INVOLVEMENT OF ENERGY METABOLISM, INTRACELLULAR Ca^{2+} HOMEOSTASIS AND OXIDATIVE STRESS IN CELL DEATH

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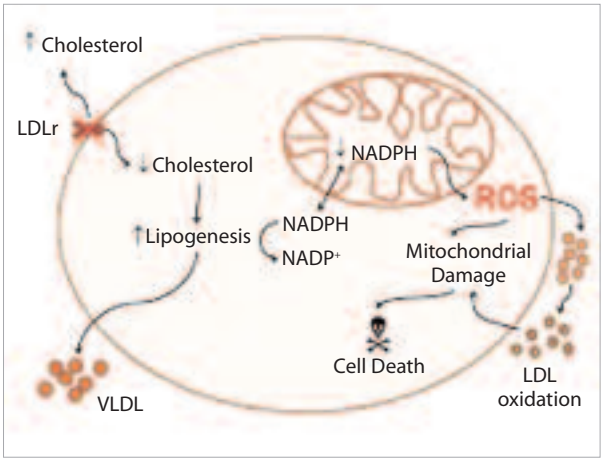


Mitochondrial RPS release in increased in LDL receptor knockout mice. (Vercesi et al., IUBMB Life 59: 263, 2007)

Many diseases are related to changes in energy metabolism, impairment of Ca^{2+}, Na^{+}, H^{+} or K^{+} homeostasis, increased reactive oxygen species (ROS) generation or the activation of mitochondrially-controlled cell death. Our Project seeks to enhance our comprehension of these diseases, studying mitochondrial oxidative metabolism in vitro and applying this knowledge towards the understanding of cellular and in vivo models of diseases known to be associated with energy metabolism defects, including dyslipidemias, atherosclerosis, stroke, methylmalonic acidemia and Parkinson's diseases. The main goals of our project are:

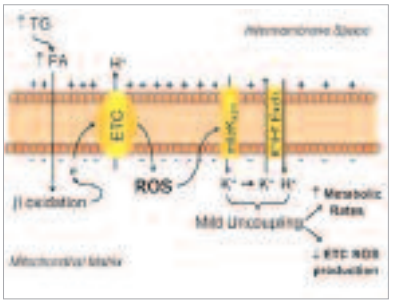
1. To verify the role of mitoK_{ATP} on the control of the mitochondrial redox state, oxidative metabolism, body mass and composition in genetically hypertriglyceridemic (hyperTG) mice;
2. To study the oxidative stress in cells and mitochondria of genetically hypercholesterolemic mice;
3. To understand the impact of the expression of the cholesteryl ester transfer protein (CETP) on the energetic metabolism and adiposity in CETP transgenic mice;
4. To study energy metabolism, oxidative stress and mitochondrial dysfunction in excitotoxicity and in dopaminergic neurodegeneration in Parkinson´s disease;
5. To characterize the mitochondrial dysfunction induced by methylmalonate;
6. Oxidative stress and mitochondrial dysfunction in lymphocyte death: influence of lymphocyte activation;
7. Oxidative stress in tumor cell death.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

1. The activation of the mitochondrial potassium channel (mitoK$_{ATP}$) previously observed in genetically hypertriglyceridemic mice seems to be a mechanism to protect these organelles against the oxidative stress normally associated with dyslipidemias.

2. The lower capacity of mitochondria from atherosclerosis-prone, hypercholesterolemic LDL receptor knockout mice to sustain a reduced state of matrix NADPH, the main source of antioxidant defense system against reactive oxygen, is the consequence of high rates of lipogenesis that consumes reducing equivalents from this coenzyme shifting it to the oxidized state.

3. In a recent work, we showed that two proteins involved in the plasma lipid transport, have opposite effects on the accumulation of body fat. The overexpression of apolipoprotein CIII causes hypertriglyceridemia and predispose to diet induced obesity. On the other hand, the overexpression of CETP (cholesteryl ester transfer protein) reverses the adipogenic effect of apolipoprotein CIII. These findings indicate a novel and unsuspected role for CETP in modulating body adiposity.



MitoKATP channels are activated in hypertriglyceridemia (Vercesi et al., IUBMB Life 59: 263, 2007)

4. We observed that *in vivo* overstimulation of N-methyl-D-aspastate (NMDA) receptors, by intracerebral infusion of sodium quinolinate in rat, causes an early impairment of the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) activity. No impairment in mitochondrial Ca^{2+} accumulation at this stage of the degeneration was detected. Our results suggest that an early impairment of SERCA function may be involved in excitotoxicity.

5. In a recent publication, we showed that methylmalonate (MMA) is an important inhibitor of succinate transport by the dicarboxylate carrier. We concluded that MMA inhibits succinate-supported mitochondrial oxygen consumption by interfering with the uptake of this substrate. Although succinate generated outside the mitochondria is probably not a significant contributor to mitochondrial energy generation, MMA-induced inhibition of substrate transport by the mitochondrial dicarboxylate carrier may have important physiopathological implications in methylmalonic acidemia.

6-7. Activated spleen lymphocytes from Walker 256 tumor bearing rats are more susceptible than controls to necrotic cell death by a mechanism mediated by higher levels of cytosolic free calcium that enters mitochondria and stimulates the production of reactive oxygen. This may explain the increased fragility of the immunological system to chemotherapy-generated oxidative stress.

MAIN PUBLICATIONS

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