Mitochondrial dysfunction and oxidative damage contribute to the pathophysiology of the neurometabolic disease propionic acidemia

Mitochondrial dysfunction and alterations in redox homeostasis may contribute to the pathophysiology of inherited metabolic diseases. Our research is focused in propionic acidemia (PA), a rare neurometabolic disease characterized by accumulation of propionyl-CoA and other toxic metabolites due to a genetic deficiency of the mitochondrial enzyme propionyl-CoA carboxylase, in the catabolic pathway of some amino acids, odd-chain length fatty acids and cholesterol. Patients usually present neonatally with a toxic encephalopathy, and develop multiorgan complications in the long term, including neurologic alterations and hypertrophic cardiomyopathy. To date, there is no efficient treatment and there is a high morbidity and mortality. Using a mouse model of the disease we have analysed parameters related to mitochondrial function and oxidative stress in different affected tissues. The results show decreased levels and/or activity of several OXPHOS complexes, mtDNA depletion and alteration in antioxidant enzymes. We have investigated the presence of oxidative damage to proteins, lipids and DNA, and the production of hydrogen peroxide and superoxide anion, which was found elevated. Lipid peroxidation analysis using TBARS assay showed a significant increase in MDA in most tissues analysed. The specific analysis of isoprostanes (IsoPs) in mouse liver and brain tissues using previously described methods allowed the detection of six lipid oxidation markers. Individual IsoPs such as 8-iso-PGE_1, as well as the total IsoPs detected, were found significantly elevated in brain samples of PA mice compared to wild-type controls. Taken together, these data support the hypothesis that oxidative damage may contribute to the pathophysiology of PA and suggest that compounds targeting mitochondrial biogenesis or reactive oxygen species production may provide a beneficial effect delaying or ameliorating the cellular damage in affected tissues. In this sense, IsoPs and other altered metabolites may qualify as potential biomarkers for monitoring disease progression and response to antioxidant therapies.