however, little is known about which proteins mediate ion transport across the mitochondrial inner membrane. Here, we uncover a novel mechanism regulating mitochondrial volume that depends on glutathione levels, the adenine nucleotide translocase, and substrate metabolism. Addition of 3 mM reduced (GSH), but not oxidized (GSSG; up to 0.3 mM), glutathione to isolated guinea pig heart mitochondria, in the absence of exogenous substrates, triggers a dramatic, switch-like, transient contraction and sustained swelling response involving matrix expansion and remodeling of inner membrane cristae. Remarkably, mitochondrial swelling could be reversed by tricarboxylic acid (TCA) cycle intermediates with a preferred selectivity of the substrate, as follows: citrate = isocitrate > succinate > malate > oxaloacetate > glutamate. Preincubation with the six TCA cycle intermediates either blunted or prevented the acute swelling response to 3 mM GSH depending on the substrate. The GSH-induced swelling occurred in parallel with acute NAD(P)H oxidation. Adding ADP and bongkrekic acid before GSH completely blocked the swelling response, or contracted mitochondria pre-swollen with GSH, indicating the adenine nucleotide translocase (ANT) was acting as a redox-sensitive pore. The response was insensitive to the permeability transition pore inhibitor cyclosporine A or the inner membrane anion channel inhibitor 4′-chlorodiazepam (4-Cl-DZP). The findings highlight an important interaction between the glutathione and pyrimidine nucleotide pools that participates in mitochondrial volume regulation by changing the conformation of the adenine nucleotide translocase.

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S14/3 Targeting molecules to mitochondria

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Mitochondrial function and dysfunction contributes to a range of important aspects of biomedical research. Consequently there is considerable interest in developing approaches to modify and report on mitochondria in cells and in vivo. One approach has been to target bioactive molecules to mitochondria by conjugating them to lipophilic cations. Due to the large mitochondrial membrane potential, the cations are accumulated within mitochondria inside cells. This approach had been used to develop mitochondria-targeted antioxidants that selectively block mitochondrial oxidative damage and prevent some types of cell death and also to develop probes of mitochondrial function. Here we outline some of the background to the development of these compounds.

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(S14) Mitochondria and ageing symposium abstracts (poster and raised abstracts)

S14.4 Random mtDNA mutations cause respiratory dysfunction through failure in complex assembly

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Mice with defective proofreading in the mitochondrial specific DNA polymerase polg, (mtDNA mutator mice) have increased mitochondrial DNA mutation rate and a premature aging phenotype, including hair loss, cardiomyopathy, early loss of fertility in females, anaemia, kyphosis, osteoporosis and progressive hearing loss. We set out to find out what effect the mutations would have on the mitochondria. Previously we have shown that there is a progressive loss of activity in respiratory chain complexes that are partially encoded by mtDNA (I, III, IV and V). We now show that isolated mitochondria from these mice display reduced oxidative capacity. Western blot analysis of single protein subunits shows that there is a reduction in levels of COX II and IV, while levels of all other analysed protein subunits appear to be normal. However, when we look at fully assembled complexes, using blue native electrophoresis, we observe a reduction in complexes I, III and IV. The detected reduction is not due to impaired mitochondrial translation as shown by in organello translation assays. We argue that point-mutations in the mitochondrial DNA alter the mitochondrialy encoded respiratory chain subunits leading to failed assembly and ultimately reduced oxidative capacity.

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S14.5 Does aging influence lymphocyte mitochondria respiration in trained people?

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One of the major explanations for age-related decrease in general functionality of cell tissues has been the decline in mitochondria functionality. However, it have been stated that exercise induces an increase in mitochondria functionality. So, the aim of this study was to analyze the influence of exercise training on lymphocyte mitochondria function with aging. Fifteen men, aged between 19 and 52 years old (average age = 32.6±10.6 years), engaged in regular physical activity participated in this study. Maximal aerobic capacity (VO_2max. ml kg^{-1} min^{-1}) was assessed by spirometry until exhaustion. Lymphocyte mitochondria oxidative activity of Complex I and Complex II were assessed. A Pearson correlation was performed in order to test variables (age, mitochondria complex I and II respiration rate) associations. Significance level was established at 5%. VO_2max was 55.66 (+6.23) ml kg^{-1} min^{-1} and mitochondrial oxidative rate was 12.9±5.5 nmol oxygen/min/mg protein and 19.9±8.1 nmol oxygen/min/mg protein for Complex I and Complex II, respectively. Our results couldn't find any significant correlation between mitochondria oxidative rates and age. Concerning the high values obtained in maximal aerobic capacity of this sample and the lack of correlation between mitochondria oxidative capacity and age, we may conclude about the positive effects of exercise training in mitochondria functionality opposing the effect of aging process.

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S14.6 Impaired thermogenesis in PolgA mtDNA polymerase mutant mice

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Impaired thermogenesis is one of the features of ageing. Activity and recruitment of mitochondria in brown adipose tissue is important