Solving the mysteries of cell bioenergetics and cardiovascular metabolomics

Metabolic processes and signalling are crucially important for the healthy functioning and energy homeostasis of the human body. **Dr Petras Dzeja**, currently working at Mayo Clinic College of Medicine in Rochester, Minnesota, focuses his studies on cardiovascular metabolomics, phosphotransfer circuits and system bioenergetics, aiming to elucidate the metabolic processes and mechanisms involved in health and cardiovascular disease.

The study of cardiovascular metabolomics and system bioenergetics is challenging but important for future medical applications. Dr Petras Dzeja has dedicated most of his professional life to researching dynamics of metabolic and energetic processes that could be responsible for cardiovascular diseases (CVDs) and the way in which these operate in both healthy individuals and those affected by CVDs. His findings, new concepts and novel methodologies have helped to shed light on important aspects of these processes, illuminating knowledge to the metabolic mechanisms of human diseases.

CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVDs) are the leading causes of death globally, both for men and women. Therefore, research into the metabolic dynamics behind these diseases is incredibly important, to find new ways of preventing and tackling them.

Studying cardiovascular metabolomics applies findings gathered from the analysis of metabolites to investigate molecular processes responsible for CVDs. Metabolites are small molecules that are formed in or as a product of metabolism. These can have various functions ranging from signalling, fuel, structure, defence and stimulatory.

Dr Dzeja's research centres on cardiovascular metabolomics and system bioenergetics. System energetics analyses network of metabolic processes that relate to the flow of energy in living organisms and the ways in which bodies convert energy into ATP (adenosine triphosphate), the molecule that transports and distributes chemical energy within cells. How this system operates and how energetic signal communication takes place in real cellular environments is still an enigma.

Dr Dzeja's work particularly focuses on emerging areas within the field of biomedical science, including new directions in metabolomics – stable isotope ^{18}O-assisted phosphometabolomics, the study of adenylate kinase biology, metabolic signalling circuits, phosphotransfer networks and the bioenergetics of normal and failing hearts.

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COMMUNICATION IN CELLULAR BIOENERGETICS

Dr Dzeja and his team have investigated the mechanisms of communication between intracellular ATP consumption and production processes, which ensure the energetic well-functioning of living organisms.

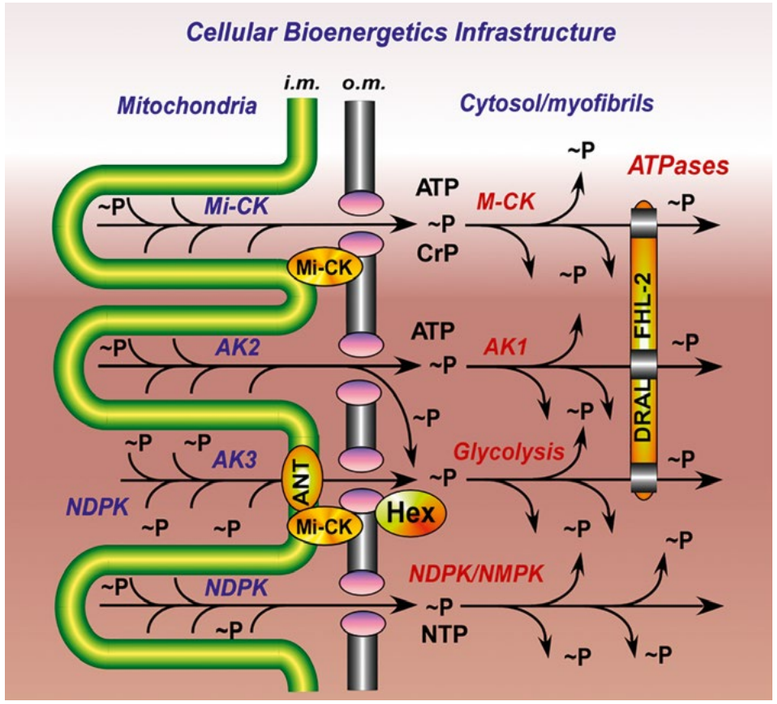
From this, he found that particular networks were critical for efficient energy distribution within the body, which helped to preserve energetic homeostasis under stress. The coordination between consumption and production of ATP was attained through a coupled near-equilibrium enzymatic network that helps to regulate the energy balance within the body.

Dr Dzeja's studies proved the importance of communication between the processes transforming cellular energy and those consuming it. Effective communication appeared to reduce the waste of energy and successfully direct high-energy enzymes to the pathways in the body that needed them the most. In contrast, a disruption in both the distribution and flow of cellular energy could be associated with cardiovascular and neurodegenerative diseases, but also with the development of tumour cells.

METABOLIC SIGNALLING NETWORKS

Dr Dzeja's research also revealed the importance of several networks involved in both cell energetics and metabolic signalling. In his work, he found that the adenylate kinase isoform network (a metabolic monitoring system that scans the cellular energy state and sends signals to metabolic sensors) plays a key role in the body's energy state monitoring and stress response, but is also associated with extracellular signalling processes.

These studies have highlighted the role of the adenylate kinase isoform network in metabolomics, including in the regulation of cell cycle processes that are crucial for tissue homeostasis and regeneration. Dr Dzeja and his team found that adenylate kinase acted as a 'hub' within the cellular homeostatic network, monitoring energy states and sending off AMP metabolic signals.



Mitochondria communicates with cellular ATP consuming sites through phosphotransfer circuits catalysed by creatine kinase (Mi-CK and M-CK), adenylate kinase (AK2, AK3 and AK1) and the glycolytic network beginning from hexokinase (Hex) at mitochondrial site and ending with pyruvate kinase (PK) at remote ATPase sites. Nucleoside diphosphokinase (NDPK) connects mitochondria with NTP consuming sites and facilitates glycogen synthesis/glycogenolysis networks to shuttle high-energy phosphoryls. DRAL/FHL-2 protein anchors phosphotransfer enzymes to sites of ATP consumption to provide "on-site fuelling". While deletion of M-CK or AK1 or both is partially compensated by the glycolytic/glycogenolytic system, deletion of AK2 in intracristae space disrupts resilience of energetic infrastructure and is embryonically lethal.

Similarly, glycolytic/glycogenolytic phosphotransfer networks were found to be important for the bioenergetics of the cardiac system, as they would help maintain cellular energy by facilitating the delivery of high-energy phosphoryls.

Not only that, but Dr Dzeja also found phosphotransfer networks to be very important in metabolomics, as they support the energetic communication and transfer of vast amounts of metabolic information. Phosphotransfer enzymes are critical for metabolic signalling – which controls the electrical activity of cells – as well as for hormone secretion and responses to stress. His research highlighted that an efficient integration of these different energetic and metabolic signalling networks is what ensures that cellular energy remains at homeostasis and can adequately respond during particular activities or stressful situations.

Achieving a better understanding of networks involved in the cellular energetic system is of particular value, as it consequently leads to a better understanding of metabolic disorders and diseases associated with disruptions in metabolic sensing, adenine nucleotide and glucose metabolism.

THE METABOLOMICS OF HEALTHY AND FAILING HEARTS

While investigating metabolic and bioenergetics processes, Dr Dzeja has also explored possible ways of discerning healthy from failing hearts. Evaluating individuals' metabolomics phenotypes, the set of metabolic characteristics resulting from the interaction of their genes with the environment, entails the measurement of their metabolite levels, as well as the rates from which scientists can deduce the fluxes and status of their metabolic system.

Dr Dzeja found that technology which tags metabolites with the stable isotope ^{18}O, could help measure metabolite levels and their turnover rates. This technology can unveil the dynamics of over ten metabolic and signalling pathways, including ATP turnover, Krebs and urea cycles, glycolysis/glycogenolysis, pentose phosphate pathway and phosphotransfer reactions. Ultimately, this would allow physicians to construct dynamic metabolomics profiles, helping them to spot metabolic imbalances that might be due to genetic defects, heart issues, ageing or neurodegenerative disorders.

This technology could therefore be useful in identifying diseases, as well as in monitoring the efficacy of particular treatments.

Dr Dzeja's work has provided an invaluable contribution to the field of biomedical science, offering a greater understanding of the processes involved in cardiovascular bioenergetics and metabolomics. Its applications could assist in finding new ways of understanding and monitoring metabolic mechanisms in CVD-affected and healthy individuals, as well as in uncovering specific disease biomarkers.

Q&A

What do you find most interesting about studying cardiovascular metabolomics and system bioenergetics?
Metabolomics, metabolic signalling and system bioenergetics are emerging areas in biomedical science. The majority of human disease, such as cardiovascular, diabetes, neurodegeneration and cancer, have a metabolic basis and can be treated with metabolic therapies. Knowledge of wiring of cellular energy metabolism and metabolic signalling circuits which regulate heart contractility and electrical activity, orchestrate gene expression and tissue regeneration is critical for advancement of medical science. Our studies uncovered remarkable plasticity of the cellular energetic system where genetic deletion of one phosphotransfer circuit is compensated by others. These studies were possible due to our developed new phosphometabolomics technology – ^{18}O-assisted ^{31}P NMR – and mass spectrometry enabling us to look at the dynamics of metabolic processes. Using metabolomics technologies, we have unveiled metabolic mechanisms in human heart failure, atrial fibrillation and adaptive metabolic transitions in cardiac resynchronization therapy.

What do you believe were your most important findings so far?
I started my career in biomedical science with the discovery of adenylate kinase energy transfer shuttle and subsequently we obtained evidence that it plays a role of major metabolic signalling and monitoring system acting in concert with AMP-activated protein kinase (AMPK) and ATP-sensitive potassium channel (K-ATP) metabolic sensors. Adenylate kinase generated AMP signals regulate a variety of important physiological processes in the human body from mitochondrial respiration and biogenesis, gene expression, blood flow, appetite, sleep, hibernation and developmental programming. We have demonstrated that dissecting the bottleneck of the adenylate kinase isoform (AK2) phosphotransfer network is embryonically lethal in mice highlighting the significance of catalysed nucleotide exchange and ligand conduction in the narrow and crowded mitochondrial intermembrane/intracristal (folds in the inner membrane of the mitochondrion) space.

What could be the possible applications of these findings in future?
Our studies of metabolomics of cardiovascular diseases offer new ways to improve cardiac resynchronisation therapy and new signature metabolite panels have diagnostic and prognostic value in heart failure patients. We have developed ^{18}O-assisted ^{31}P NMR and mass spectrometric technology, which is used in other centres in Europe and USA for phosphometabolomic studies of human diseases. Our AK2 knockout experiments suggest that phosphotransfer-mediated ligand conduction in the mitochondrial intracristae space, within cristae shape microfluidic nano-channels, is necessary for ATP export. Solid state biochemistry, ligand conduction and nano-channel phosphoenergetics might be the future directions in cellular bioenergetics.

What have you found to be the main metabolic differences between a healthy and failing heart?
The heart is a remarkable organ, constantly pumping blood throughout your entire life. Normal heart function depends on tight integration of mitochondria and phosphotransfer circuits, ensuring cellular energy homeostasis and an adequate response to a broad range of functional activity and stress challenges. Derangements of mitochondrial substrate metabolism, energy transfer and metabolic signalling circuits precipitate heart dysfunction, electrical instability and arrhythmias and sudden cardiac death. Failing hearts have failing energetics which could be corrected by metabolic therapies and functional unloading to stimulate regenerative processes.

What are your plans for future research and investigation?
Although components of the cellular energetic grid consisting of mitochondria, glycolytic/glycogenolytic networks and phosphotransfer circuits transferring and distributing high-energy phosphoryls are largely known, their network infrastructure, metabolic flux distribution within nodes and integral response to diseases and genetic deficiencies is still unknown. Integration of genetic and energetic circuits is a critical step in cell specification and differentiation. Recent studies indicate that development of the cellular energetic and metabolic signalling matrix is critical for stem cell differentiation and tissue regeneration.
Future studies will include the significance of the adenylate kinase isoform (AK1-AK9) network in cell energetics and metabolic signalling, integration of adenylate kinase node in cellular phosphotransfer network and the significance of newly discovered phenomena of synchronisation-desynchronisation of Ca^{2+}-Mg^{2+} waves and signalling, and vesicle-mediated transfer to cell nucleus of ATP and signalling molecules.

Detail

RESEARCH OBJECTIVES

Dr Dzeja's topics of study include cardiovascular phosphometabolomics, system bioenergetics, phosphotransfer enzymes and networks, metabolic signalling circuits in heart failure and regeneration, and metabolic sensors in health and disease.

FUNDING

- National Heart, Lung, and Blood Institute (NHLBI)
- National Institutes of Health (NIH)

COLLABORATORS

Dr Dzeja is an active member of the international team focusing on system bioenergetics and metabolomics, which includes Drs Andre Terzic, Slobodan Macura and Yong-Me Cha, Mayo Clinic, Rochester MN; Prof Be Wieringa, Radboud University, Nijmegen, The Netherlands; Prof Valdur Saks and Prof Uwe Schlattner, Joseph Fourier University, Grenoble, France; Prof Joanne Ingwall, Harvard University, Boston, MA. Late Prof Nelson Goldberg, University of Minnesota, Minneapolis, MN.

BIO

Dr Dzeja received his BS in Biochemistry from the Vilnius University, and PhD from Kaunas Medical Academy, Lithuania. He completed postdoctoral training at the University of Minnesota and Mayo Clinic, USA. He currently works as Associate Professor and Co-Director of Metabolomics NMR Core at the Mayo Clinic in Rochester, MN.

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