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Abstracts

S10 Uncoupling Proteins

Lectures

10L.1 UCP2 bioenergetics and metabolism

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In mammals the two proteins UCP2 and UCP3 are highly similar to the mitochondrial uncoupling protein found in the brown adipose tissue (UCP1). Accordingly, it was proposed that UCP2 and UCP3 are also uncoupling proteins *i.e.* allowing proton reentry into mitochondrial matrix in a regulated way and moreover the regulation of UCP1, UCP2 and UCP3 were considered as similar by several authors. Our recent publications [1–7] support the hypothesis is that the uncoupling activity is not the reason to UCP2 presence in mammals and conservation through evolution of UCPs. 1) UCP2 expression is tightly controlled in the short time. The UCP2 protein is very poorly expressed in comparison with the mRNA content of a cell [1]. This is explained by (i) the constitutive inhibition of UCP2 mRNA translation by the 5′ untranslated region [2], (ii) the short (20–30 min) half life of UCP2 [3]. Glutamine was shown to relieve the constitutive inhibition of UCP2 translation [4]. This control of expression by a known respiratory substrate points to the possibility that UCP2 be more on the side of metabolism (substrate use) than bioenergetics (respiratory control). 2) UCP2/3 influences cellular metabolism in absence of uncoupling. Ucp2-KO mice show an alteration of macrophage activity [8]. Studies comparing macrophages from Ucp2-KO mice with their control showed disturbance of glutamine catabolism [5]. Although respiration was faster in presence of UCP2 this increase could not be explained by uncoupling but rather by a more efficient substrate supply to mitochondria in presence of UCP2. Similarly it was noticed modification in cells recombinantly expressing UCP3 that did not support uncoupling [6], this seems to be related to pyruvate metabolism [6,7]. It is possible to feed mitochondrial oxidation by glutamine and fatty acids in absence of glucose. The control of UCP2 expression is consistent with the proposal that UCP2 would divert mitochondria from oxidizing pyruvate when glutamine and fatty acids are available.

References

[1] Pecqueur C *et al.* (2001) *J. Biol. Chem.* **276:** 8705–8712.
[2] Hurtaud C *et al.* (2006) *Cell. Mol. Life Sci.* **63:** 1780–1789.
[3] Rousset S *et al.* (2007) *FEBS Lett.* **581:** 479–482.
[4] Hurtaud C *et al.* (2007) *Cell. Mol. Life Sci.* **64:** 1853–1860.
[5] Nubel T *et al.* (2008) *Biochim. Biophys. Acta* **1777:** 48–54.
[6] Mozo J *et al.* (2006) *Biochem J.* **393:** 431–439.
[7] Pecqueur *et al.* (2008) *FASEB J.* **22:** 9–18.
[8] Arsenijevic *et al.* (2000) *Nat. Genet.* **26:** 435–439.

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10L.2 The regulation and turnover of mitochondrial uncoupling proteins

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Uncoupling proteins (UCP1, UCP2 and UCP3) are important in regulating cellular fuel metabolism and as attenuators of reactive oxygen species production, through strong or mild uncoupling. The generic function and broad tissue distribution of the uncoupling protein family means that they are increasingly implicated in a range of pathophysiological processes including obesity, insulin resistance and diabetes mellitus, neurodegeneration, cardiovascular disease, immunity and cancer. The significant recent progress describing the turnover of novel uncoupling proteins, as well as current views on the physiological roles and regulation of UCPs, is outlined.

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10L.3 Role of UCP2 in the cancer cell

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The uncoupling proteins (UCPs) are mitochondrial transporters whose biological function is, in principle, to modulate the efficiency of the oxidative phosphorylation although the actual molecular mechanism may vary among the different family members. Up till now, only the physiological role of the uncoupling protein from brown fat (UCP1) has been unequivocally defined: it is a regulated proton carrier that allows the generation of heat for adaptive thermogenesis. The function of the remaining members of the UCP protein family is not established, but available data point to a role in the antioxidant defence system [1,2]. Although the acceleration of respiration due to UCP-mediated uncoupling would lead to a reduction in the production of superoxide, it has also been proposed that UCPs induce a metabolic shift that promotes glycolysis and therefore indirectly lowers the mitochondrial production of reactive oxygen species (ROS) [3]. Nevertheless, there are many examples where UCPs are upregulated in physiological situations where there is oxidative stress and data suggesting that their presence lowers ROS

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levels. The uncoupling protein UCP2 is found in many animal tissues and organs and its expression levels are often increased in pathological processes in which there is oxidative stress (lipotoxicity, atherosclerosis, chronic inflammation, etc.). Tumour cells have a high intrinsic level of oxidative stress and, in these cells, UCP2 can also play a protective role that has made this protein a target for cancer treatment [4]. Thus, it has been shown that in colon cancer UCP2 expression is increased and that this induction appears linked to NF-κB activation and oxidative stress. Increased UCP2 levels have also been associated with resistance to chemo- and radiotherapy in sublines of leukemia and melanoma. Additionally, it has been shown that overexpression of UCP2 in tumour cells reduces ROS levels and apoptosis when treated with antitumour drugs such as doxorubicin or camptothecin. We present data showing that inhibition of UCP2 in tumour cells causes oxidative stress and that the inhibition acts synergistically with chemotherapeutic agents to reduce cell viability.

References

[1] Rial E, Zardoya R (2009) *J. Biol.* **8:** 58.
[2] Krauss S, Zhang CY, Lowell BB (2005) *Nat. Rev. Mol. Cell. Biol.* **6:** 248–2461.
[3] Bouillaud F (2009) *Biochim. Biophys. Acta* **1787:** 377–383
[4] Baffy G (2010) *Mitochondrion* **10:** 243–252.

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10L.4 Mitochondrial uncoupling proteins in unicellular eukaryotes

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Uncoupling proteins (UCPs) are members of the mitochondrial anion carrier protein family that are present in the mitochondrial inner membrane and mediate free fatty acid (FFA)-activated, purine nucleotide (PN)-inhibited proton conductance. Since 1999, the presence of UCPs has been demonstrated in some non-photosynthesising unicellular eukaryotes, including amoeboid and parasite protists, as well as in non-fermentative yeast and filamentous fungi. In the mitochondria of these organisms, UCP activity is revealed upon FFA-induced, PN-inhibited stimulation of resting respiration and a decrease in membrane potential, which are accompanied by a decrease in membranous ubiquinone (Q) reduction level. UCPs in unicellular eukaryotes are able to divert energy from oxidative phosphorylation and thus compete for a proton electrochemical gradient with ATP synthase. Our recent work indicates that membranous Q is a metabolic sensor that might utilise its redox state to release the PN-inhibition of UCP-mediated mitochondrial uncoupling under conditions of phosphorylation and resting respiration. As this regulatory feature was demonstrated for microorganism UCPs (*A. castellanii* UCP), plant and mammalian UCP1 analogues, and UCP1 in brown adipose tissue, the process could involve all UCPs. We discuss the functional connection and physiological role of UCP and alternative oxidase, two main energy-dissipating systems in the plant-type mitochondrial respiratory chain of unicellular eukaryotes, including the control of cellular energy balance as well as preventive action against the production of reactive oxygen species.

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10L.5 UCP1 ablation increases the production of reactive oxygen species by mitochondria isolated from brown adipose tissue

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We provide evidence that ablation of uncoupling protein 1 increases the rate of reactive oxygen containing species production (as detected by Amplex Red) by mitochondria from brown adipose tissue, no matter what electron transport chain substrate is used (succinate plus rotenone (about 1.5-fold, $p = 0.033$), glycerol-3-phosphate (2-fold, $p = 0.030$), pyruvate plus malate (2-fold, $p = 0.044$). The substrate glycerol-3-phosphate resulted in the greatest amount of reactive oxygen containing species production. Consistent with these data are our observations that (a) the mitochondrial membrane potential is maximal when is uncoupling protein 1 is ablated and (b) oxygen consumption rates in mitochondria from uncoupling protein 1 knock-out mice, are significantly lower than those from wild-type mice. In summary, we show that uncoupling protein 1 can affect reactive oxygen containing species production by isolated mitochondria from brown adipose tissue.

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Posters

10P.1 Absence of mitochondrial uncoupling protein 1 affects apoptosis and T-cell profile in mice

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The thymus is a primary lymphoid organ the progenitor cells of which develop into mature thymocytes. Following antigen selection processes these CD4/CD8 double positive cells develop into naïve single positive (CD4 or CD8) T cells which migrate to the peripheral lymphoid tissue, such as spleen and lymph nodes. This maturation and selection process results in the apoptosis of 90% of thymocytes. UCP1 has been shown to be present in mouse thymocyte but not spleenocyte mitochondria. Flow cytometric analysis of cell profiles in thymus and spleens show that there are (i) more immature double positive thymocytes in thymus [10% increase, $p = 0.04$] and spleen [2-fold increase, $p = 0.02$] and (ii) less single positive CD8 (mature) thymocytes in the thymus [2-fold decrease, $p = 0.002$] and spleen [2-fold decrease, $p = 0.01$] of $UCP1^{-/-}$ mice compared to wild-type C57Bl/6 mice [x-fold, p value]. In an endeavour to explain these cell profile differences, we were able to show that spontaneous apoptosis is less prevalent in thymocytes isolated from $UCP1^{-/-}$ mice compared to those isolated from C57Bl/6 mice [20% decrease, $p = 0.006$], indicating a role for UCP1 in T-cell selection in the thymus.

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10P.2 Characterization of the sensitivity of 4-hydroxynonenal-activated proton conductance to GDP and carboxyatractylate in skeletal-muscle and heart mitochondria

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