ISSN 0006-2979, Biochemistry (Moscow), 2023, Vol. 88, No. 10, pp. 1596-1607 © Pleiades Publishing, Ltd., 2023.
Published in Russian in Biokhimiya, 2023, Vol. 88, No. 10, pp. 1926-1939.

REVIEW

Mitochondrial Network: Electric Cable and More

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Received July 12, 2023
Revised September 20, 2023
Accepted September 22, 2023

Abstract—Mitochondria in a cell can unite and organize complex, extended structures that occupy the entire cellular volume, providing an equal supply with energy in the form of ATP synthesized in mitochondria. In accordance with the chemiosmotic concept, the oxidation energy of respiratory substrates is largely stored in the form of an electrical potential difference on the inner membrane of mitochondria. The theory of the functioning of extended mitochondrial structures as intracellular electrical wires suggests that mitochondria provide the fastest delivery of electrical energy through the cellular volume, followed by the use of this energy for the synthesis of ATP, thereby accelerating the process of ATP delivery compared to the rather slow diffusion of ATP in the cell. This analytical review gives the history of the cable theory, lists unsolved critical problems, describes the restructuring of the mitochondrial network and the role of oxidative stress in this process. In addition to the already proven functioning of extended mitochondrial structures as electrical cables, a number of additional functions are proposed, in particular, the hypothesis is put forth that mitochondrial networks maintain the redox potential in the cellular volume, which may vary depending on the physiological state, as a result of changes in the three-dimensional organization of the mitochondrial network (fragmentation/fission–fusion). A number of pathologies accompanied by a violation of the redox status and the participation of mitochondria in them are considered.

DOI: 10.1134/S0006297923100140

Keywords: mitochondria, reticulum, network, electricity, membrane potential, fragmentation, fission, cardiomyocytes, spermatozoa, oxidative stress, redox, preeclampsia, fetal growth retardation

MITCHELL'S CHEMIOSMOTIC CONCEPT. RESOLVED AND UNRESOLVED ISSUES

Historically, in the sixties of the twentieth century, there was a transition from a purely chemical concept of oxidative phosphorylation to a chemiosmotic one, providing spatial separation and functional coupling of oxidation processes (which creates a protonmotive force) and usage of this force for the phosphorylation of ADP, and this concept became dominant in bioenergetics [1-3]. However, it should be noted that there are still disputes on accuracy of terminology and on principles of coupling. In the first case, it is not very clear how much the term "osmotics" is relevant to this concept, because there were no osmotic rearrangements in the entire proton cycle. The author of this concept himself (P. Mitchell) interpreted "osmotics" in terms of the existence of topologically closed membranes, called coupling membranes, which represent an osmotic barrier for substances in general and for protons in particular, and within which proton transport systems exist that carry out osmotic stabilization and enable the transport of metabolites [4]. The recent discovery of the K^+ transport cycle in the mitochondrial membrane, which also drives ATP synthesis [5-9], is more consistent with the name of the chemiosmotic concept due to the fact that the transport of potassium ions due to its high solvating properties (unlike proton) can significantly change the osmotic

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properties of the media on both sides of the coupling membrane, which will inevitably be accompanied by a not always compensated transport of water to one or another volume.

The second, not commonly recognized part of Mitchell's concept was the postulate that the coupling of oxidation and phosphorylation is carried out due to the primary transfer of a proton from one aqueous phase washing the coupling membrane to the aqueous phase on the other side of the membrane, followed by the transfer of a proton from the second phase to the initial one, while carrying out the chemical synthesis of ATP in ATP synthase localized in membrane [10-13]. This part included the concept of a delocalized proton, in contrast to the concept of coupling due to a localized proton which is also transported through the membrane without its release into the bulk aqueous phase [14, 15]. Among these two elements of the chemiosmotic concept, which can be subjected to some criticism, there is one point that remains unshakable and fundamental in this concept – it is the postulation and proof of the generation of electric potential in coupling membranes [16]. Of the known set of coupling membranes, which includes the cell membranes of some aerobic bacteria, the membranes of chromatophores of photosynthetic bacteria, the thylakoid membranes of chloroplasts and the inner membranes of mitochondria, only the coupling membranes of mitochondria will be discussed in this review. In the latter, as a result of the operation of proton pumps of complexes I, III and IV, an asymmetric distribution of protons is achieved on both sides of the inner membrane with a resultant increase in their concentration in the intermembrane space, which corresponds to the cytosolic side. As a result, it would be more correct to consider Mitchell's primary concept chemio-electric, and only taking into account the recent discovery of potassium energetics – electro-chemio-osmotic. However, the great value of Mitchell's discovery as a fundamental theory that allows us to attribute the function of cellular electric power plants to mitochondria stays beyond doubt.

THE POSSIBILITY OF ELECTRICITY TRANSPORT ALONG BIOLOGICAL MEMBRANES. STRUCTURAL BACKGROUND

In 1971, V. P. Skulachev in one of his fundamental works [17] postulated the possibility of intracellular energy transport in the form of a membrane potential. He wrote: "The system of intracellular (and mitochondrial) membranes and cristae may hinder energy transfer by such a hydrophilic energy carrier as ATP. The problem would be simplified if energy could be transmitted along the membrane in the form of an electric field. In this way, it would be possible, for example, to unite in the common system thousands of energy-producing individual enzyme complexes, which fitted into spatially distant areas of the mitochondrial membrane."

One of the strongest confirmations of Skulachev's postulate was the discovery of the mitochondrial network in the striated muscle of the diaphragm [18] and the results of studies of its development in ontogenesis [19]. It was a fundamental work that broke the existing paradigm of traditional two-dimensional thinking at that time, based on the analysis of single electron microscopic sections. The method of reconstruction of intracellular volume from a series of consecutive tissue sections was used in the study, which allowed to establish the three-dimensional organization of mitochondria. The revealed complex structure formed by these was called the mitochondrial reticulum. Thus, these works were to some extent the structural basis for confirming the hypothesis of the functioning of mitochondria as an electric cable.

VISUALIZATION OF MITOCHONDRIA BY PENETRATING FLUORESCENT AGENTS

A little later, a method for visualizing mitochondria in a cell using selective accumulation of a positively charged fluorescent probe (rhodamine 123, which is a methyl ester of unsubstituted rhodamine [20]) was introduced into practice. This discovery should also be recognized as revolutionary, because before that, mitochondria in the cell were visualized almost exclusively using transmission light microscopy [21]. The earliest, although not very sensitive, way of visualizing mitochondria in a cell was the very rarely used method of staining by Janus Green B [22], based on the reduction of the dye by processes of mitochondrial activity. To visualize mitochondria, it was necessary to use a dye in high concentrations, since detection was based on a change in the optical absorption of the dye. The use of fluorescent dyes carrying a delocalized positive charge in the molecule allowed the dye to accumulate in the matrix of mitochondria in many thousands of times of its concentration in the cytoplasm of the cell. As a result, mitochondria could be visualized in the cell using low concentrations, while the selectivity of staining was very high. Almost simultaneously with rhodamine 123, ethyl ester of unsubstituted rhodamine was used to stain structures carrying the membrane potential, which is the driving force for accumulation of fluorescent dye in mitochondria [23]. The simplicity of the procedure for selective staining of mitochondria in a cell and the development of fluorescence microscopy allowed this approach to be quickly extended to determine the structure of the chondriome in different cells.

VOLATILITY OF THE MITOCHONDRIAL RETICULUM

Five years after the introduction of rhodamine dyes for the visualization of mitochondria, the volatility of the organization of the mitochondrial reticulum was demonstrated for the first time. The first agent causing the rapid transformation of the mitochondrial filament into a series of rounded fragments (the phenomenon was then called mitochondrial fragmentation, which corresponds to the later name of mitochondrial fission) was benzodiazepine diazepam, which was mitochondrially toxic, potentially causing oxidative stress [24]. Later, many classical mitochondrial drugs were placed in the category of initiators of mitochondrial fragmentation (rotenone, antimycin A, cyanide, oligomycin, dicyclohexylcarboxyamide, etc. [25, 26]). The nature of the high volatility of mitochondrial filaments, being directly dependent on oxidative stress, became clear [27-30]. An example of mitochondrial fragmentation caused by rotenone, an inhibitor of mitochondrial complex I, is shown in Fig. 1.

The phenomenon of mitochondria fragmentation (their fission) has become the subject of research for many scientific groups, and this research continues, as a result of which a whole set of proteins involved in this process has been identified (e.g., see review [31]). However, no one has yet analyzed the minimum size of the mitochondrial fragment and its composition. This seemingly simple question is not too trivial related to the problem of heterogeneity of the mitochondrial population and their asymmetric division [32-34], as a result of which the fragmentation products formed may differ greatly in composition and subsequent fate. On the other hand, the question remains: do all mitochondrial fragments have mitochondrial DNA in their interior in order to ensure at least a small degree of relative autonomy? However, the last question may not be too fundamental, given that when oxidative stress is eliminated, the reverse process of fragmentation is observed, when mitochondrial fragments can begin to fuse. However, the question of how different or identical the fragments should be in composition in order to fuse remains open.

ORGANIZATION OF THE MITOCHONDRIAL RETICULUM

The mitochondrial reticulum can be organized in two ways. One system is formed in such a way that the mitochondrial matrix is uniform and forms a continuum throughout the mitochondria, even under conditions of their branching. An example of such an organization is the giant mitochondrial reticulum in normal fibroblasts (Fig. 2), mammalian astroglial cells, *Saccharomyces cerevisiae* cells [35], *Xenopus* egg [36], and insect spermatids forming the so-called nebenkern [37]. According to the second scenario, the mitochondrial reticulum is organized by separate small mitochondrial units, each with its own matrix isolated from each other, united by the dense contacts with each other. The oldest, but not very well-known example is the mitochondria in several spermatozoa [38-41], in particular of mammals, where individual mitochondria, connecting to each other with the help of a certain "cement", thus forming the midpiece of the sperm, organized by these mitochondria by helix with a different number of spiral units depending on the type of animal. Among the diverse terminology describing intermitochondrial formations in spermatids, the term nuage is often found, which has a wider

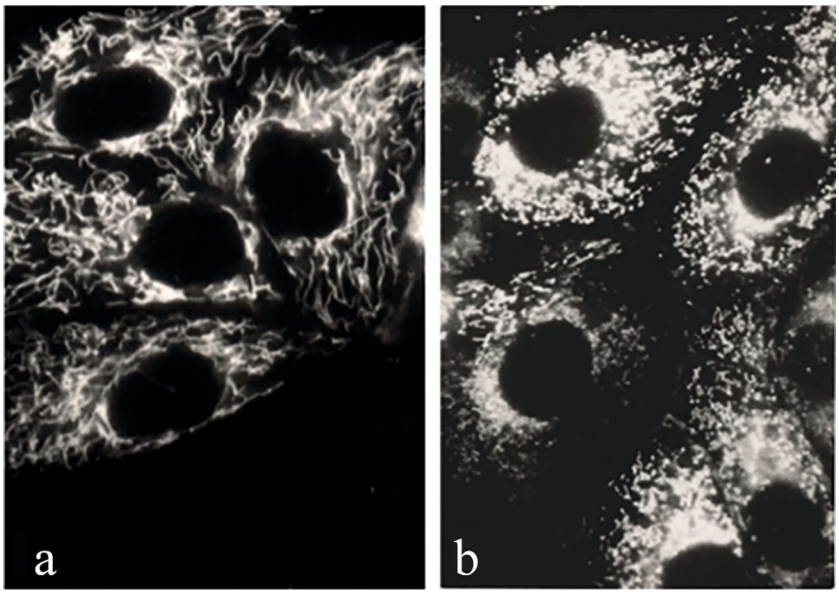

Fig. 1. Fragmentation of mitochondria in embryonal porcine kidney cell culture. a) Control cells; b) after treatment with rotenone (1 μM, 24 h).

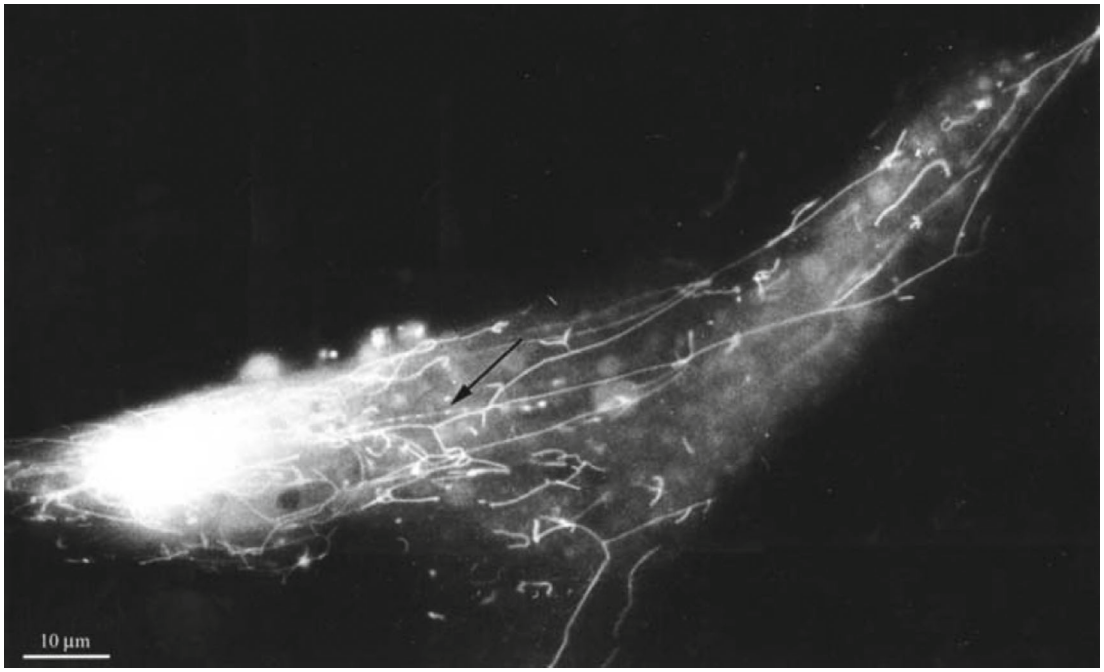

Fig. 2. Mitochondrial network in human skin fibroblasts (stained with ethylrodamine). The arrow points to a fragmented mitochondrial filament.

application for describing intracellular structures [40] (also see the review [41]). Almost 50 years ago, "intermembrane junctions" were described in detail in skeletal muscle in the form of an electron-dense material connecting neighboring mitochondria within one cell (the so-called four-membrane junctions, that is, covering the space between the inner membranes of two mitochondria, including both outer membranes). At the same time, 6-membrane junctions of the same type were described for the so-called nexus zone, where a contact is formed between mitochondria, which also includes two plasma membranes of neighboring cells [18, 19, 42]. The organization of the mitochondrial reticulum in ontogenesis was considered in detail [19].

Almost half a century later, the same type of research was reproduced [43, 44], but the novelty of these later works was limited only by a more sophisticated methodological base, the use of new terms "connectome" and "interactome" and the correlation of the structural organization of the mitochondrial tree with muscle activity. The latter is an important point, because it assumes the appropriate organization of the mitochondrial reticulum in the skeletal musculature [45], which in a best way corresponds to the energy needs of the muscle cell. It should be noted that the problem of matching energy needs and the delivery of components and energy production in the cell (energy supply-demand problem) is one of the key elements of the occurrence of cardiac, brain and other cellular and organ pathologies that occur when this match is violated, and mitochondrial organization and communication play a fundamental role in these processes [45].

No doubt that the structural interaction of mitochondria with each other and with other cellular elements is only one part of intracellular communication. Basically, this communication is realized through the exchange of chemical signaling molecules that can be hidden in membrane vesicles generated by various cell elements, including mitochondria [46-49].

Ultimately, the hypothesis of the functioning of extended mitochondrial structures as electrical energy-transmitting cables consisted in an adequate and uniform supply of all cell components with electrical energy that can be transformed into chemical energy of the ATP.

PROOF OF THE FUNCTIONING OF EXTENDED MITOCHONDRIAL SYSTEMS AS ELECTRICAL CABLES

Only three years have passed since the discovery of the fragmentation of the mitochondrial reticulum, when experimental evidence of the functioning of the mitochondria as an electrical cable was carried out [50]. As an object, normal skin human fibroblasts were used, in which mitochondria normally form a single network of very long single or branched filaments hundreds of microns long. Since fluorescent penetrating dyes such as rhodamine 123 or ethylrodamine can detect only energized mitochondria (which have a membrane potential that allows the dye to accumulate theoretically up to 10,000-fold concentrations in the mitochondrial matrix compared to extracellular content), a change

in the membrane potential along the entire length of the extended mitochondria after a local lesion of the mitochondrial filament was noted. The lesion was carried out using a focused laser beam, while the size of its spot was comparable to the thickness of the mitochondrial filament and was a fraction of a micron. The experimental result confirmed the hypothesis of the equipotential nature of the mitochondrial filament, since a local collapse of the mitochondrial membrane caused complete de-energization of the entire extended mitochondrion, manifested in the loss of fluorescence of the mitochondrial dye along its entire length [50]. Later, similar experiments were carried out with neonatal cardiomyocytes, whose mitochondria are also organized in the form of a branched tree. But unlike fibroblasts, where the mitochondrial matrix is continuous and extends over the entire length without breaks, the entire mitochondrial reticulum in this case is organized by separate mitochondrial units united by means of intermitochondrial junctions. As a result, the mitochondrial network of neonatal cardiomyocytes has many unconnected mitochondrial matrixes. In this case, with a local lesion of one element of the mitochondrial network, a part of the general network was deenergized. This meant that structurally and functionally, in a neonatal cardiomyocyte, mitochondria in a single cell are organized as separate equipotential clusters, also consisting of separate mitochondria united by intermembrane junctions [51]. The complete electrical short circuit observed under the deenergization of a separate cluster meant that the intermitochondrial junctions are electrically permeable, providing communication of neighboring mitochondrial matrixes presumably due to the presence of ion channels in the inner and outer membranes of the contacting mitochondria. Moreover, the architecture of the cristae in the intermitochondrial junctions was interesting – they were located clearly perpendicular to the plane of the contact zone, which probably facilitated the propagation of the membrane potential through the mitochondrial network [52].

Later, it was found that in the intermitochondrial junctions of cardiomyocytes, which are represented by an osmiophilic substance on electron microscopic images, a pore protein of the outer membranes, a voltage-dependent anion channel, is abundantly present [53], which could be considered as a structural confirmation of ion-channel communication between mitochondria in the junctional zone.

Subsequently, using the same approaches, an electrical connection was demonstrated between the mitochondria of the sperm [54] and trichome cells [55]. This also suggested the presence of ion channels in the contact zone of the mitochondria of spermatozoa (which, as we have already indicated above, were visualized as electron dense formations, which served as the basis for their name “mitochondrial cement” [40, 41]).

More than 25 years after the establishing and proof of the existence of mitochondria as an electric cable, a work from the laboratory of Robert Balaban was published in *Nature*, exactly reproducing the already described idea, principle and methodological nature of the organization and functioning of the mitochondrial reticulum in cardiomyocytes [56], with the only difference that a more modern methodological base was used. Later, in a number of other publications (e.g., see [57]) from the same laboratory, for unknown reasons, unambiguously interpreted experiments performed in Moscow were questioned (read ...However, there are contradictory reports of the functional connectivity of the cardiac mitochondrial reticulum [57]...), however with subsequent proof of the correctness of early ideas and proofs.

In addition to the examples of ignoring the primary source of the cable theory of extended coupling membranes, including the inner membranes of mitochondria, the foundations of the cable theory of the functioning of the mitochondrial reticulum have been criticized to some extent, which requires special consideration [58]. On a very good methodological basis, it has been shown that cristae within the same mitochondria can have different transmembrane potential. The authors of this study themselves clearly understood some discrepancy between their data and the cable theory and offered a reasonable explanation, the basics of which we discussed earlier (see Fig. 3 in [59]), when they cited both old and modern data on the structure and organization of cristae [60, 61]. These data can be conditionally presented as evidence of the presence of submitochondrial particles inside the mitochondria that have or do not have electrical contact with the inner mitochondrial membrane, which undermines the old ideas that mitochondrial cristae form a continuum with the inner membrane. Based on this understanding of the structure of mitochondria, the cristae may represent separate organizations of coupling membranes that do not always have an electric connection with the inner membrane, and they may have different transmembrane potential. At the same time, the inner membrane of the mitochondria is a continuous and equipotential structure, and it is the material basis of the mitochondrial electrical cable theory.

However, one more scenario cannot be excluded, which, without a critical assessment of the methodological features of the data obtained [62], can be interpreted as the absence of cable properties of extended mitochondria. This concerns experiments to assess the energization of mitochondria using the JC-1 dye, the fluorescence of which depends on the concentration of the probe. At high concentrations of JC-1 corresponding to its concentration in the matrix of highly energized mitochondria, so-called J-aggregates, when excited, emit light in the red region, while in low-potential mitochondria, where the probe concentration is not so high, J-aggregates are not formed, and when excited, light is

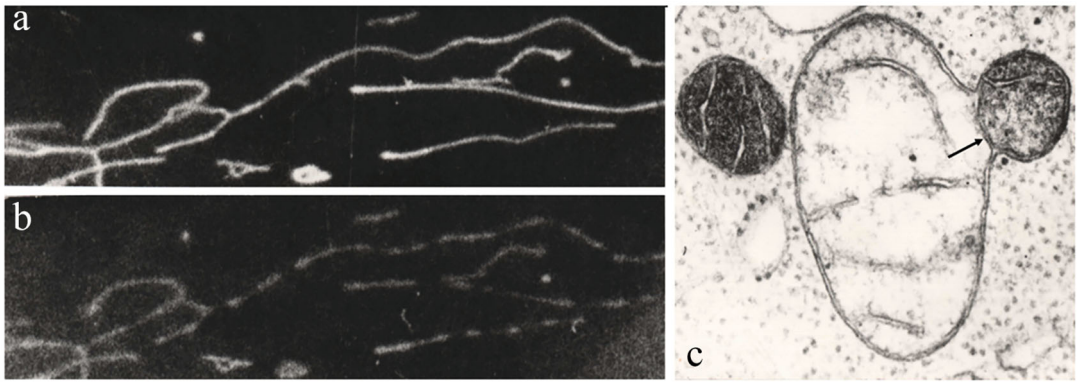

Fig. 3. Fragmentation of mitochondria in cells. Staining with ethylrodamine. a) Normal human fibroblast. b) The same cell after 10 s of exposure to excitation light. c) Electron microscopy of mitochondria in an embryonic porcine kidney cell exposed to rotenone (1 μM, 24 h). The presence of separate morphological compartments divided by septa (indicated by an arrow) can be seen.

emitted in the green region of the spectrum. So, when using conventional fluorescence microscopy, it was noticed that along one mitochondrial filament, it was possible to observe the alternation of regions with red and green fluorescence, which could be interpreted as the absence of equipotency along the length of the filament and a certain alternation of low- and high-potential compartments along the length of a single mitochondrial filament [62].

There are two issues to consider when using and interpreting fluorescent signals from JC-1. Firstly, this agent is sufficiently lipophilic and will be distributed not only in accordance with the values of the membrane potential on the inner mitochondrial membrane, but also in accordance with the lipophilic environment in the mitochondria, which may not be the same throughout the entire volume of mitochondria. But the main thing is that this "multicoloration" of a single mitochondrion in a cell does not appear immediately, but in the process of observation, which may be the result of a photodynamic effect, leading first to the formation of septa inside mitochondrion dividing one extended mitochondrion into a number of electrically isolated compartments (Fig. 3) with subsequent fragmentation of the mitochondrial filament.

This process of septa formation can occur within seconds when irradiated with sufficiently strong light that excites the dye. Electron microscopic data confirm that during the initiation of fragmentation of the mitochondrial reticulum, the septa can divide the mitochondria into compartments of different configurations corresponding to different degrees of energization (Fig. 3b, as well as Fig. 6b in [29]).

There were significantly fewer critics of the electric cable theory of mitochondria than those who supported this concept. A very important work supporting the basic principles of the cable theory was the solution of the question of how continuous the matrix is throughout the entire space of the mitochondrial tree. In one of the studies, a photoactivated green fluorescent protein located exclusively in the mitochondrial matrix was used to tag individual mitochondrial networks in a cell in combination with real-time monitoring of the mitochondrial membrane potential [63]. At the same time, matrix continuity was found within a single equipotential mitochondrial cluster. The invariable equipotentiality of individual mitochondrial networks suggested that the heterogeneous nature of the membrane potential in the mitochondria of the cell reflects the differences between individual networks.

Other researchers also came to the same conclusion about the continuity of the matrix within one unsepted mitochondria (a single electrical cable) and the impossibility of functional communication of the matrixes of neighboring mitochondria. The obtained data served as a structural and functional basis for understanding the morphological and functional heterogeneity of mitochondria in the cell [64, 65].

Concluding this section, we can say with sufficient confidence that the functioning of the mitochondria as an electrical cable is proven. However, it is likely that mitochondrial networks may carry other hypothetical functions, which we will discuss.

OTHER HYPOTHETICAL FUNCTIONS OF EXTENDED MITOCHONDRIAL STRUCTURES

Ensuring uniform distribution of redox potential throughout the cell volume. Considering a single, but united, matrix-continuous mitochondrial network, throughout which $\Delta\psi$ is the same (the entire network is equipotential), and the membrane potential itself reflects the work of proton pumps driven by the oxidation of reduced equivalents, primarily NAD(P)H, it must be taken into account that the membrane potential in steady state conditions should be in thermodynamic equilibrium with the redox potential created by

the pair NAD(P)H/NAD(P). In turn, this pair is in equilibrium with the reduced glutathione/oxidized glutathione (GSH/GSSG) pair, while both are the main redox buffer systems in the cell [66].

Thus, due to the equipotential nature of the mitochondrial network, ideally covering the entire thickness of the cell, this network provides a uniform distribution of the redox potential over this volume, being in some way a "stirrer", not allowing the creation of large local areas with different redox potential. The situation may change dramatically under conditions of forced fragmentation/fission of the mitochondrial network, when each mitochondrial fragment will create a redox environment around itself in accordance with the magnitude of the membrane potential on the inner membrane of this fragment. Considering that fragmentation is associated with the presence of oxidative stress, which leads to an increase in the heterogeneity of mitochondria by membrane potential [29, 34], the heterogeneity of the redox potential distribution in the cell after mitochondrial fragmentation is quite expected.

Oxygen pipeline. It is known that the solubility of oxygen in lipid membranes and their hydrophobic components is higher than in the aqueous phase, as a result of which the oxygen concentration in mitochondrial membranes is higher than the cytosol. Even though it is in the inner membrane of the mitochondria the main oxygen consumer (cytochrome oxidase) is localized, membranes can still be considered as oxygen buffers that help facilitate the diffusion of O_2 along the mitochondrion. This will to some extent ensure the balancing of the oxygen distribution over the cell volume and prevent the creation of local hypoxic regions (of course, this will greatly depend on the activity of mitochondrial respiration, which determines the diameter of the so-called Krogh cylinder (the volume distribution of oxygen in the tissue around the capillaries carrying oxygen, depending on the rate of oxygen supply and usage [67]).

Proton pipeline. In the case of equivalence not only of the membrane potential along the entire length of the mitochondria, but also of the entire electrochemical potential of hydrogen ions ($\Delta\mu H^+$) [which includes not only the values of the membrane potential, but also the gradient of hydrogen ions (ΔpH)], the value of ΔpH will also be the same along its entire length. With the same pH values in the matrix, this will lead to the fact that the environment of the giant mitochondrion will have the same pH values, even without taking into account the possibility of accelerated proton conduction through the membranes by the Grothgus mechanism [68] for ordered water molecules in the near membrane layers [69]. Thus, as in the case of the supposed "stirring" of the redox potential, the giant mitochondria will "stir" the pH along the entire length of its environment.

Balancing intracellular concentrations of potassium ions. Given the recently discovered mitochondrial potassium energetics [6-8], driven by the transmembrane potential, we can expect a uniform distribution of potassium ions throughout the intracellular volume in the environment of giant mitochondrion.

Thus, in many ways, the mitochondrial network can serve as a structure that enables uniform distribution of different components throughout the cell and serve as a kind of "stirrer" in the cell.

MEDICAL ASPECTS

In the above material, we focused on the problems of adequate supply of the living system with the necessary material for the normal course of metabolism, in particular energy metabolism, whether it is a cell, organ, or organism. Full compliance of a supply-demand mechanism existing in a living cell defines the concept of homeostasis, and deviations in any direction can be fraught with the emergence of a pathological phenotype. These deviations can be caused by physical and chemical effects on the system, and one of these factors is the effect accompanied by the occurrence of oxidative stress. The pathogenesis of oxidative stress is too obvious, and giving examples of this kind takes up most of the scientific literature. We can only briefly touch those medical problems that make up a small fraction of the vast number of widely discussed neurological or cardiological aspects, leaving aside the problems of obstetrics and neonatology, although the problem of maintaining redox homeostasis in cells there is no less important.

From our logical assumption that the mitochondrial network can serve to provide the equilibrium of the redox potential in the cell, it follows that oxidative stress as the cause or effect of internal disorders and subsequent changes in the network structure lead the intracellular contents away from the equilibrium state, which inevitably leads to a change in intracellular metabolic homeostasis. This embraces a huge number of pathologies, and we will only take as an example the general problems of obstetrics, gynecology, and neonatology, which make up the leading part of morbidity and child and adult mortality. Special attention should be paid to oxidative stress accompanying various pathologies that are the subject of these branches of medicine [70, 71], in particular, such as preeclampsia, defined as hypertension and proteinuria that occurred after 20 weeks of gestation and fetal growth retardation [72, 73]. One of the causes of preeclampsia is placental implantation, which leads to remodeling of the mother's arteries and a decrease in blood flow to the fetus. This can cause a sharp susceptibility to fluctuations in the blood flow and, as a consequence, lead to changes in the redox status of both placental and fetal cells, typical for ischemia–reperfusion phenomenon. Reperfusion injury of the placenta is accompanied by the generation of reactive oxygen

and nitrogen species, with the formation of oxidized products carrying signaling and pathogenic properties with a significant increase in their concentrations, which primarily leads to dysfunction of endothelial cells [74, 75]. Thus, these products are risk factors for cardiovascular diseases, which suggests a possible functional relationship between the placenta and the cardiovascular system, and such signaling is based on components that support or violate the redox status of the mother and fetus [76].

It has become clear that it is mitochondria that properly determine the redox status of the biological system and the placenta, in particular [77-80]. As we pointed out earlier, it is the lability of mitochondrial structures and functions that is largely an indicator of the redox status of the cell, and not only. The process of mitochondrial fragmentation, as an almost mandatory response to the resulting oxidative stress, is also mandatory in the mechanism of mitochondrial quality control [29, 33]. The difference between the first and second options is that oxidative stress leads to global fragmentation of the mitochondrial population in a single cell, while in the process of programmed destruction of non-functional mitochondria, fragmentation is local, and it is preceded by internal restructuring of mitochondria, followed by the separation of a fragment of mitochondria with malfunctioning contents from the mitochondrial network (which can maintain its three-dimensional structure), and this is the principle of mitophagy (mitoptosis) [29]. However, in both cases, fragmentation (fission) occurs with the participation of fission proteins (e.g., Drp1 and Fis1), the level of which in the placenta correlates with the severity of the disease of the mother and fetus, including the weight of the latter [81, 82], which indicates a direct relationship of pathology with the mitochondrial structure, which can serve as an indicator of the pathological phenotype of the cell.

The evidence of the involvement of oxidative stress in the pathogenesis and the need to maintain the rare state of the cell and its components, primarily mitochondria, led to the understanding that one of the possibilities of therapeutic intervention is the normalization of the redox status in the cells of the organ. In a recent study using human umbilical vein endothelial cells, it was shown that after exposure them to the blood plasma of pregnant women with preeclampsia, there is a decrease in the mitochondrial functions of these cells associated with increased generation of reactive oxygen species [83]. At the same time, increased expression of TNF-α, TLR-9, and ICAM-1 inflammatory markers was observed in the cells. Mitochondria-targeted antioxidant MitoTempo reduced the production of superoxide by mitochondria in cells exposed to blood plasma of pregnant women with preeclampsia, normalized mitochondrial metabolism and significantly restored the inflammatory profile of cells. These data confirm the functional role of mitochondrial redox signaling in the pathogenesis of preeclampsia and suggest therapeutic pathways aimed at preserving mitochondrial structure and functions.

Contributions. P.A.A., N.V.A., V.A.B., L.D.Z., S.D.Z., I.B.P., V.A.P., D.S.S., E.I.Y., D.N.S., E.Y.P., G.T.S., and D.B.Z. general discussion of the ideology and future plans; D.B.Z. writing the manuscript; D.N.S., E.Y.P., G.T.S., and D.B.Z. management and supervision of the study; P.A.A., N.V.A., V.A.B., L.D.Z., S.D.Z., I.B.P., V.A.P., D.S.S., E.I.Y., D.N.S., E.Y.P., and G.T.S. editing the manuscript.

Funding. This work was supported by the Russian Science Foundation (grant no. 19-14-00173-P).

Ethics declarations. The authors declare no conflict of interest in financial or any other sphere. This article does not contain any studies involving animals or human participants performed by any of the authors.

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