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

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SEL.3

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 b0 of complex III. Molecular dynamics showed that there are two stable conformations of SkQ1 with the quinol residue localized near peroxyl radicals at C3 or C12 of the cardiolipine 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 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, retinopa-thies, 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.

References

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W.2

Single channel properties and modulation of intracellular chloride channels
Karol Ondrias1, Zuzana Tomaskova1, Viera Kominkova1,
Adam Szewczyk2, Lubica Malekova1
1Institute of Molecular Physiology and Genetics SAV, Laboratory of Intracellular Ion Channels, Slovak Republic
2Nencki 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 KCi 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

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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

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