The article by Barth et al in this issue points to a critical facet in heart failure investigation, namely, the molecular divergence observed between preclinical models of disease and clinical authenticity. These authors compared gene expression patterns from hearts of human, dogs, and rodents. Women and men appear to differ from mice in respect to the transcriptome dynamics of the failing heart. Not surprised? The implications of this finding may be potentially game changing for the future design of translational strategies to advance discovery science into patient care.

Heart failure is a significant health problem, affecting nearly 1 in 5 adults, with a cost of >$40 billion per year. Barth et al present data from a meta-analysis of several studies to suggest that the gene expression patterns in preclinical animal models of heart failure are significantly different than those in human heart failure. Specifically, Barth et al show that the significant downregulation of metabolic signaling pathways and reciprocal upregulation of cell signaling in rodent and dog models are not found in all human heart failure specimens. If dissimilar patterns in gene expression reflect different pathophysiological characteristics, the current course of testing new therapies for human heart failure in rodent and dog models may be questioned.

Modeling heart failure in rodents and dogs is typically performed on an accelerated time course compared with natural disease progression in humans. The gene expression changes seen in pre-clinical models of heart failure in this study may more closely simulate acute heart failure syndrome versus chronic heart failure. Chronic human heart failure may present with changes referred to as remodeling and include dilatation of the ventricular chamber, reduction in contractile function, and increase in cardiac filling pressures and wall stress. These clinical phenotypic changes of heart failure are paralleled by significant histological, cellular, and molecular changes in most structural and functional components of the myocyte, including alterations in myocyte geometry and size, progressive interstitial fibrosis, upregulation of cytokines and inflammation, changes in myosin isoforms, and compromised myocardial energetics, β-adrenoceptor density, and calcium handling proteins. The study by Barth et al has prompted the questions, “Why is metabolic signaling different in humans versus preclinical models of disease?” and, “How might this influence the current model of testing new drugs/devices in preclinical models?”

Approximately 5 million patients in the United States alone have heart failure, and >500,000 new patients are diagnosed as having heart failure each year. Worldwide, the prevalence of heart failure has increased to pandemic proportions, and cardiovascular disease is recognized as the leading cause of global mortality. Alarming, individuals with the most advanced stage of disease do not respond to standard medical therapy. This raises the following fundamental question: “What strategies are needed to advance heart failure research and to ensure improved cardiovascular health by 2020?” Indeed, “What innovations are warranted to optimize the process of drug discovery and development and attain the most rigorous testing of human tissue for validated preclinical studies reflecting the intimate substrate of human disease?” Put simply, science has changed in the past 10 years. How do we best implement what we have learned into improving the process of drug discovery?

High-throughput systems biology technologies have recently advanced the comprehension of corrupted intracellular circuitry in heart disease. Although multiple causes contribute to heart failure pathogenesis, available evidence suggests that the failing heart is an engine out of fuel, whereby altered bioenergetics contribute to the mechanisms of organ failure. A failing heart returning to a fetal gene program has been considered to be a common feature of the hemodynamically and metabolically stressed heart. Returning to a fetal gene program includes fetal gene metabolism (ie, increased use of carbohydrate metabolism). This is thought to be due to the increased efficiency of carbohydrate substrate per mole of oxygen consumed in addition to the quicker mobilization of carbohydrate energy stores under conditions of stress. A dependence on cytosolic nicotinamide adenine dinucleotide–producing glycolytic transport systems (including α-glycerophosphate, malate-aspartate, and malate-citrate shuttles) is also a hallmark of fetal gene programs, all of which help to maintain a high glycolytic flux. This study begins to challenge and may eventually narrow or help to redefine this concept in human heart failure. A glycolytic gene up-regulated in the protein-protein interaction network

**Heart Failure Transcriptome**

**When Discoveries Change Practice?**

Jennifer L. Hall, PhD; Andre Terzic, MD, PhD

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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was the rate-determining enzyme phosphofructokinase. Oxidative phosphorylation genes that were down-regulated and identified in network hubs included an NADH ubiquinone oxidoreductase (the first enzymes in the electron transport chain of mitochondria) and isocitrate dehydrogenase 3b (IDH) (which encodes the tricarboxylic acid cycle enzyme isocitrate dehydrogenase).1 Interestingly, signal transducer and activator of transcription 3 was an important hub linking signaling to metabolism. How this interaction mechanistically occurs is not altogether clear. Barth et al1 cite several important examples of genetic models that shed light on this interaction. A limitation of the overarching concept that a failing heart returns to a fetal gene program was always due to the restricted amount of human data supporting this notion. The lack of human data is largely a limitation of the ability to procure normal “nonfailing” human heart samples and sufficient samples with additional clinical information to separate heart failure conditions and stratify the disease. Barth et al address an important issue in the field of human heart analyses by assessing the effects of cardioplegic solution on gene expression as a possible contributor, confounding data interpretation.1 It will be interesting for future studies to directly assess the effects of glucose metabolic flux and/or glycolytic enzyme activity in response to cardioplegic solution and potential differences in metabolic flux and enzyme activity in acute versus chronic human heart failure.

A possible limitation of the present meta-analysis is the inability to examine cell types provided with each of the samples in the 48 combined studies.1 It is possible that downregulation of metabolic pathways and upregulation of cell signaling pathways may be dependent in part on respective cytotypes and their individual metabolic flux properties. Of the 10 genes most highly up-regulated with heart failure, many are associated with fibrosis, including several collagens, connective tissue growth factor, and fibronectin.1 One of the many strengths of this study is the decreased expression of genes involved in oxidative metabolic signaling pathways correlating with biomarkers of disease severity, including higher pro–brain natriuretic peptide levels and a higher pulmonary capillary wedge pressure.1 Interestingly, patients receiving an intraaortic balloon pump and individuals requiring cardiac transplantation within 1 month of onset of clinical symptoms had lower myocardial expression of oxidative phosphorylation genes compared with hemodynamically stable patients.1 Conversely, the use of dative phosphorylation genes compared with hemodynamic clinical symptoms had lower myocardial expression of oxidative cytotypes and their individual metabolic flux properties.

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