

paid the regulation of uncoupling proteins and to carrier transport mechanisms.

doi:10.1016/j.bbabbio.2010.04.035

SEL3

Interruption of the organismal senescence program

V.P. Skulachev

Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Russian Federation

E-mail: skulach@belozersky.msu.ru

Mitochondria-targeted cationic plastoquinone derivatives (SkQs) operate as antioxidants in two quite different ways: (i) directly (by preventing cardiolipin peroxidation) and (ii) indirectly (by fatty acid cycling resulting in mild uncoupling which inhibits ROS formation in State 4). The quinol and cationic moieties of SkQs are involved in cases (i) and (ii), respectively. In case (i) SkQH₂ interrupts propagation of chain reactions involved in peroxidation of unsaturated fatty acids in cardiolipin, the formed SkQ^{•+} being reduced back to SkQH₂ by heme b_H of complex III. Molecular dynamics simulation showed that there are two stable conformations of SkQ1 with the quinol residue localized near peroxy radicals at C₉ or C₁₃ of the cardiolipin linoleate residues. In case (ii), fatty acid cycling is involved, which consists of (a) transmembrane movement of the SkQ cation/fatty acid anion pair and (b) back flows of SkQ cation and protonated fatty acid. The cycling results in H⁺ conductance of planar phospholipid membranes and liposomes. In mitochondria, the cycling causes mild uncoupling, thereby decreasing membrane potential and ROS generation coupled to reverse electron transport. In yeast cells, dodecyltriphenylphosphonium (C₁₂TPP), the cationic part of SkQ1, induces uncoupling that is mitochondria-targeted since C₁₂TPP is specifically accumulated in mitochondria and increases the H⁺ conductance of the mitochondrial inner membrane. The outer cell membrane conductance is not affected by C₁₂TPP. In human cell cultures, plastoquinonyl decyltriphenylphosphonium (SkQ1) and its analog, plastoquinonyl decylrhodamine 19 (SkQR1) arrest H₂O₂-induced apoptosis. When tested *in vivo*, SkQs (i) prolong lifespan of fungi, crustaceans, insects, fish, and mice, (ii) suppress appearance of many traits typical for age-related senescence (cataract, retinopathies, achromotrichia, balding, osteoporosis, decline of immune system, myeloid shift of blood cells, activation of apoptosis, induction of β-galactosidase, phosphorylation of H2AX histones, etc.), and (iii) lower tissue damage and save the lives of young animals after treatments resulting in kidney ischemia, rhabdomyolysis, heart attack, heart arrhythmia, and stroke. It is assumed that SkQs interrupt execution of programs responsible for both senescence and fast "biochemical suicide" of organism after a severe metabolic crisis.

doi:10.1016/j.bbabbio.2010.04.036

W.1

Towards a quantitative systems level understanding of live-cell mitochondrial physiology in health and disease

Werner J.H. Koopman, Peter H.G.M. Willems

Dept. of Biochemistry NCMLS, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

E-mail: w.koopman@ncmls.ru.nl

Mitochondria are critically involved in cell cycle regulation, apoptosis, Ca²⁺ signaling, organismal development, immune responses and dynamic modulation of metabolic capacity. Mitochondrial dysfunction takes a central place in the etiology of many human disorders including diabetes, genetic oxidative phosphorylation defects, cancer and neurodegenerative disorders. At the (sub)cellular level, metabolism is linked to dynamic alterations in mitochondrial motility, position, structure, mass and function. We focus on gaining a quantitative and mechanistic understanding of the coupling between mitochondrial dynamics and function, and its regulation, at the (sub)cellular level. To this end, chemical and proteinaceous reporter molecules are introduced in living cells followed by perturbation of mitochondrial dynamics and/or function by genetic and/or chemical means. The effects of these maneuvers are studied using classical biochemical techniques, quantitative (sub)cellular (high-content) live cell microscopy, cellular and mitochondrial single-molecule spectroscopy, image processing and analysis, and quantitative deterministic/stochastic *in silico* modeling. This approach is used to obtain a systems level understanding of live-cell mitochondrial physiology by investigating: (I) the pathophysiology of mitochondrial dysfunction in patient cells and knockout mouse models, (II) the physicochemical properties of the mitochondrial matrix, (III) how cells can adapt to mitochondrial dysfunction at the metabolic, structural and functional level, and (IV) which drugs mitigate mitochondrial dysfunction at the cellular and organismal level.

References

- [1] Dieteren C *et al.* (2008) *J. Biol. Chem.* **283**: 34753–34761.
- [2] Distelmaier F. *et al.* (2009) *Brain* **132**: 833–842.
- [3] Distelmaier F. *et al.* (2009) *Mol. Med.* **87**: 2009 515–522.
- [4] Eisenberg I. *et al.* (2008) *Hum. Mol. Genet.* **17**: 2008 3663–3674.
- [5] Forkink M *et al.* (2010) *Biochim. Biophys. Acta-Bioenergetics* (in press).
- [6] Koopman W *et al.* (2010) Antioxidants and Redox Signaling (in press).
- [7] Valsecchi Biochim. F. *et al.* (2009) *Biophys. Acta Mol Basis Dis* **1792**: 1130–1137.
- [8] Willems *et al.* (2009) *Int. J. Biochem. Cell Biol.* **41**: 1773–1783.

doi:10.1016/j.bbabbio.2010.04.037

W.2

Single channel properties and modulation of intracellular chloride channels

Karol Ondrias¹, Zuzana Tomaskova¹, Viera Kominkova¹, Adam Szewczyk², Lubica Malekova¹

¹*Institute of Molecular Physiology and Genetics SAV, Laboratory of Intracellular Ion Channels, Slovak Republic*

²*Nencki Institute of Experimental Biology, Laboratory of Intracellular Ion Channels, Poland*

E-mail: karol.ondrias@savba.sk

The work focuses on observation of the properties, functional significance, and modulation of mitochondrial chloride (mtCl) single channels using bilayer lipid membrane (BLM) method. The crude rat heart mitochondria and submitochondrial particles (inner membrane vesicles) were isolated from the hearts of male Wistar rats. The vesicles containing mtCl channels were fused into BLM and the single chloride channel currents were measured at 250/50 mmol/l KCl cis/trans solutions. Measurements of parameters such as conductance, Cl[−]/K⁺ selectivity, voltage or pH dependence as well as their modulation by endogenous and exogenous compounds (ATP, Mg²⁺, H₂S) using