart failure; Arrhythmia

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Introduction

Heart failure (HF) remains a leading cause of morbidity and mortality in the developed and developing world, affecting >5 million people in the United States alone.[1] Patients with HF are at risk of dying primarily of progressive pump failure or sudden cardiac death (SCD). Pharmacological therapies for SCD targeting ion channels have been uniformly disappointing, showing either no benefit in survival or even an increase in the incidence of ventricular tachyarrhythmias and SCD.[2] Thus, a better understanding of the underlying pathophysiological processes leading to electrophysiological remodeling in the failing myocardium is required to develop new targeted pharmacological interventions.

During the development of HF, the myocardium undergoes profound electrical remodeling, characterized by prolongation of the action potential duration (APD), changes in Ca^{2+} homeostasis, and slowing of conduction. Previously, we noted that the prolongation of the APD occurred early during the development of HF and coincided with profound transcriptional changes characterized by the downregulation of metabolic and upregulation of signaling transcripts.[3] For instance, about half of the transcripts (18 of 37) associated with the downregulation of the sarcoplasmic Ca^{2+}-ATPase *Serca2* (encoded by *Atp2a2*), a hallmark of HF, were directly linked to oxidative phosphorylation (OXPHOS), glycolysis, fatty acid β-oxidation, and the tricarboxylic acid cycle in a canine model of nonischemic cardiomyopathy.[3] To extend these observations beyond the selected individual ion channels, we examined coexpression patterns of >130 myocardial ion channels, transporters, and pumps across a

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whole range of physiological and pathophysiological conditions in order to test the hypothesis that altered expression of these ion channel transcripts occurs in the context of coordinated changes in metabolism and signaling processes. As a result, we demonstrate that myocardial transcription is characterized by an orchestrated regulation of energy supply (metabolism) and energy expenditure (contraction and ion homeostasis), suggesting that electromechanical and metabolic remodeling processes are intricately linked.

Methods

First, we identified ion channel genes that were reliably expressed in nonfailing and failing murine myocardium using a publicly available microarray data set (Gene Expression Omnibus accession number GSE8000). On the basis of their Gene Ontology (GO) annotations as "ion channels," we selected sodium (*Scn_*), calcium (*Cacn_*), chloride (*Clcn_*, *Clca_*, and *Clic_*), and potassium (*Kcn_*) ion channel transcripts that showed expression levels above background (arbitrarily set at >50 fluorescence units). In addition, we selected transcripts encoding for the Na^+/K^+-ATPase (Atp1_), sarcoplasmic reticulum Ca^{2+}-homeostasis (*Atp2a2*, *Pln*, *Casq2*, *Ryr2*, *Srl*, and *Slc8a1*), as well as connexins (*Gja_*, *Gjb_*, and *Gjc_*), yielding a total of 132 transcripts (Online Supplemental Table 1).

Second, we used the freely available Web-based tool StarNet[4] to compute the correlation coefficients of transcripts coexpressed with the aforementioned ion channels as well as 20 representative OXPHOS transcripts. We used StarNet to perform a meta-analysis computation of correlation coefficients for all genes with the ~39,000 transcripts on the Affymetrix U430 2.0 murine microarray across 2145 publicly available microarray samples from a wide range of mouse tissues (full cohort). As a result, correlation coefficients of >130 million gene pairs were computed. A similar calculation of Pearson correlation coefficients with genes on the U430 2.0 murine microarray was performed with a subset of 239 myocardial microarrays derived from 18 cardiac data sets (cardiac cohort; Online Supplemental Table 2).[4] In a first step, the 10 closest neighbors, that is, genes showing the highest positive correlation of their expression values to the gene of interest, were identified (closest neighbor 1 [CN1]). Then, the 10 closest neighbors for the CN1 genes were identified (=CN2). After repeating this procedure a total of 4 times, complex networks of up to 1000 genes coexpressed with the gene of interest were generated (CN1–CN4). These coexpressed transcripts were subsequently grouped into GO classes, exported into Microsoft Excel and visualized using the Genesis software package.[5] The GO is a major bioinformatics initiative to unify the representation of genes across all species. It provides an ontology of defined terms representing gene product properties, covering 3 domains: cellular component, molecular function, and biological process.[6]

Overrepresentation of specific transcription factor binding sites in a given gene set was statistically analyzed by a hypergeometric test incorporated into WebGestalt (WEB-based GEne SeT AnaLysis Toolkit).[7] The results obtained with murine data were compared with those of human myocardial specimens using the largest publicly available human HF microarray data set, encompassing 210 failing and nonfailing myocardial samples (Gene Expression Omnibus accession number GSE5406). In addition, protein-protein interaction networks were generated using the GeneMANIA database[8] in order to identify set of genes that are most likely to share function with a gene of interest based on their interactions. Of note, physical interaction data in GeneMANIA is obtained through many diverse methodologies including affinity-capture mass spectrometric methods, protein overlay, coimmunoprecipitation, and 2 hybrid systems. A flowchart of the experimental design is shown in Figure 1.

Results

Using the publicly available Web-tool StarNet,[4] we identified transcripts coexpressed with 132 ion channel transcripts across 2145 microarrays from a wide variety of murine tissues and a myocardium-specific subcohort of 239 murine microarrays. Figure 2 demonstrates significant differences between the full and cardiac cohorts and highlights the special relationship between mitochondria and ion channels in the myocardium: transcripts coexpressed with ion channels in the myocardium were twice as likely to be associated with mitochondria, electron transport, and fatty acid metabolism compared to the full cohort. Specifically, 35% of ion channels were coexpressed with mitochondrial transcripts in

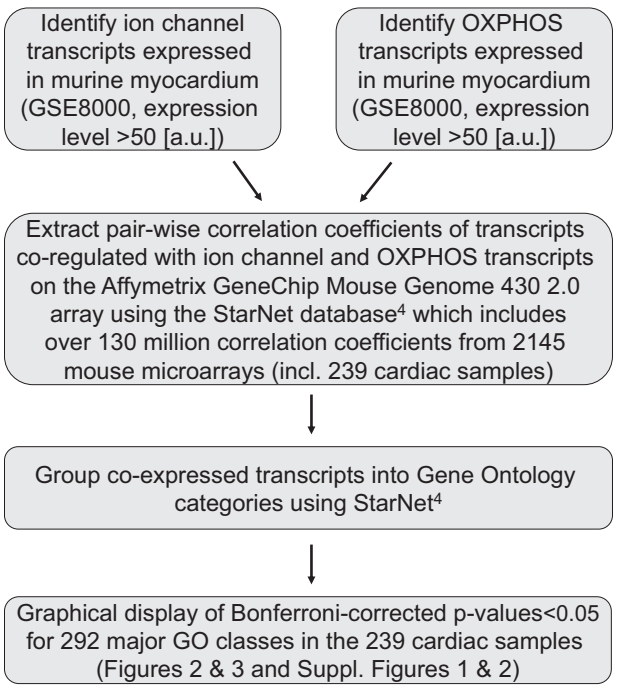

Figure 1 Flowchart of the experimental design. GO = Gene Ontology; OXPHOS = oxidative phosphorylation.

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