



Mini Review

# Mild depolarization of the inner mitochondrial membrane is a crucial component of the mechano-chemiosmotic mechanism of coupling

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The human body receives the main energy in the form of ATP (about 50 kg per day), mainly by oxidative phosphorylation in the mitochondria, and a small part from glycolysis. It has been recognized a long ago that several major human diseases (2 type diabetes, cancer, heart diseases, etc.), and aging are associated with mitochondrial dysfunction. Mitochondrial dysfunction causes a dramatic fall of ATP production and an increase in ROS production. A recent interesting study from Vysokikh, et al. [1] demonstrates that, a moderate decrease in mitochondrial membrane potential, coupled with the respiratory synthesis of ATP consumed by mitochondria-bound hexokinase and creatine kinase (mild depolarization), prevents mitochondrial reactive oxygen species (mROS) generation. The antioxidant mechanism based on the mild depolarization of mitochondria, resulting in the inhibition of mROS generation, is present in the majority of the main tissues of mammals. Aging arrests depolarization in short-lived mice but not in long-lived naked mole rats (NMRs) and bats. These experimental data and conclusions fully prove one of the points of our mechano-chemiosmotic mechanism [2-6], which unfortunately, do not known to authors. In article [2] was noted: "We believe that in the presence of oxidative substrate, phosphate ions, ADP, and other essential ions for the formation of ATP, in energization of mitochondria, we will

observe (<https://www.youtube.com/watch?v=CeZxSyeDBwk>) the following processes in the sequence:

Polarization of inner membrane → movement of potassium ions to the matrix, and calcium ions to the intermembrane space → swelling of the mitochondrial matrix → shrinkage of intracrystal space → reduction of Cyt  $c_1$  → depolarization of the inner membrane → movement of calcium ions into the matrix, and potassium ions to the intermembrane space → contraction of the mitochondrial matrix → ATP synthesis → swelling of intracrystal space → oxidation of Cyt  $c_1$  → release of protons into the external medium (cytosol) → a repeat of the cycle."

The authors give much value to dependence, suggesting that the mitochondrial mild depolarization is a crucial component of the mitochondrial anti-aging system [1]. This mild depolarization model requires correct usage of concepts. The mild depolarization of mitochondria observed by the authors in their experiments shows integral picture of the membrane potential changes (a mild polarization-depolarization) of many mitochondria determined in a mitochondrial suspension. In the single mitochondria must be observed a cyclic mild polarization-depolarization. As we noted [2] cyclic polarization – depolarization serves for the functioning of ATP synthase. The authors describe the



molecular mechanism of mild depolarization [1] in details how a decrease in  $\Delta\psi$  occurs during the  $\text{ATP}^{4-}/\text{ADP}^{3-}$  antiport, only with respect to ADP precisely, but it was not taken into account that other agents, for example, calcium ions, can also cause depolarization. Therefore, such an explanation cannot be complete, but is only private without taking into account the physiological conditions in the cell. The authors assume that the slow, permanent attenuation of mild depolarization in mice represents a result of the operation of the aging program, an effect that increases mROS production by the respiratory chain. Similar to mild depolarization,  $\text{SkQ}_x$  decreases the ROS level specifically in the mitochondria. They note that unfortunately, the molecular details of mROS generation remain obscure. At the same time, other authors together with Skulachev V.P. showed that ROS causes a reduction of cristae resulting in formation of cristae-free regions inside mitochondria and a mitochondrial antioxidant  $\text{SkQ}_x$  prevents development of age-dependent destructive changes of mitochondria [7]. As authors noted in ref.1, superoxide production by the respiratory chain is assumed to be catalyzed mainly by Complex I. Although the formation of mROS in the Complex III is also discussed in the literature [8]. In any case, the formation of mROS must occur in the sites of ETC up to, including the  $\text{bc}_1$  complex as follows below. Taken together, from our point of view, the mild depolarization of the inner mitochondrial membrane is a crucial component of the mechano-chemiosmotic mechanism of coupling ATP synthesis to electron transfer and cyclic low-amplitude swelling-shrinkage of mitochondria [2-6]. Also, the mild depolarization is not a cause, but a concomitant factor in reducing ROS formation and aging. Moreover, unlike the suggestion of the authors in ref. 1, we assume that a mROS formation and aging are dependent on the cyclic low-amplitude swelling-shrinkage of mitochondria. According to the mechano-chemiosmotic mechanism an asymmetric contact of dimers of opposite  $\text{cyt } \text{bc}_1$  complexes is formed in the intracristal space during shrinkage of organelles, which is a mechanical regulator of electron transfer from the [2Fe-2S] cluster to heme  $\text{c}_1$ . It should be noted that mROS is formed when the mitochondria are in a swollen state, and the amount of ROS depends on the time during which the mitochondria are in the swollen state. It is known that for up to 4 days of hypoxia, the cristae of plant mitochondria become parallel packing, and during hypoxia on the fifth to seventh day after coronary artery ligation in the muscle fibers of the myocardium, it revealed a large number of mitochondria with densely packed cristae. However, in the further continuation of hypoxia, on the contrary, mitochondria swell. Obviously, hypoxia is of double nature, depending on its extent, length, and timing. In the accordance with this a formation of ROS was experimentally demonstrated in hypoxia [9], while episodic hypoxia mounts defense against cellular stress and apoptosis, decreasing mROS [10]. Thus, the change in the structure of the inner membrane of mitochondria, causing a swelling-shrinkage of the intracristal space, regulates an electron transfer, ROS production, and ATP synthesis in mitochondria. In turn, the cyclic low-amplitude swelling-shrinkage depends on the amount of water in the cell. It is known that in the cells of old organisms there is less water than young organisms. Thus, the hyperosmotic conditions caused by water deficiency in the cytosol of old organisms increase the time of cyclic swelling-shrinkage of mitochondria,

which is the reason for the delay in electron transfer to the ETC and increasing the mROS amount. An excess amount of mROS is also formed during hyperpolarization in highly swollen mitochondria. Restoring the functional activity of mitochondria by intake of sufficient water, positively charged amino acids (Arg and Lys), and regular physical activity leads to a decrease in the formation of mROS, which is the most effective physiological antioxidant acting precisely on the cause of the mROS formation and for the prevention of ischemic and other diseases [3-6]. There are data supporting the idea that exercise may protect against aging and may also positively affect telomeres by promoting telomerase recruitment at telomeres of somatic stem cells that express the enzyme [11]. It should be noted that unlike the empirical recommendations of doctors at present only the mechano-chemiosmotic mechanism scientifically substantiates the importance of the role of physical exercises and the need to drink regularly clean water for healthy longevity, taking into account structural changes in mitochondria and the energy production. Despite the fact that we created the mechano-chemiosmotic mechanism on the basis of numerous literature data for a long period and our own results, direct evidence of some provisions of this mechanism on single mitochondria and other structures of mitochondria is required. Unfortunately, in the first publications of the mechano-chemiosmotic mechanism, we ignored the role of the calcium uniporter in the movement of calcium ions between the matrix and the intracristal space, as well as the role of alternative oxidase in mitochondria, which performs an important function in the regulation of mROS formation [6]. According to recently published data [12], the mitochondrial calcium uniporter interacts with the subunit  $c$  of the ATP synthase, therefore, the movement of calcium ions in different directions through the  $c$ -ring and the calcium uniporter occurs in concert.

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