conditions. These results demonstrate the presence of iPLA2 in lung mitochondria and support the hypothesis that the activation of mitochondrial phospholipases by mild oxidative stress can provide free fatty acids as cycling substrates for UCP2. However, attenuation of ROS production by UCP2 is not significant.

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### S10.21 Quinones inhibit the mitochondrial permeability transition pore at two sites

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We have studied the quinone structural features that confer modulatory properties on the mitochondrial permeability transition pore (PTP). Reduced derivatives of ubiquinone (Ub) 0 with acetoxy or methoxy substitutions of the carbonyl groups became ineffective at PTP inhibition. Consistent with a key role of the Ub0 oxidation-reduction state for its interactions with the PTP, DTT prevented the inhibitory effects on the pore when added before but not after Ub0. Of note, the addition of DTT after Ub0 prevented the toxic effects of Ub0 on respiration. The combination of Ub0 and DTT thus allowed inhibition of the PTP without mitochondrial toxicity, which in the absence of DTT reveals itself with a bell-shaped curve where the Ub0-dependent increase of mitochondrial $Ca^{2+}$ retention capacity (a measure of PTP inhibition) is superceded by a decrease as the Ub0 concentration is raised above about 50 μM. The PTP inhibitory effects of decylUb were instead unaffected by reducing agents, and Ub0 and decylUb displayed additive effects on PTP inhibition, indicating that they act at different inhibitory sites on the PTP.

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### S10.22 Novel mitochondria-targeted antioxidants are capable to defense cells from the oxidative damage

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Synthesized in the Skulachev's laboratory new type of mitochondria-targeted antioxidants — plastoquinone derivatives (SkQs) were investigated. The aim of our study was to estimate of antioxidant properties of the SkQ family members plastoquinonyl decyltriphenylphosphonium (SkQ1) and plastoquinonyl decylrhodamin 19 (SkQR1), a fluorescent derivative. These compounds combined with a positively-charged penetrating cations were selectively targeted to mitochondria, being accumulated inside, and can be reduced by the respiratory chain. Using confocal microscope we observed that SkQR1 was accumulated by mitochondria. Uncoupling action of FCCP, leading to mitochondrial depolarization, prevented the SkQR1 staining. In human cell cultures HeLa and K562 very low concentrations (nanomolar) of antioxidants were found to prevent ROS-induced apoptosis and necrosis. Oxidative stress initiated by addition of small amount $H_2O_2$ to living cells, caused secondary generation of endogenous ROS and lowered the level of reduced glutathione. SkQ1 and SkQR1 prevented oxidative damage as well as glutathione oxidation, C1/2 being around 2nM and 0.5 nM respectively. It is concluded that cationic plastoquinone derivatives are rechargeable, mitochondria-targeted antioxidants of very high efficiency.

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### S10.23 Variegate porphyria induces higher $H_2O_2$ production in stimulated lymphocytes due to an impaired respiratory function

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Our aim was to analyse the effects of VP on the production of ROS by lymphocytes and determine the possible mitochondrial sources of these ROS. Twelve women affected by VP and twelve control healthy women participated in the study. $H_2O_2$ production was measured using 2,7-dichlorofluorescin-diacetate as indicator in basal conditions and after stimulation with PMA. In addition three treatments with allopurinol, rotenone or myxothiazol were performed in PMA-stimulated lymphocytes. No differences were observed between porphyric and control women in the basal production of $H_2O_2$. The stimulation with PMA increased $H_2O_2$ production in both groups but lymphocytes from porphyric women produced higher levels of $H_2O_2$ than controls. The treatments with allopurinol and rotenone did not modify $H_2O_2$ production but after treatment with myxothiazol $H_2O_2$ production decreased back to basal levels in both groups. In conclusion, lymphocytes from women affected by VP produce the same amount of $H_2O_2$ in basal conditions than control women, but after stimulation lymphocytes from porphyric women produce higher levels of $H_2O_2$. This increased $H_2O_2$ production is due to an impaired function of the mitochondrial respiratory chain rather than to other ROS sources such as xanthine oxidase.

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### S10.24 Involvement of p38 in camptothecin induced expression of UcP2 in rat neonatal cardiomyocytes

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Camptothecin (CPT), a topoisomerase I inhibitor, is used for treatment of certain types of malignancies. Uncoupling protein 2 (UcP2) is proposed to protect cardiomyocytes against oxidative stress. Modulation of UcP2 level appears important because the protein increases in failing human heart. $p38^{MAPK}$ belongs to a group of protein serine/threonine kinases that become activated in response to extracellular stimuli and mediate signal transduction in cell growth, differentiation and apoptosis. We found that CPT treatment induces UcP2 expression on both mRNA and protein level in cardiomyocytes. This induction is accompanied by short-term increase in production of ROS (<1 h) preceded by activation of $p38^{MAPK}$ (<30 min). Activation of $p38^{MAPK}$ by CPT was comparable to anisomycin, a protein synthesis inhibitor that activates stress-related MAPKs, namely $p38^{MAPK}$ in mammalian cells. Pretreatment of cardiomyocytes with $p38^{MAPK}$ inhibitor, SB203580, blocked activation of $p38^{MAPK}$ by both compounds and abolished the camptothecin-mediated UcP2 induction. Our results