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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.

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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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