**K\textsubscript{ATP} channel-dependent metaboproteome decoded: systems approaches to heart failure prediction, diagnosis, and therapy**

D. Kent Arrell\textsuperscript{1,2,3,4}, Jelena Zlatkovic Lindor\textsuperscript{1,2,3,4}, Satsuki Yamada\textsuperscript{1,2,3,4}, and Andre Terzic\textsuperscript{1,2,3,4*}

\textsuperscript{1}Marriott Heart Disease Research Program, Mayo Clinic, Stabile 5, 200 First Street SW, Rochester, MN, USA; \textsuperscript{2}Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Stabile 5, 200 First Street SW, Rochester, MN, USA; \textsuperscript{3}Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Stabile 5, 200 First Street SW, Rochester, MN, USA; and \textsuperscript{4}Department of Medical Genetics, Mayo Clinic, Stabile 5, 200 First Street SW, Rochester, MN, USA

Received 11 November 2010; revised 16 January 2011; accepted 8 February 2011; online publish-ahead-of-print 14 February 2011

**Abstract**

Systems biology provides an integrative platform by which to account for the biological complexity related to cardiac health and disease. In this way, consequences of ATP-sensitive K\textsuperscript{+} (K\textsubscript{ATP}) channel deficiency for heart failure prediction, diagnosis, and therapy were resolved recently at a proteomic level. Under stress-free conditions, knockout of the Kir6.2 K\textsubscript{ATP} channel pore induced metabolic proteome remodelling, revealing overrepresentation of markers of cardiovascular disease. Imposed stress precipitated structural and functional defects in Kir6.2-knockout hearts, decreasing survival and validating prediction of disease susceptibility. In the setting of hypertension, a leading risk for heart failure development, proteomic analysis diagnosed the metabolism-centric impact of K\textsubscript{ATP} channel deficiency in disease. Bioinformatic interrogation of K\textsubscript{ATP} channel-dependent proteome prioritized heart-specific adverse effects, exposing cardiomyopathic traits of aggravated contractility, fibrosis, and ventricular hypertrophy. In dilated cardiomyopathy induced by Kir6.2-knockout pressure overload, proteomic remodelling was exacerbated, underlying a multifaceted molecular pathology that indicates the necessity for a broad-based strategy to achieve repair. Embryonic stem cell intervention in cardiomyopathic K\textsubscript{ATP} channel knockout hearts elicited a distinct proteome signature that forecast amelioration of adverse cardiac outcomes. Functional/structural measurements validated improved contractile performance, reduced ventricular size, and decreased cardiac damage in the treated cohort, while systems assessment unmasked cardiovascular development as a prioritized biological function in stem cell-reconstructed hearts. Thus, proteomic deconvolution of K\textsubscript{ATP} channel-deficient hearts provides definitive evidence for the channel’s homeostatic contribution to the cardiac metaboproteome and establishes the utility of systems-oriented approaches to predict disease susceptibility, diagnose consequences of heart failure progression, and monitor therapy outcome.

**Keywords**

ATP-sensitive K\textsuperscript{+} channel • Bioinformatics • Cardiac • K\textsubscript{ATP} channel • Kir6.2 • Genetics • Heart disease • Metabolism • Networks • Protein expression • Proteomics • Regenerative medicine • SUR2A • Stem cells • Systems biology

This article is part of the Spotlight Issue on: Metabolic Remodelling in Heart Failure

**1. Introduction**

High-throughput technologies have expanded the comprehension of cardiac pathobiology by resolving corrupted signalling circuitry, effectors, and mediators in disease.\textsuperscript{1} Systems biology and network medicine have increasingly enabled the understanding of compromised pathways on a global scale, and have guided judicious development of prognostic discriminators of disease variability and selection of treatment response predictors, honing therapeutic objectives to match resolved disease profiles.\textsuperscript{2} Decoding maladaptive signatures prior to onset of overt disease permits rational forecast of individual susceptibility.\textsuperscript{3} Accordingly, anticipatory medicine promises a shift

\textsuperscript{*} Corresponding author. Tel: +1 507 284 2747, fax: +1 507 266 9936, Email: terzic.andre@mayo.edu

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2011. For permissions please email: journals.permissions@oup.com.
from a reactive paradigm in managing symptoms toward proactive interventions tailored to prevent disease progression or design cures to nullify disease vulnerability. The focus of this overview, in the context of applying emerging systems approaches to understanding cardiac dysfunction, is the ATP-sensitive $K^+$ (K$_{ATP}$) channel, a metabolism-gated cardioprotective heteromultimeric complex. We here highlight advances in decoding molecular consequences of channel dysfunction at the proteome-wide level, and underscore implications for a systems comprehension of K$_{ATP}$ channelopathy on heart failure prediction, diagnosis, and therapy.

2. Cardiac K$_{ATP}$ channels in health and disease

K$_{ATP}$ channels are biosensors that enable high-fidelity readout of metabolic distress signals. Unique among ion channels, these checkpoints perform a rheostat-like operation adjusting membrane potential-dependent functions to match energetic demands of the working heart. K$_{ATP}$ channel complexes form through co-assembly of the KCNJ11-encoded Kir6.2 pore subunits with the regulatory ATP-binding cassette sulfonylurea receptor. Abundant in myocardial sarcolemma, where they were originally discovered, K$_{ATP}$ channels have also been reported to reside within intracellular membranes including secretory granules, nuclei, mitochondria, and endoplasmic/sarcoplasmic reticulum. K$_{ATP}$ channel deficit impairs tolerance to sympathetic surge, endurance challenge, or haemodynamic load, and compromises the protective benefit of ischaemic preconditioning and postconditioning, whereas disruption of the K$_{ATP}$ channel blunts this protective response. Genetic investigations have linked K$_{ATP}$ channel mutations to human cardiac diseases, including heritable dilated cardiomyopathy and cardiac arrhythmia, both of which have been verified in murine knockout models deprived of operational channels. More recently, a common polymorphism in the KCNJ11 gene encoding the Kir6.2 pore-forming subunit has been identified as a risk factor for maladaptive cardiac remodelling in the population-at-large, and linked to abnormal cardiopulmonary performance in patients with heart failure. In fact, multiple mechanisms underlying K$_{ATP}$ channelopathies have been proposed, including abnormal ligand–channel interaction, defective catalytic signal processing, suboptimal subunit trafficking, and aberrant pore conductance. Although the K$_{ATP}$ channel’s relationship with cell metabolism contributes to stress tolerance, a broader understanding of multifaceted effects on the cellular milieu, including implications for heart disease, has been lacking. Through use of systems biology, it is only recently that an initial insight into the molecular consequences of channel deficiency has been obtained, and linked to disease predisposition, progression of overt organ failure, and targeted therapy.


Systems biology provides an integrative platform by which to account for the biological complexity related to cardiac health and disease. Beyond traditional reductionist efforts focused on individual molecules or pathways, systems strategies incorporate the multiplicity of relationships among these components and their established interactions within acquired high throughput data sets to comprehend the system as a whole. Comprising one or more elements of genomic (± epigenetic markers), transcriptomic (± microRNA), proteomic (± post-translational modifications), or metabolomic information, systems analyses necessitate interdisciplinary convergence of biological, computational, and mathematical tools by which to formulate insights, or to synthesize models or hypotheses (Figure 1).
facilitate analytical iteration, with initial hypotheses or models subject to further refinement and/or interpretation following biological testing or validation. While 'omic data at any level, individually or in combination, may serve as an initiation or focal point, the proteome is responsible for execution of the majority of physiological processes, and is the culmination of combinatorial epigenetic, transcriptional, translational, and post-translational effects arising at various levels across lifespan and the health-disease spectrum, which ultimately define the phenotype. Accordingly, molecular systems approaches benefit from assessment of protein modulation. Moreover, proteins function not in isolation but rather as discrete elements within extensive networks of interacting components, so assembly of biologically relevant interactomes serves as a means of accounting for documented interrelationships. Networks can then be scrutinized by their constituent elements (nodes, edges), architectural indices of connectivity (e.g. scale-free topology, or nodes which often exhibit greater relevance due to connectivity characteristics within the network, such as hubs or bridging nodes) or for overrepresentation by ontological or disease markers, for subsequent insight, model or hypothesis generation (Box 1). While attractive for systems approaches, there are certain limitations to network analysis with respect to quality of input data, differences in data assessment and output by various pathway analysis algorithms, and the relative flexibility of network architecture for portraying biological dynamics. With proper consideration of caveats, however, proteome-centric systems biology offers a rational platform by which to prioritize and guide interpretation of complex systems behaviour (Figure 1), such as that associated with the spectrum of heart disease progression from a presymptomatic state to one of overt failure.

4. Network-based prediction of K<sub>ATP</sub> channel-dependent cardiac disease susceptibility
Forecasting disease susceptibility requires detection of molecular signatures predictive of cardiac vulnerability prior to symptom onset. Indeed, experimentally, systems approaches to delineate maladaptive subclinical proteomic profiles have the potential to reveal individual disease susceptibility traits. In turn, this would enable enrichment of traditional reactive interventions for heart disease management with

![Figure 1](https://academic.oup.com/cardiovascres/article-abstract/90/2/258/283585)

Proteome-centric network-based systems approach. High throughput data acquisition comparing health vs. disease from various levels of biological complexity, e.g. comparative proteomics, can be integrated by data mining and bioinformatic processing into networks that comprise an expanded neighbourhood of system perturbation. Network composition, topological parameters, and ontological representation provide foci and targets for hypothesis generation and experimental testing. In conjunction or independently, interaction networks also provide a global template for computational modelling, simulation, and prediction. Together, these approaches facilitate efforts towards comprehension of biological systems and their emergent properties, and readily enable iterative refinement to maximize resolution of predictive, diagnostic, and therapeutic application paradigms.

D.K. Arrell et al.
rationally designed proactive strategies aimed at alleviating or precluding disease manifestation.

Feasibility of forecasting cardiac outcome from a presymptomatic proteomic signature was recently systematically investigated by proteome-wide network systems analysis in the setting of K<sub>ATP</sub> channel deficiency produced by knockout of the KCNJ11 gene, encoding the pore-forming Kir6.2 subunit. Two-dimensional gel electrophoresis resolution of ventricular cytosolic subproteomes obtained from wild-type and Kir6.2 knockout cohorts matched by age (8–12-week-old young adults) and sex (all male), exposed nearly 9% of detected protein species as significantly altered as a consequence of channel deletion (Figure 2A and B). Ontological annotation revealed that the 102 K<sub>ATP</sub> channel-dependent proteins, identified following tandem mass spectrometry, encompassed a broad spectrum of cellular functions, indicating the proteomic/molecular complexity of remodeling associated with ablation of ventricular plasmalemmal K<sub>ATP</sub> channels. Metabolism was prioritized among the entirety of delineated changes (Figure 2B), with 63 of the 102 altered proteins functioning directly in bioenergetics, including several components each from the tricarboxylic acid cycle, fatty acid β-oxidation, glycolysis, ...
5. Systems-oriented diagnosis of adverse cardiac effects in response to K\textsubscript{ATP} channel-deficient metaboproteome changes

In the spectrum of cardiac disease progression, differential responsiveness to stress influences which individuals will transition from a state of risk to one of overt disease.66 Hypertension, for example, is a leading risk factor for development of cardiomyopathy and heart failure.57–59 Yet adaptation to hypertensive stress load is highly variable. Adverse manifestations of hypertension include ventricular enlargement, interstitial fibrosis, and ultimately organ dysfunction, significantly contributing to morbidity and mortality in the population.60–62 However, homeostatic processes ensuring stress tolerance are only partially understood,63,64 warranting elucidation of individual cardioprotective components and their underlying systems organization within the hypertensive myocardium. In this regard, systems-oriented strategies serve a diagnostic function, documenting composite molecular substrates for assessment and stratification of the differential capacity to respond to cardiac stressors.

To gain a broader understanding of the K\textsubscript{ATP} channel’s relationship with the cellular milieu and its implication on stress response to cardiac risk factors, consequences of myocardial channel deficiency in the setting of mineralocorticoid/salt-induced hypertension65 were investigated by a proteomic systems approach.35 Following establishment of comparable hypertension in wild-type and Kir6.2 knockout counterparts, all age- and sex-matched young adult males, comparative two-dimensional gel electrophoresis analysis was conducted on ventricular cytosolic subproteomes, where 9% of detected protein species were significantly altered due to the absence of functional K\textsubscript{ATP} channels.35 Consistent with the extent and diversity of changes observed in the absence of stress,34 ontological annotation of the K\textsubscript{ATP} channel-defendent protein differences identified following tandem mass spectrometry comprised an array of cellular functions, yet had an overarching metaboproteomic focus. In this instance, 64% of altered proteins (73/114) were of metabolic function, including constituents of oxidative phosphorylation and electron transfer subunits, the tricarboxylic acid cycle, fatty acid \(\beta\)-oxidation, and glycolysis, as well as amino acid and nucleic acid metabolism.35

The sensitivity and specificity of proteomic screening detected significant changes to a number of proteins with previously established cardiac K\textsubscript{ATP} channel relationships, including adenylate kinase 1, creatine kinase M, glyceraldehyde-3-phosphate dehydrogenase, lactate dehydrogenase isoforms A and B, long-chain acyl-CoA dehydrogenase, and triosephosphate isomerase.47–55,66 Overall, the proteomic systems organization within the hypertensive myocardium. In this instance, 64% of altered proteins (73/114) were of metabolic function, including constituents of oxidative phosphorylation and electron transfer subunits, the tricarboxylic acid cycle, fatty acid \(\beta\)-oxidation, and glycolysis, as well as amino acid and nucleic acid metabolism.35

The sensitivity and specificity of proteomic screening detected significant changes to a number of proteins with previously established cardiac K\textsubscript{ATP} channel relationships, including adenylate kinase 1, creatine kinase M, glyceraldehyde-3-phosphate dehydrogenase, lactate dehydrogenase isoforms A and B, long-chain acyl-CoA dehydrogenase, and triosephosphate isomerase.47–55,66 Combining proteomic studies, a total of 174 different proteins exhibited significant expression differences in response to K\textsubscript{ATP} channel deficiency, including 95 unique metabolic proteins,34,35 which subsumes all 9 bioenergetic enzymes previously linked to K\textsubscript{ATP} channel activity47–55,66 while increasing their total by an order of magnitude.

Network analysis was used to chart physiological and pathophysiological systems processes associated with the hypertensive Kir6.2-dependent subproteome. The resolved scale-free K\textsubscript{ATP} channel-dependent network unmasked ontological linkage to modules of bioenergetic and metabolism-related processes, integrating multiple energy producing, consuming, and distributing pathways.35 By encompassing hallmarks of cardiovascular energy metabolism,67 the composite network neighbourhood provided a systems framework for diagnostic interrogation of K\textsubscript{ATP} channel impact in the setting of hypertension.68 From a broad spectrum of 134 pathological conditions and toxicological pathways curated in Ingenuity Pathways Knowledge Base (one of several pathway/interaction analysis algorithms enabling network assembly and interrogation of -omic data sets through the application of published interactions and established molecular associations with associated (patho)physiological conditions and/or phenotypes), the K\textsubscript{ATP} channel-dependent network exclusively extracted three adverse effects: ‘Cardiac Damage’, ‘Cardiac Enlargement’, and ‘Cardiac Fibrosis’, indicating a critical role for K\textsubscript{ATP} channels in coordinating an appropriate adaptive response to hypertensive stress.35 Diagnosed maladaptive responses were validated functionally and structurally, with Kir6.2 deficient hearts demonstrating, relative to wild-type counterparts, poor cardiac muscle performance, increased heart to body weight ratios and exaggerated collagen deposition, indicating damage, enlargement, and fibrosis, respectively.35 Thus, Kir6.2 ablation engenders unfavourable
proteomic remodelling in hypertensive hearts, providing a composite molecular substrate for pathological stress-associated cardiovascular disease in the setting of K\textsubscript{ATP} channel deficiency. Diagnosis of severe adverse cardiac effects, predicted from the resolved Kir6.2-dependent metaboproteome network, establishes a vital role for K\textsubscript{ATP} channels in adaptability under pathophysiological stress.

6. Stem cell therapy rescues K\textsubscript{ATP} channel-dependent cardiac structure/function deficiencies

Defects in K\textsubscript{ATP} channels predispose to the pathogenesis of heart failure.\textsuperscript{20,21,29,32,69} The multifaceted molecular pathology underlying K\textsubscript{ATP} channel deficit indicates the need for a broad-based strategy to achieve repair. The emergence of stem cell technology provides a rational foundation for targeted heart repair without necessitating whole organ replacement.\textsuperscript{70–74} Although continuous rejuvenation of cardiac muscle has been recognized as a self-repair mechanism, the regenerative reserve is insufficient to salvage the failing heart.\textsuperscript{75–78} In fact, the cardiomyopathic process is precipitated by depletion of the resident cardiac stem cell pool.\textsuperscript{79} Introduction of progenitor cells into the diseased heart offers thereby a means of promoting the healing process, as recently demonstrated by embryonic stem cell therapy in the context of K\textsubscript{ATP} channel ablation recapitulating human dilated cardiomyopathy type 1O (CMD 1O).\textsuperscript{80} In this regard, it has been established that stem cell progeny acquire a cardiogenic phenotype with functional excitation–contraction coupling associated with maturation of the cellular energetic matrix, and when transplanted into damaged heart contribute to repopulation of functional myocardium, improving contractile performance.\textsuperscript{81–86} Stem cell lineage commitment and integration within diseased host myocardium has been further documented,\textsuperscript{87–90} but the molecular substrate underlying repair remains unknown.

Transverse aortic constriction (TAC) imposes sustained pressure overload on the left ventricle resulting in contractile dysfunction and cardiomyalgia, characteristic of congestive heart failure in the KCNJ11 Kir6.2 knockout, consistent with human K\textsubscript{ATP} channel-deficient dilated cardiomyopathy.\textsuperscript{80,91} To assess molecular consequences of TAC-imposed stress in the absence and presence of stem-cell intervention in age- and sex-matched young adult male cohorts, pre-stressed KCNJ11 knockouts were compared with pressure-overloaded Kir6.2 knockouts randomized into untreated and embryonic stem cell-treated cohorts.\textsuperscript{36} Comparative two-dimensional gel electrophoresis resolved 12% of proteome species as significantly altered in the untreated group subject to TAC-induced pressure overload, whereas 7% of the proteome differed from controls in the cell therapy cohort. Tandem mass spectrometric identification indicated that altered proteins were primarily metabolic in nature, comprising 64% and 68% of identified changes in the untreated and stem cell-treated K\textsubscript{ATP} channel-deficient cardiomyopathic groups, respectively. Both groups also exhibited similar breakdowns in total numbers of altered proteins involved in oxidative phosphorylation (n = 13 in untreated, 8 in treated), the tricarboxylic acid cycle (n = 13 in untreated, 12 in treated), and other substrate metabolism (n = 44 in untreated, 43 in treated). When compared with untreated hearts, however, cell therapy eliminated 68% of disease-induced protein changes and reduced extent of fold change in an additional 16%, reorganizing the proteome landscape of failing hearts.\textsuperscript{36} Generation of protein–protein interactions further supported a divergence between observed changes in the untreated and stem cell-treated K\textsubscript{ATP} channel-deficient cardiomyopathic networks. Roughly two-thirds of proteins comprising nodes of either network were mutually exclusive of the other, despite similar representation of categorical functions, suggesting different functional consequences in the absence and presence of stem cell therapy.\textsuperscript{36} Bioinformatic interrogation of networks demonstrated an overrepresented ‘Cardiac Disease’ category associated with the untreated cardiomyopathic network, consistent with heart disease susceptibility, the extent of which was reduced by three orders of magnitude for the stem cell-treated network. Further screening of the untreated cardiomyopathic network for associated pathological conditions and toxicological pathways within the Ingenuity Pathways Knowledge Base extracted seven overrepresented cardiac adverse effects, namely ‘Cardiac Damage’, ‘Cardiac Dilation’, ‘Cardiac Dysplasia’, ‘Cardiac Enlargement’, ‘Cardiac Inflammation’, ‘Cardiac Hypertrophy’, and ‘Cardiac Fibrosis’. Conversely, assessment of the embryonic stem cell-treated cardiomyopathic network indicated that six of these seven detrimental outcomes were no longer statistically overrepresented, suggesting functional and structural benefit of stem cell intervention in the setting of cardiomyopathy.\textsuperscript{36} To functionally validate bioinformatic prediction, cardiac function and structure were assessed in vivo in untreated and stem cell-treated cohorts by prospective echocardiography and pathoanatomical analysis. The untreated cardiomyopathic cohort demonstrated significant and progressive cardiac dysfunction and associated heart chamber enlargement, precipitating without therapy high mortality rates and poor survival. In contrast, stem cell intervention significantly improved cardiac contractility and prevented cardiac dilation, nullifying premature mortality.\textsuperscript{36} Serial monitoring of fractional shortening from the point of randomization indicated continuous deterioration without cell therapy, but improved fractional shortening with cell therapy at multiple time points. A significant decline in the ejection fraction due to cardiomyopathy was reversed towards pre-stress levels by stem cell treatment. Functional improvement was supported by favourable structural remodelling in response to stem cell therapy. While cardiac dilation in untreated hearts was marked over the duration of follow-up, cell therapy was effective in maintaining diastolic dimension.\textsuperscript{30} Moreover, progressive structural deterioration measured as a significant decrease in wall thickness and increase in left ventricular volume that occurred in response to pressure overload without treatment were prevented following stem cell delivery. Histological analysis indicated engraftment of transdifferentiated stem cells into host heart, cell cycle activation, and indices of remuscularization with halved fibrotic zones and normalized sarcomeric and gap junction organization.\textsuperscript{80} Thus, bioinformatic prediction of amelioration of specific cardiomyopathic traits were validated in response to cell therapy.\textsuperscript{36} Direct comparison between the untreated and treated cardiomyopathic groups identified 61 proteins altered by stem cell intervention.\textsuperscript{36} Systems interrogation of the network generated from these proteins unmasked ‘Cardiovascular System Development’ as a prioritized biological function in stem cell-reconstructed cardiomyopathic hearts. In contrast, this function was not prioritized in the untreated cardiomyopathic network, indicating a cardio-rejuvenative substrate induced by stem cell intervention.\textsuperscript{36} Thus, iterative proteome-wide network resolution unmasked a regenerative signature induced by embryonic stem cell treatment of failing heart in the context of K\textsubscript{ATP} channel-deficient cardiomyopathy.
7. Conclusions

Comprehensive proteomic studies have recently resolved the $K_{\text{ATP}}$ channel-dependent subproteome within the heart, providing direct evidence for the channel’s metabolism-centric requirement. Del- etion of the $KCNJ11$ gene encoding the $K_{\text{ATP}}$ channel pore protein Kir6.2 altered roughly one-tenth of detected protein species within the left ventricle, underscoring the vital importance of $K_{\text{ATP}}$ channel activity in maintaining cardiac metabolic homeostasis. At a presympto- matic state, $K_{\text{ATP}}$ channel deficiency leads to extensive, complex remodelling of the metaboloproteome, and results in a phenotype susceptible to cardiac dysfunction anticipated on the basis of observed protein changes. This broadens channel implication beyond conditions of stress to maintenance of cardiac homeostasis. In turn, disease vulnerability translates to an inability under conditions of stress to adapt and respond appropriately to increased cardiac demand. Progressively deleterious structural and functional myocardial consequences ensue, including reduced contractility, interstitial fibrosis, and ventricular hypertrophy, eventually resulting in the heart failure syndrome. The multifaceted nature of $K_{\text{ATP}}$ channel-fibrosis, and ventricular hypertrophy, eventually resulting in the dial consequences ensue, including reduced contractility, interstitial

matic state, $K_{\text{ATP}}$ channel deficiency leads to extensive, complex Kir6.2 altered roughly one-tenth of detected protein species within a preclinical model of $K_{\text{ATP}}$ channel-deficient hearts, proteomic screening and/or prediction. As described here in the context of a comprehension of underlying mechanisms of multi-systems heart dysfunction provides an initial systems survey for surrogate (e.g. proteomic or metabolomic analysis of blood mic analyses. Indeed, proteomic sampling may not be readily systems biology strategies readily incorporate multiple data complement to traditional linear feedback approaches of data pro- cessing. Conceptually, this may include different triggers or aetiologies of heart failure, specific targets such as metabolic remodelling, or investigation of potential therapeutic avenues. Future multidisci- plinary, patient-tailored heart failure studies would be enhanced by addition of phenotype-guided and systems biology conceptually oriented approaches to complement existing strategies. Since systems biology strategies readily incorporate multiple data sources, subsequent investigation will likely expand beyond proteo- mic analyses. Indeed, proteomic sampling may not be readily acquired in a clinical setting, necessitating a more minimally invasive surrogate (e.g. proteomic or metabolomic analysis of blood samples). However, the application of proteomics in a preclinical model of cardiac dysfunction provides an initial systems survey for comprehension of underlying mechanisms of multi-systems heart failure, providing important leads for complementary investigation from these less invasive surrogate techniques to facilitate clinical screening and/or prediction. As described here in the context of a preclinical model of $K_{\text{ATP}}$ channel-deficient hearts, proteomic network-based systems analyses provide a flexible template on which to assemble observed molecular changes, facilitating their integration with subsequent mechanistic analyses to interpret and understand their collective effects on maintenance of cardiac homeostasis in health and disease.

Acknowledgements

A.T. holds the Marriott Family Professorship in Cardiovascular Research at Mayo Clinic.

Conflict of interest: none declared.

Funding

D.K.A. is the recipient of a Marriott Individualized Medicine Career Devel- opment Award, and S.Y. is the recipient of a Marriott Mitochondrial Award. Work in the laboratory of the authors was supported by the National Institutes of Health grants HL 64822 and HL 83439.

References

15. Lorenz E, Terciz A. Physical association between recombinant cardiac $K_{\text{ATP}}$-sensitive $K^+$ channel subunits Kir6.2 and SUR2A. J Mol Cell Cardiol 1999;31:423–434.


