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.

Solving the mysteries of cell bioenergetics and cardiovascular metabolomics

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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. They 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 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.

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Mitochondria communicates with cellular ATP consuming sites through phosphotransfer circuits catalysed by creatine kinase (CK). ADP and ATP are exchanged in 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 isozyme (AK2) phosphotransfer network is embryonically lethal in mice highlighting the significance of catalysed nucleotide exchange and ligand conduction in the narrow and complex multidimensional phosphotransfer/intermembrane/ extramitochondrial (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 18O-assisted 31P NMR and mass spectrometry technologies, which is used in other centres in Europe and USA for phosphometabolomic studies of human diseases. Our AK2 knockouts suggest that phosphotransfer-mediated ligand conduction in the mitochondrial intermembrane space, within cristae shape microfluidic nano-channels, is necessary for ATP export. Solid state biochemistry, ligand conduction and nano-channel phosphometabolomics 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, desynchronisation of Ca2+-Mg2+ waves 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, glycoglycolytic/glycolenolyc networks and phosphotransfer circuits transferring and distributing high-energy phosphorus 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-de synchronisation of Ca2+/Mg2+ waves and signalling, and vesicle-mediated transfer to cell nucleus of ATP and signalling molecules.

**What do you find most interesting about metabolic signalling?**

Metabolomics, metabolic networking and system bioenergetics are emerging areas in biomedical science. The majority of human disease, such as cardiovascular disease, diabetes, neurodegeneration and cancer, have a metabolic basis and can be treated with metabolic therapies. Knowledge of wiring 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 – 18O-assisted 31P 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.