HF and evaluation of mitochondrial ischemia–reperfusion injury in the human heart.

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S12.23 Mitochondrial OXPHOS system is enhanced in human lung cancer

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The typical metabolic remodeling of most cancer cells includes the enhancement of glycolysis, but a class of tumors present more with an improved oxidative phosphorylation system. Little is known about the determinants of these extreme opposite situations, and the role played by mitochondria in tumorogenesis. Here, we approached this problem by determining the relative contribution of glycolysis and oxidative phosphorylation (OXPHOS) in lung cancer. We chose to study broncho-pulmonary tumors since they are the first cause of cancer for men in France, with a poor prognosis, aiming to identify therapeutic strategies at the mitochondrial level. We analyzed several mitochondrial features on normal and malignant lung surgical pieces, as well as corresponding cellular models. We measured cellular respiration, coupling degree, ATP synthesis, OXPHOS complexes activity, and PDH activity as well as protein expression levels. We also looked at mitochondrial membrane composition and overall structure of the organellar network by fluorescence microscopy. Lastly, we performed a quantitative analysis of energy metabolites by NMR, and the follow-up of cell proliferation in glucose versus galactose medium. We conclude that lung cancer belong to the OXPHOS class, with a predominant participation of mitochondria to the synthesis of vital ATP. Our results also evidence interesting differences in mitochondrial membrane composition between cancer and normal tissues.

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S12.24 Mutations in UCP2 in congenital hyperinsulinism reveal a role in human beta cell disease

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Congenital hyperinsulinism (CHI) is a genetic disorder characterised by severe hypoglycaemia caused by disproportionate insulin secretion. The most common mechanism underlying CHI is dysfunction of the pancreatic ATP-sensitive potassium channel (K^+_{ATP}). Although mutations in other genes have been described, the pathogenesis and genetic origins of this disease remain unexplained in more than half of all patients. Uncoupling protein 2 (UCP2) knockout mice exhibit hypoglycaemia because of increased insulin secretion, which supports a role for UCP2 in the regulation of insulin secretion. However, its contribution to the development of human beta cell disease has not yet been investigated. The aim of this study was to explore whether UCP2 is involved in human CHI. Ten CHI children, without detectable mutations in other known CHI-causing genes, were studied. Parental-inherited heterozygous UCP2 variants encoding amino-acid changes were found in two unrelated CHI childs. Functional assays were carried out in yeasts and in insulin-secreting cells revealing that the two UCP2 mutants have an impaired activity. Our results demonstrate, for the first time, a role for UCP2 in the regulation of insulin secretion and glucose metabolism in humans and a link between UCP2 mutations and human disease.

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S12.25 Low level radiation and bystander factor(s) damage to mitochondria

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This study aimed to further characterise the, mitochondrial response to both direct irradiation and bystander factor(s). The 'bystander effect' describes radiation-like damage in unirradiated cells in the vicinity of irradiated cells. Cells were exposed to either γ radiation or growth medium taken from irradiated cells. Analysis was performed on mitochondrial DNA 4 to 96 h post exposure and included analysis of common deletion and point mutations, mitochondrial genome copy number, oxygen consumption rates and mitochondrial mass. A novel deletion was observed in HPV-G cells exposed to radiation and bystander factor(s). Point mutation analysis identified point mutations, in a non-consistent manner, in only the D-loop region and only in cells exposed to 5 Gy direct radiation. CHO-K1 cells showed a significant, though transient, reduced oxygen consumption rates. The latter apparent recovery was likely due to the substantial increase in mitochondrial mass observed in these. HPV-G cells showed a sustained increase in oxygen consumption rates post ICCM exposure and a transient increase 4 h post exposure to 5 Gy direct irradiation. Significant increases were observed in mitochondrial mass per exposed HPV-G cells. Findings are indicative of a stress response to mitochondrial dysfunction and DNA damage that increases the number of mitochondria per cell.

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S12.26 Effect of salicylic acid on the expression of mitochondrial energy dissipation systems in soybean

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Salicylic acid (SA) is a phenolic compound involved in plant stress responses. SA application generates reactive oxygen species (ROS) and induces alternative oxidase (AOX) expression. The aim of this work was the study of the effects of SA on the expression of AOX and other mitochondrial energy dissipation systems present in plants eg the rotenone-insensitive NADH dehydrogenases (ND) and uncoupling proteins (UCP). The three AOX genes present in soybean were previously identified as well as two incomplete UCP sequences. Here