Investigating the adaptive mitochondrial shuttles and metabolic reprogramming of transporters in complex I (Ndufs4) knockout mice

Daneël Nel

North-West University, Sasolburg, Free State, South Africa

Introduction: Mitochondrial disease is one of the most prevalent diseases among children, with a prevalence of 1 in 5000 children. Leigh syndrome is the result of a Complex I (CI) deficiency and disrupts the redox balance needed for the function of various dehydrogenase enzymes. Due to the extensive heterogeneity of the disease, it still remains a challenge to diagnose and treat mitochondrial diseases. One of the most overlooked areas for possible treatment is the solute carriers of the inner mitochondrial membrane. These solute carriers function together to form shuttle systems that have the ability to transport electrons over the impermeable inner mitochondrial membrane, which can possibly aid in recovery of the disrupted redox balance.

Methodology: Targeted transcriptomic analysis was done on brain tissue collected from a CI deficient (NDUFS4 knockout) mice model to analyze the selected solute carriers' part of the malate-aspartate shuttle and the citrate-pyruvate shuttle. The proteins of the glycerol-3- phosphate shuttle was also included due to its ability to also carry electrons over the inner mitochondrial membrane. This was done by making use of the Ion GeneStudio™ S5 Semiconductor Sequencer accompanied by the Ion Chef™ Instrument. Targeted metabolomics was also done on the brain tissue on the metabolites transported by the solute carriers, also to deduce if there are any changes in their abundance with diseases like Leigh syndrome. This was done via GC-TOF-MS and LC-MS/MS analysis.

Results: Three of the targeted genes in the mouse disease model were significantly up- regulated. These genes were malic enzyme 3, the glutamate carrier and the phosphate-malate exchanger. Metabolomic analysis of the cerebral metabolites in the respective shuttles showed no significant concentration differences despite the up-regulation of the above- mentioned enzymes and transporters.

Conclusions: Up-regulation of the mentioned genes could be an attempt to circumvent the dysfunction of complex I and to maintain the remaining function of the respiratory chain and the TCA cycle for energy production. Although the metabolomics data did not confirm this hypothesis, previous studies have indicated that only certain areas of the brain are severely affected by Leigh syndrome. It is thus possible that the effect Leigh syndrome has on the brain is diluted by the very large and unaffected areas of the brain, making it difficult to detect changes on a metabolic level.

Keywords: Mitochondria, Mitochondrial shuttles, Solute carriers, Transcriptomics, Metabolomics, Gene expression, Adaptive response, Complex I deficiency, OXPHOS system,Ndufs4 mouse model