P/16 Uncoupling Protein 2: Physiology data and biochemistry questions

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The mitochondrial Uncoupling Protein 2 UCP2 is a member of the mitochondrial carrier family and belongs to the UCP subfamily. It is widely expressed in tissues. In immune cells, UCP2 has a regulatory function through its effect on the production of reactive oxygen species and MAPK signalling. $Ucp2^{-/-}$ mice are resistant to infection by parasites and intracellular bacteria but are more sensitive to chronic inflammation and experimental neurodegeneration. We found that autoimmune diabetes was strongly accelerated in $Ucp2^{-/-}$ mice compared to $Ucp2^{+/+}$ mice with increased intra-islet lymphocytic infiltration. These data highlight UCP2 as a new player in autoimmune diabetes. In addition, in agreement with the known inhibitory role of UCP2 on insulin secretion, loss of function of UCP2 contributes to congenital hyperinsulinism in patients. The question of whether UCP2 fully uncouples respiration from ATP synthesis is still debated. $Ucp2^{-/-}$ cells display enhanced proliferation associated with a metabolic switch from fatty acid oxidation to glucose metabolism. This metabolic switch requires the unrestricted availability of glucose, and $Ucp2^{-/-}$ cells more readily activate autophagy than wild-type cells when deprived of glucose. Altogether, these results suggest that UCP2 promotes mitochondrial fatty acid oxidation while limiting mitochondrial catabolism of pyruvate. UCP2 expression is also required for efficient oxidation of glutamine in macrophages. This role of UCP2 in glutamine metabolism appears independent from its uncoupling activity.

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P/17 Nitric oxide: Mitochondrial interactions in physiology and pathophysiology

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At physiological concentrations nitric oxide (NO) inhibits mitochondrial cytochrome *c* oxidase in competition with oxygen. Using a technique based on visible light spectroscopy we have demonstrated that endogenous NO enhances the reduction of the electron transport chain, thus enabling cells to maintain their VO_2 at low $[O_2]$. This favours the release of superoxide anion, which initiates the transcriptional activation of NF-κB as an early stress signalling response. We have recently used this technique to demonstrate that NO is inactivated by cytochrome *c* oxidase in its oxidised state and that cessation of such inactivation at low $[O_2]$ may account for hypoxic vasodilatation. Many cells respond to a decrease in oxygen availability via stabilisation of hypoxia-inducible factor-1α (HIF-1α), whose accumulation is normally prevented by the action of prolyl hydroxylases. We have found that inhibition of mitochondrial respiration by low concentrations of NO leads to inhibition of HIF-1α stabilisation. This prevents the cell from registering a state of hypoxia at low $[O_2]$, which would otherwise result in upregulation of defensive genes associated with, for example, glycolysis and angiogenesis. Furthermore, upon inhibition of mitochondrial respiration in hypoxia, oxygen is redistributed toward non-respiratory oxygen-dependent targets.

Our results demonstrate that NO acts not only as a physiological regulator of cell respiration but also as a signalling agent in the mitochondria and a controller of the distribution of available oxygen. Such mechanisms may also be involved in the initiation of pathophysiology.

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P/18 An attempt to arrest the aging program by means of mitochondria-targeted plastoquinone

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A concept is developed considering aging as an evolution-facilitating program which is unnecessary and counterproductive for human and, therefore, should be arrested. To do this, an attempt is undertaken to inactive mitochondria-produced reactive oxygen species (ROS) which seem to mediate execution of the aging program. We synthesized mitochondria-targeted, rechargeable, hydrophobic antioxidant composed of plastoquinone and cation of decyltriphenylphosphonium (SkQ1). It is shown that very low (nmol/kg/day) amounts of SkQ1 increase the lifespan of a fungus (*Podospora anserine*), invertebrates (*Ceriodaphnia affinis* and *Drosophila melanogaster*) and a mammal (mouse). Even more important, in mice SkQ1 abrogates development of such typical traits of senescence as osteoporosis (kyphosis), decrease in resistance to infections, depression, alopecia, loss of whiskers, gray hairs, disappearance of regular oestrous cycles, etc. In rats, pretreatment with SkQ1 or its homolog, SkQR1, has favourable effect in the cases of experimental heart arrhythmia, heart and kidney infarction or stroke. In rats, rabbits, cats, dogs and horses, drops of 250 nM SkQ1 prevent development of certain types of cataract, retinopathies and uveitis and in some cases return vision to animals that became blind due to these pathologies. These data are consistent with the assumption that SkQ1 interferes with execution of aging program and is promising in treating some age-related diseases.

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P/19 Evidence for the presence of a peroxide in the binuclear site of oxidized cytochrome *c* oxidase: The new catalytic cycle

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Cytochrome *c* oxidases, members of the superfamily of heme-copper containing terminal oxidases, catalyse the reduction of molecular oxygen to water. Catalytic cycles consist of the oxidized O-state, the one and two electron reduced E and R-states. The R-state reacts with oxygen to form the P-state, input of the third electron leads to the F-state, which is converted to the O-state again after receiving the fourth electron. The P- ("Peroxy") and F- (Ferryl) states are oxoferryl states. Presently the binuclear heme Fe_{a3}–Cu_B active site is believed to contain either a hydroxyl group