ISSN 2079-0864, Biology Bulletin Reviews, 2021, Vol. 11, No. 2, pp. 134–142. © Pleiades Publishing, Ltd., 2021.
Russian Text © The Author(s), 2020, published in Uspekhi Sovremennoi Biologii, 2020, Vol. 140, No. 5, pp. 433–442.

Cellular ATP Synthase

E. V. Uzlova[a], * and S. M. Zimatkin[a]

[a] *Grodno State Medical University, Grodno, Republic of Belarus*

**e-mail: uzlovaliza@gmail.com*

Received June 2, 2020; revised June 2, 2020; accepted June 7, 2020

Abstract—This review presents a collection and analysis of the currently available data on the structure and organization, localization, working mechanisms, and functions of the enzyme that synthesizes adenosine triphosphate (ATP), ATP synthase. It is universal (present in all prokaryotic and eukaryotic cells) in nature and is unique in its characteristics. The proper assembly and functioning of ATP synthase are the required conditions for the normal process of oxidative phosphorylation, the result of which is energy storage in the form of ATP. A large number of diseases, including neurodegenerative and mitochondrial diseases, are associated with ATP synthase disorders.

Keywords: ATP synthase, mitochondria, prokaryotes, eukaryotes, oxidative phosphorylation

DOI: 10.1134/S2079086421020109

INTRODUCTION

Adenosine triphosphate (ATP) is a universal source of energy in living organisms, and its synthesis is an integral part of a cell's life. The main mode of ATP formation, oxidative phosphorylation (Schapira, 2006), is the result of the joint work of the electron-transport chain (ETC) and mitochondrial ATP synthase. The ETC includes the so-called complexes: I, NADH-dehydrogenase complex; II, succinate dehydrogenase (the only enzyme of the Krebs cycle associated with the mitochondrial membrane, and it serves as a carrier of electrons to ubiquinone); III, cytochrome bc_1; IV, cytochrome *c* oxidase and ATP synthase, which is sometimes considered the V complex of the chain, although it does not participate in the process of electron transfer (Fig. 1). In this case, ATP synthase is of particular interest, since it is the main component in the process of ATP synthesis and plays a key role in the development of neurodegenerative diseases (Kucharczyk et al., 2009).

ATP synthase is an enzyme consisting of protein subunits that represents a "molecular machine" equipped with a unique rotary mechanism (Allegretti et al., 2015; Morales-Rios et al., 2015; Zhou et al., 2015). ATP synthase is a universal enzyme, since it is present in both prokaryotic and eukaryotic cells. There are three groups of ATP synthases: P-, F- and V-type ATPases (Nelson and Taiz, 1989; Nelson, 1992). They differ both in structure and function. It is noteworthy that the F-ATPase passed to eukaryotic organisms as a result of symbiogenesis; therefore, it is found both in prokaryotes and in the two-membrane organelles of eukaryotes (Nelson, 1992).

According to the International Union of Biochemists and Molecular Biologists, the currently accepted name for this enzyme is H^+-transporting two-sector ATPase. The systematic name is ATP phosphohydrolase (H^+-transporting). Other names for this enzyme are ATP synthase, F_1-ATPase, F_oF_1-ATPase, H^+-transport ATPase, mitochondrial ATPase, conjugation factors (F_o, F_1 and CF_1), chloroplast ATPase (cF_ocF_1), bacterial Ca^{2+}/Mg^{2+} ATPase (International Union..., 2020).

Since 1984, ATP synthase has been listed in the classification of enzymes as an enzyme of the third class, hydrolase (code 3.6.1.34). In 2000, it was transferred to grade 7, translocase, but it retained the systematic name ATP phosphohydrolase. In the modern classification, ATP synthase is denoted as 7.1.2.2 (BRENDA..., 2020; International Union..., 2020).

ORGANIZATION OF ATP SYNTHASE OF PROKARYOTIC, YEAST, AND PLANT ORGANISMS

The most modern method to determine the structure and organization of ATP synthases in organisms is cryoelectron microscopy. It allows one to visualize the structure of a multitude of chaotically located macromolecules without their crystallization and to obtain a high-quality 3D image (Milne et al., 2013; Nannenga and Gonen, 2014). At present, the results of cryoelectron microscopy indicate a similar structure of functionally significant parts of ATP synthases in bacteria and all eukaryotes (Davies et al., 2012).

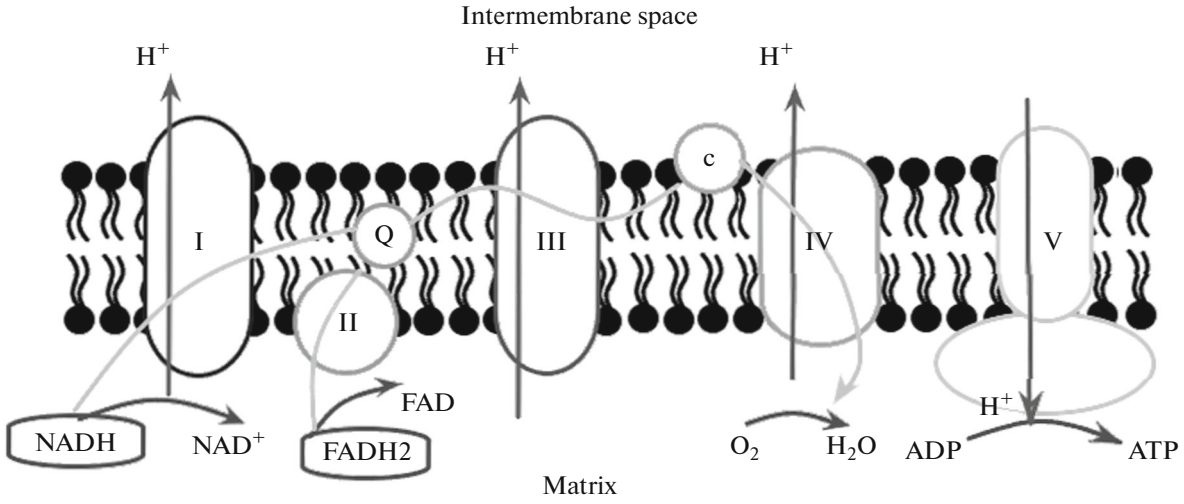

Fig. 1. Location and interaction of ETC complexes in the inner mitochondrial membrane (I–V, ETC complexes; Q, ubiquinone; c, cytochrome *c*).

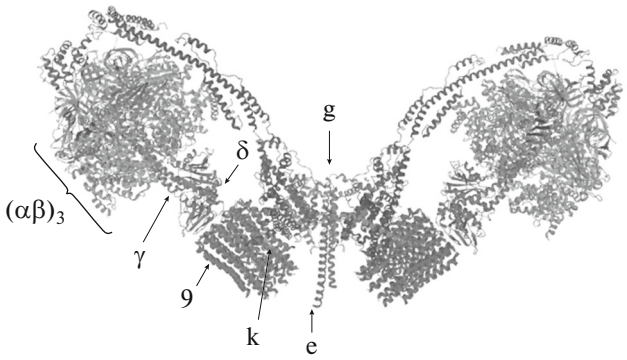

Fig. 2. Structure of ATP synthase of *Saccharomyces cerevisiae* (subunits α, β, γ, 9, k, e, g) (modified according to Berman et al., 2000; Guo et al., 2017).

Prokaryotic bacterial ATP synthase is the simplest structure: it contains eight subunits, five in the F_1 component and three in the F_o component. In Archaea, in addition to ATP synthases of the F_oF_1 type, the A_oA_1-type was found. It structurally resembles the ATP synthases of vesicles of yeast, plants, and animals (Deckers-Hebestreit and Altendorf, 1996; Allegretti et al., 2015).

The best studied eukaryotic ATP synthase is the yeast ATP synthase (*Saccharomyces cerevisiae*) (Fig. 2). The enzyme structures necessary for the performance of its functions can be divided into four conventional structural units: the main catalytic group ($(\alpha\beta)_3$), the central bar (γ, δ, ε), the peripheral rod (4, d, h), and the membrane region (9_{10}, 6, 8, f). The first two structural units belong to the F_1 component, and the last two belong to the F_o component. Oligomycin sensitivity conferring protein (OSCP) connects the peripheral core and the catalytic domain (Davies et al., 2012). Also, in addition to the 13 main subunits, yeast ATP synthase includes four additional subunits, e, g, i, and k (Rubinstein et al., 2003; Lau et al., 2008). Subunits e, g, and k were first discovered in ATP-synthase dimers (Arnold et al., 1998), and it is assumed that the main task of these subunits is the dimerization process (Davies et al., 2012).

Plant chloroplast ATP synthase (cF_1F_O ATPase) has 26 subunits, 17 of which are fully or partially immersed in the membrane. The hydrophilic $(\alpha\beta)_3$ catalytic group of the cF_1 component corresponds to that of other eukaryotes. The cF_o component includes a ring of 14 c subunits; the central core consists of γ and ε subunits, and the periphery consists of b, b', and δ. In addition, three different states are distinguished in chloroplast ATP synthase; the structure of each was determined via cryoelectron microscopy (Hahn et al., 2018). The presence of three different functionally active states of chloroplast ATP synthase is due to three conformational states ε subunits (Richter et al., 2005).

ORGANIZATION OF ATP SYNTHASE OF MAMMALIAN MITOCHODRIA

Mammalian mitochondrial ATP synthase is more complex and very diverse. It has a mushroom-like structure with a channel inside and includes two components: the F_o (or the conjugation factor F_o, where the index "o" stands for oligomycin), which permeates the inner membrane of mitochondria and is hydrophobic, and the F_1 (short for "fraction 1" (part 1), or the conjugation factor F_1), which is located in the matrix and is hydrophilic. Each of these components, in turn, consists of many subunits (Walker and Dickson, 2006; Devenish et al., 2008; Watt et al., 2010).

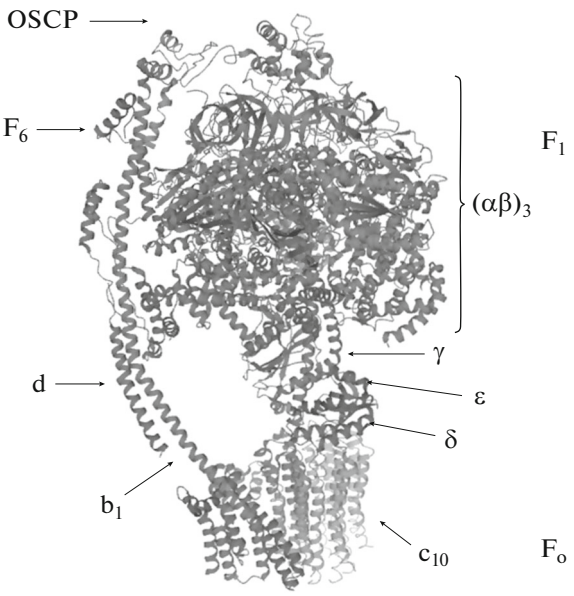

Fig. 3. Structure of the ATP synthase of mitochondria of bovine cardiomyocytes, conformation 1A (OSCP, subunits F_6, d, b_1, c_{10}, α, β, γ, δ, ε) (modified according to Berman et al., 2000; Zhou et al., 2015).

The F_1-component in eukaryotes, the "head" of the mushroom-like structure, consists of nine subunits: three α, three β, and one γ, δ, and ε (Watt et al., 2010). The polypeptide chains α and β are arranged such that they form a spherical hexamer $(\alpha\beta)_3$ with six binding sites (three of which are catalytic and three are non-catalytic) and a cavity (Kagawa et al., 1992; Mohanty et al., 2015; Xu et al., 2015). The subunits γ and ε are located in the hexamer cavity $(\alpha\beta)_3$; γ is positioned and rotated at an angle of 120° to the hexamer, and δ is located on the outside. Together, these three subunits are part of the central rod (Devenish et al., 2008; Xu et al., 2015) (Fig. 3).

The diameter of the F_1 coupling factor reaches 9 nm (Fernández-Morán et al., 1964); therefore, ATP synthase can be seen in an electron microscope on the cristae of the inner mitochondrial membrane and via cryoelectron tomography (Fig. 4) (Blum et al., 2019).

F_1F_o-ATPase isolated from the mitochondria of bovine cardiomyocytes has been well studied. During the rotational cycle, it changes its structure, assuming different conformations. The structure of the conformations has been determined and studied (Zhou et al., 2015).

It is very important that the key components for the assembly of ATP synthase are the γ and δ subunits. The lack of these subunits or their defects are prerequisites for a decrease in the amount of ATP synthase. At the same time, the absence of the γ subunit in lower eukaryotes is not critical; the $(\alpha\beta)_3$ hexamer remains stable and is accompanied by compensatory mutations in the gene encoding the β subunit (Smith and Thorsness, 2005; Pecina et al., 2018). Thus, the results of a series of studies reported the existence of yeast ATP synthase dimers without subunits e and g, which casts doubt on their role in dimerization (Paumard et al., 2002; Gavin et al., 2005; Wittig and Schagger, 2008).

F_o-ATPase is highly variable and, depending on the type of organism, it may contain more or fewer subunits (Meier et al., 2005; Pogoryelov et al., 2009; Vollmar et al., 2009; Jonckheere et al., 2012). F_o consists of a c ring (rotary ring) containing eight copies of the subunit and one copy of each of subunits a and b (Walker and Dickson, 2006; Devenish et al., 2008; Watt et al., 2010). The C ring is linked to the b subunit through the a subunit (Devenish et al., 2008; Xu et al., 2015). In addition to these three main subunits, which are also present in bacteria, eukaryotes also have others: oligomycin-sensitive protein (the protein got its

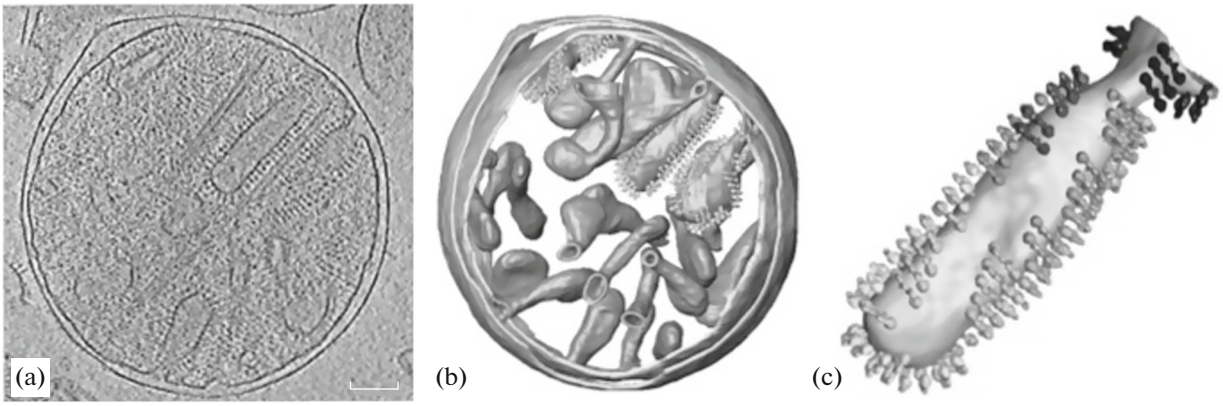

Fig. 4. Location of ATP synthase on the inner mitochondrial membrane of *Polytomella* sp.: (a) cristae of the inner mitochondrial membrane surrounded by ATP synthase dimers; (b) segmented structure showing the location of ATP synthase dimers (dimers are depicted as "spikes" on the inner membrane); (c) mitochondrial crista surrounded and "formed" by dimers. Cryoelectron tomography (modified according to Blum et al., 2019).

name due to the antibiotic oligomycin, the action of which suppresses the action of ATP synthase) (Devenish et al., 2000; Salomon et al., 2001), as well as b, d, F_6, and sometimes f, e, and g. The functions of some of these subunits have not yet been established. It is known that the subunits b, d, f, e, g, and F_6 form the peripheral core of ATP synthase (Walker and Dickson, 2006; Devenish et al., 2008) (Fig. 3).

MECHANISMS OF MITOCHONDRIAL ATP SYNTHASE

ATP synthase uses the energy created by the proton electrochemical gradient to phosphorylate adenosine diphosphate (ADP) to ATP in the F_1 component (Nijtmans et al., 1995; Capaldi and Aggeler, 2002; Zeviani and Di Donato, 2004). The mechanism of its operation is called rotational or rotational catalysis (Boyer, 1975). During a complete turnover of the γ subunit, each catalytic site changes three conformations (Boyer, 1993). In this case, two functional parts can be distinguished in ATP synthase: the moving part, the so-called rotor (c ring, γ, δ, and ε), and the stator (F_6, oligomycin-binding protein, α, β, a, b, and d) (Devenish et al., 2008).

The mechanism of ATP synthase operation is represented as follows: the energy generated by the proton gradient is supplied from the intermembrane space to the matrix through the inner membrane with the F_o component; the proton gradient then creates a proton motion force, which includes the pH difference and the electric-membrane potential (Campanella et al., 2009). The energy released due to this drives two rotary engines connected to each other: the c ring in F_o and the γ, δ, ε subunits in F_1 (Boyer and Kohlbrenner, 1981). It is precisely the rotation γ subunit that provides the energy for ATP synthesis.

A significant contribution to the study of the mechanism of the ATP synthase was made by a group of Japanese scientists who managed to "attach" to F_1-ATP synthase magnetic particles and activate it. Clockwise movement resulted in ATP synthesis in an amount of 5 molecules per second, while counterclockwise movement or no movement led to ATP hydrolysis (Itoh et al., 2004). It is also noteworthy that ATP synthase has an extremely high efficiency, close to 100% (Kinosita et al., 2000).

ATP synthase is also capable of performing the reverse process of rotational catalysis, ATP hydrolysis and the pumping of protons through the inner membrane. In normally functioning mitochondria, ATP synthase works towards ATP synthesis. If the normal course of respiration in mitochondria is at risk, ATP synthase begins to carry out the process of ATP hydrolysis, and, since the breakdown of a large amount of ATP is undesirable, ATP synthase is inhibited by a special protein, the inhibition factor IF_1 (Pullman and Monroy, 1963; Devenish et al., 2008). Its activity depends on the pH level. IF_1 blocks F_1-ATPase activity (van Heeke et al., 1993), binding to two F_1 components, and plays an extremely important role in cell protection during ischemia (Campanella et al., 2008, 2009).

ATP synthase is sometimes unable to perform the function of ATP synthesis; this is what happens in brown adipose tissue. There is a very low level of oxidative phosphorylation in the cells due to the presence of the UCP1 thermogenin protein (Nicholls, 2017), a transmembrane uncoupling protein. Its mechanism of action is to increase the permeability of the inner membrane for protons, which, due to the uncoupling of cellular respiration and oxidative phosphorylation, leads to a significant decrease in the proton gradient and a decrease in ATP synthesis (LaNoue et al., 1986; Crichton et al., 2017).

There is also an important feature of bacterial F_1F_o-ATPase. It is able to "switch" from the transport of hydrogen protons to the transport of sodium ions. This was first discovered in *Propionigenium modestum* (Laubinger and Dimroth, 1988) and later in methanogenic bacteria (Becher and Muller, 1994) and *Acetobacterium woodii* (Reidlinger and Muller, 1994).

In addition to energy supply, ATP synthase is also involved in the formation of the structure of the cristae of the inner mitochondrial membrane (Allen, 1995; Paumard et al., 2002; Davies et al., 2012). This is due to the existence of ATP synthase in the form of V-shaped dimers with an angle of 70°–90° between the dimer fragments that connect in so-called ribbons located along the strongly curved edges of the inner membrane cristae, which "stretch" to hundreds of nanometers (Schagger and Pfeiffer, 2000; Paumard et al., 2002; Minauro-Sanmiguel et al., 2005; Strauss et al., 2008; Davies et al., 2011; Hahn et al., 2016; Blum et al., 2019). At the same time, structurally simple bacterial and plant ATP synthases do not form dimers due to the absence of subunits responsible for dimerization (Lapaille et al., 2010): chloroplast ATP synthase is monomeric (Daum et al., 2010), and no dimers have been reported in bacteria at all. No individual monomeric ATP synthases were found in the cristae of other eukaryotic organisms (yeast, animals) (Blum et al., 2019).

It was proven via electronic cryotomography that ATP synthase dimers form spontaneously and thus "bend" membranes, which is the first step in the formation of the structure of the inner mitochondrial membrane (Fig. 5) (Blum et al., 2019).

The study of the structure of yeast dimers showed that the most important components for the dimerization of ATP synthase are the components e and g. This was confirmed by their removal, which led to disturbances in the processes of dimerization and the formation of cristae of the inner membrane (Hahn et al., 2016).

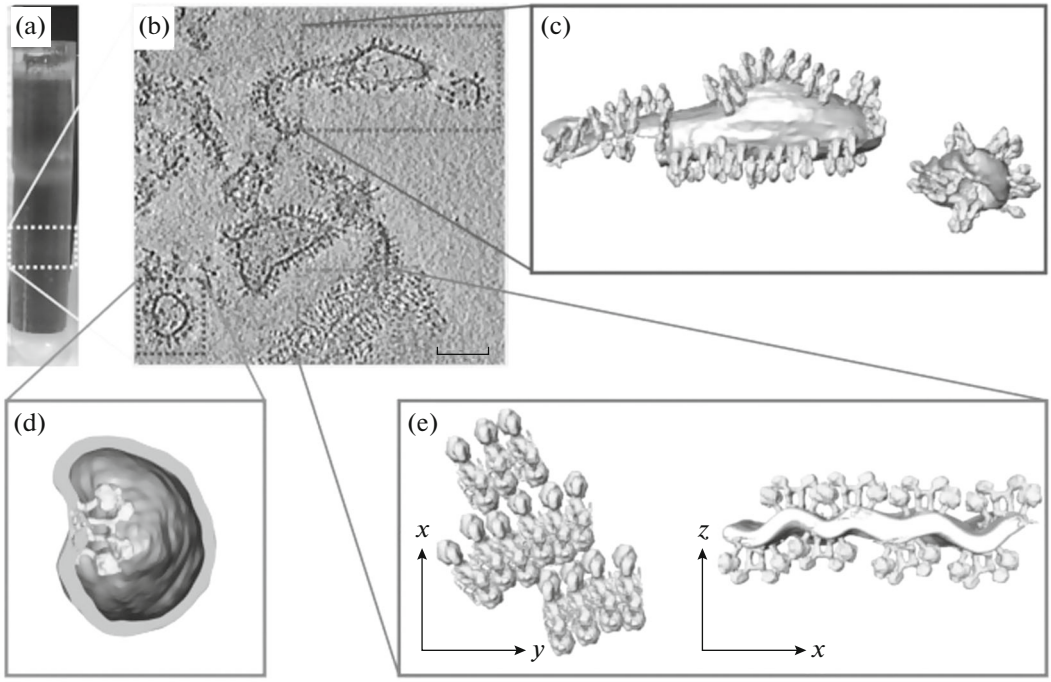

Fig. 5. ATP synthase dimers of *Polytomella* sp. and bending membranes: (a) the highlighted lower band of the gradient contains proteoliposomes; (b) tightly packed membranes with dimers; (c) dimers; (d) ATP synthase is directed into the vesicle by the F_1 component causes local curvature of the membrane; (e) membrane with parallel rows of dimers. Cryoelectron tomography (modified according to Blum et al., 2019).

A study in mutant mice with human IF_1 expression in nerve cells demonstrated a possible relationship between the activities of ATP synthase and cell death (Formentini et al., 2014). IF_1, which blocks the synthase and hydrolase activities of ATP synthase (Garcia-Bermudez and Cuezva, 2016), is used by cancer cells to inhibit its ability to synthesize reactive oxygen species, because their synthesis leads to the initiation of apoptotic processes. It turned out that the mediated IF_1 metabolic preconditioning resulted in "mild" oxidative stress and an increase in the functional threshold at which damage led to cell death. By inhibiting the activities of ATP synthase, IF_1 mice appeared to be partially protected from damage by some agents (e.g., quinolinic acid) despite very low amounts of ATP and ADP. Thus, prevention of the synthesis of reactive oxygen species made it possible to avoid significant damage to nerve cells, which suggests that ATP synthase plays a significant role in cell death and makes the enzyme a potential "target" for its prevention (Formentini et al., 2014).

ATP-SYNTHASE DISORDERS

The correct assembly and functioning of ATP synthase are essential conditions for normal cell activity. A fairly large number of different diseases are associated with an impaired assembly and/or function of ATP synthase, including neurodegenerative and mitochondrial diseases, obesity, cancer, immunodeficiency, diabetes, and cystic fibrosis (García et al., 2000; Ahmad and Laughlin, 2010; Bartolome et al., 2013). Mutations in some subunits of ATP synthase lead to disturbances in its assembly, which leads to changes in the morphology of mitochondrial cristae (Strauss et al., 2008); this once again confirms the role of ATP synthase as a necessary condition for the formation of folds (cristae) of their inner membrane. For example, such changes are found in Leigh's disease (an a-subunit mutation), NARP syndrome (an F_6-subunit mutation), mitochondrial cardiomyopathy, etc. (Kucharczyk et al., 2009; Dautant et al., 2018). As a result, ATP synthase has become an effective potential target for drugs (Ahmad et al., 2011). Currently, there are more than 300 known natural and synthesized molecules that can bind to the complex and change its activity (Hong and Pedersen, 2008; Ahmad et al., 2013).

The literature data indicate a link between mitochondria and neurodegenerative diseases such as Parkinson's, Alzheimer's, Huntington's, and amyotrophic lateral sclerosis (Federico et al., 2012). There are also a number of metabolic disorders associated with mitochondrial dysfunction (Scholte, 1988), the main feature of which is disruption of the ETC (Federico et al., 2012).

ATP-SYNTHASE OF THE BRAIN

The central nervous system is most dependent on the normal functioning of mitochondria, since neurons require a large amount of energy for their work (Magistretti and Pellerin, 1996; Raichle and Gusnard, 2002; Peters et al., 2004; Filosto et al., 2011; Magistretti and Allaman, 2015). Since the level of ATP synthesis is a central indicator of brain bioenergetics, its function, aging, and neurodegeneration and ATP synthase is directly responsible for this process, its study in brain structures is highly relevant. In terms of structure and functions, the brain has a very complex organization, which also implies the heterogeneity of the distribution of ATP synthase in it. However, the available information is fragmentary; it concerns a very small part of its structures only pathological conditions, which is insufficient for an assessment and comparison of the energy potential of different microdepartments and types of brain cells.

The available information indicates that brain ATP synthase is a "key" target for damaging factors. The cause of systematic violations of various subunits, especially subunits α and β, is lipoxidation, which leads to a loss of V activity. The results of immunohistochemical studies indicate damage to brain neurons, the presence of modifications of ATP synthase in various areas of the cerebral cortex, and an increases in their number with aging and pathology. In Alzheimer's disease, the entorhinal cortex suffers from the very early stages of the disease (Terni et al., 2010). Lipoxidation of ATP synthase was also found in the hippocampus and parietal cortex in Alzheimer's disease, but at a later stage than in the entorhinal cortex (Reed et al., 2008; Terni et al., 2010). It is especially important that, despite the inactivation of ATP synthase, the expression level of the protein components of this enzyme does not decrease (Terni et al., 2010).

Significant wavelike changes (increase, decrease, normalization) in the amount of ATP synthase were found in the Purkinje cells of the cerebellum and the cells of the frontal and parietal cortex during cholestasis (Emelyanchik et al., 2018).

Examination of the brain structures of rats with hypertension indicated mitochondrial dysfunction and significant disturbances in the assembly and functioning of ATP synthase in the brainstem. Based on this, it was suggested that it is precisely the lack of ATP and an increase in reactive oxygen species that lead to impairment of cardiovascular homeostasis (Lopez-Campistrous et al., 2008).

CONCLUSIONS

ATP synthase is a universal and unique enzyme in its characteristics. For many decades, ATP synthase of various origins has been the object of close study, and now we have a large amount of information on its structure and organization, mechanisms of work and functions, and disorders in pathology.

ATP synthases of all organisms contain well-studied, identical, basic structural units necessary for the performance of enzymatic functions. At the same time, the "unique" units of some specific types of ATP synthases remain unexplored. Since the functions of ATP synthase include not only the synthesis or hydrolysis of ATP but also the formation of the structure of mitochondrial cristae in eukaryotes, it can be argued that the correct assembly and operation of ATP synthase are key conditions for normal cell activity. A large number of diseases, including neurodegenerative and mitochondrial diseases, are associated with ATP synthase disorders. One of the least studied issues is the question of the distribution of ATP synthase in various parts and types of brain cells. The relevance of this issue is determined by the fact that ATP synthase is a molecular marker of mitochondria and characterizes its "energy potential."

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflicts of interest.

Statement on the welfare of humans or animals. This article does not contain any studies involving animals performed by any of the authors.

REFERENCES

Ahmad, Z. and Laughlin, T.F., Medicinal chemistry of ATP synthase: a potential drug target of dietary polyphenols and amphibian antimicrobial peptides, *Curr. Med. Chem.*, 2010, vol. 17, no. 25, pp. 2822–2836. https://doi.org/10.2174/092986710791859270

Ahmad, Z., Okafor, F., and Laughlin, T.F., Role of charged residues in the catalytic sites of *Escherichia coli* ATP synthase, *J. Amino Acids*, 2011, vol. 2011, art. ID 785741. https://doi.org/10.4061/2011/785741

Ahmad, Z., Okafor, F., Azim, S., and Laughlin, T.F., ATP synthase: a molecular therapeutic drug target for antimicrobial and antitumor peptides, *Curr. Med. Chem.*, 2013, vol. 20, no. 15, pp. 1956–1973. https://doi.org/10.2174/092986731132015003

Allegretti, M., Klusch, N., Mills, D.J., et al., Horizontal membrane-intrinsic α-helices in the stator *a*-subunit of an F-type ATP synthase, *Nature*, 2015, vol. 521, no. 7551, pp. 237–240. https://doi.org/10.1038/nature14185

Allen, R.D., Membrane tubulation and proton pumps, *Protoplasma*, 1995, vol. 189, pp. 1–8. https://doi.org/10.1007/BF01280286

Arnold, I., Pfeiffer, K., Neupert, W., et al., Yeast mitochondrial F_1F_0-ATP synthase exists as a dimer: identification of three dimer-specific subunits, *EMBO J.*, 1998, vol. 17, no. 24, pp. 7170–7178. https://doi.org/10.1093/emboj/17.24.7170

Bartolome, F., Wu, H.C., Burchell, V.S., et al., Pathogenic VCP mutations induce mitochondrial uncoupling and reduced ATP levels, *Neuron*, 2013, vol. 78, no. 1, pp. 57–64. https://doi.org/10.1016/j.neuron.2013.02.028

Becher, B. and Müller, V., Delta mu Na^+ drives the synthesis of ATP via an delta mu Na(+)-translocating F_1F_0-ATP synthase in membrane vesicles of the archaeon *Methanosarcina mazei* Go1, *J. Bacteriol.*, 1994, vol. 176, no. 9, pp. 2543–2550. https://doi.org/10.1128/jb.176.9.2543-2550.1994

Berman, H.M., Westbrook, J., Feng, Z., et al., The protein data bank, *Nucleic Acids Res.*, 2000, vol. 28, pp. 235–242. https://doi.org/10.1093/nar/28.1.235

Blum, T.B., Hahn, A., Meier, T., et al., Dimer of mitochondrial ATP synthase induce membrane curvature and self-assemble into rows, *Proc. Natl. Acad. Sci. U.S.A.*, 2019, vol. 116, no. 10, pp. 4250–4255. https://doi.org/10.1073/pnas.1816556116

Boyer, P.D., A model for conformational coupling of membrane potential and proton translocation to ATP synthesis and to active transport, *FEBS Lett.*, 1975, vol. 56, no. 1, pp. 1–6. https://doi.org/10.1016/0014-5793(75)80212-2

Boyer, P.D., The binding change mechanism for ATP synthase—some probabilities and possibilities, *Biochim. Biophys. Acta, Bioenerg.*, 1993, vol. 1140, no. 3, pp. 215–250.

Boyer, P.D. and Kohlbrenner, W.E., The present status of the binding-change mechanism and its relation to ATP formation by chloroplasts, in *Energy Coupling in Photosynthesis*, Selman, B.R. and Selman-Reimer, S., Eds., Amsterdam: Elsevier, 1981, vol. 20, pp. 231–240.

BRENDA:EC3.6.3.14, H^+-transporting two-sector ATPasa, BRENDA: the Comprehensive Enzyme Information System. https://www.brenda-enzymes.org/index.php. Accessed April 29, 2020.

Campanella, M., Casswell, E., Chong, S., et al., Regulation of mitochondrial structure and function by the F_1F_0-ATPase inhibitor protein, IF_1, *Cell Metab.*, 2008, vol. 8, no. 1, pp. 13–25. https://doi.org/10.1016/j.cmet.2008.06.001

Campanella, M., Parker, N., Tan, C.H., et al., IF_1: setting the pace of the F_1F_0-ATP synthase, *Trends Biochem Sci.*, 2009, vol. 34, no. 7, pp. 343–350. https://doi.org/10.1016/j.tibs.2009.03.006

Capaldi, R.A. and Aggeler, R., Mechanism of the F_1F_0-type ATP synthase, a biological rotary motor, *Trends Biochem. Sci.*, 2002, vol. 27, no. 3, pp. 154–160. https://doi.org/10.1016/s0968-0004(01)02051-5

Crichton, P.G., Lee, Y., and Kunji, E.R., The molecular features of uncoupling protein 1 support a conventional mitochondrial carrier-like mechanism, *Biochimie*, 2017, vol. 134, pp. 35–50. https://doi.org/10.1016/j.biochi.2016.12.016

Daum, B., Nicastro, D., Austin, J. II, et al. Arrangement of photosystem II and ATP synthase in chloroplast membranes of spinach and pea, *Plant Cell*, 2010, vol. 22, no. 4, pp. 1299–1312. https://doi.org/10.1105/tpc.109.071431

Dautant, A., Meier, T., Hahn, A., et al., ATP synthase diseases of mitochondrial genetic origin, *Front. Physiol.*, 2018, vol. 9, p. 329. https://doi.org/10.3389/fphys.2018.00329

Davies, K.M., Strauss, M., Daum, B., et al., Macromolecular organization of ATP synthase and complex I in whole mitochondria, *Proc. Natl. Acad. Sci. U.S.A.*, 2011, vol. 108, no. 34, pp. 14121–14126. https://doi.org/10.1073/pnas.1103621108

Davies, K.M., Anselmi, C., Wittig, I., et al., Structure of the yeast F_1F_0-ATP synthase dimer and its role in shaping the mitochondrial cristae, *Proc. Natl. Acad. Sci. U.S.A.*, 2012, vol. 109, no. 34, pp. 13602–13607. https://doi.org/10.1073/pnas.1204593109

Deckers-Hebestreit, G. and Altendorf, K., The F_1F_0-type ATP synthases of bacteria: structure and function of F_0 complex, *Ann. Rev. Microbiol.*, 1996, vol. 50, pp. 791–824. https://doi.org/10.1146/annurev.micro.50.1.791

Devenish, R.J., Prescott, M., Boyle, G.M., and Nagley, P., The oligomycin axis of mitochondrial ATP synthase: OSCP and the proton channel, *J. Bioenerg. Biomembr.*, 2000, vol. 32, no. 5, pp. 507–515. https://doi.org/10.1023/a:1005621125812

Devenish, R.J., Prescott, M., and Rodgers, A.J., The structure and function of mitochondrial F_1F_0-ATP synthases, *Int. Rev. Cell Mol. Biol.*, 2008, vol. 267, pp. 1–58. https://doi.org/10.1016/S1937-6448(08)00601-1

Emel'yanchik, S.V., Karnyushko, O.A., and Zimatkin, S.M., Changes in the immunoreactivity of ATP-synthase in neurons of cerebral cortex and cerebellum of rats with cholestasis, *Vestn. Smolensk. Gos. Med. Akad.*, 2018, vol. 17, no. 2, pp. 55–60.

Federico, A., Cardaioli, E., Da Pozzo, P., et al., Mitochondria, oxidative stress and neurodegeneration, *J. Neurol. Sci.*, 2012, vol. 322, nos. 1–2, pp. 254–262. https://doi.org/10.1016/j.jns.2012.05.030

Fernández-Morán, H., Oda, T., Blair, P.V., and Green, D.E., A macromolecular repeating unit of mitochondrial structure and function, *J. Cell Biol.*, 1964, vol. 22, no. 1, pp. 63–100. https://doi.org/10.1083/jcb.22.1.63

Filosto, M., Scarpelli, M., Cotelli, M.S., et al., The role of mitochondria in neurodegenerative diseases, *J. Neurol.*, 2011, vol. 258, no. 10, pp. 1763–1764. https://doi.org/0.1007/s00415-011-6104-z

Formentini, L., Pereira, M.P., and Sánchez-Cenizo, L., In vivo inhibition of the mitochondrial H^+-ATP synthase in neurons promotes metabolic preconditioning, *EMBO J.*, 2014, vol. 33, no. 7, pp. 762–778. https://doi.org/10.1002/embj.201386392

García, J.J., Ogilvie, I., Robinson, B.H., and Capaldi, R.A., Structure, functioning, and assembly of the ATP synthase in cells from patients with the T8993G mitochondrial DNA mutation. Comparison with the enzyme in Rho^0 cells completely lacking mtDNA, *J. Biol. Chem.*, 2000, vol. 275, no. 15, pp. 11075–11081. https://doi.org/10.1074/jbc.275.15.11075

García-Bermúdez, J. and Cuezva, J.M., The ATPase inhibitory factor 1 (IF_1): a master regulator of energy metabolism and of cell survival, *Biochim. Biophys. Acta, Bio-*

energ., 2016, vol. 1857, no. 8, pp. 1167–1182. https://doi.org/0.1016/j.bbabio.2016.02.004

Gavin, P.D., Prescott, M., and Devenish, R.J., Yeast F_1F_0-ATP synthase complex interactions in vivo can occur in the absence of the dimer specific subunit e, *J. Bioenerg. Biomembr.*, 2005, vol. 37, no. 2, pp. 55–60. https://doi.org/10.1007/s10863-005-4128-8

Guo, H., Bueler, S.A., and Rubinstein, J.L., Atomic model for the dimeric F_o region of mitochondrial ATP synthase, *Science*, 2017, vol. 358, no. 6365, pp. 936–940. https://doi.org/10.1126/science.aao4815

Hahn, A., Parey, K., Bublitz, M., et al., Structure of a complete ATP synthase dimer reveals the molecular basis of inner mitochondrial membrane morphology, *Mol. Cell*, 2016, vol. 63, no. 3, pp. 445–456. https://doi.org/10.1016/j.molcel.2016.05.037

Hahn, A., Vonck, J., Mills, D.J., et al., Structure, mechanism and regulation of the chloroplast ATP synthase, *Science*, 2018, vol. 360, no. 6389, p. eaat4318. https://doi.org/10.1126/science.aat4318

Hong, S. and Pedersen, P.L., ATP synthase and the actions of inhibitors utilized to study its roles in human health, disease and other scientific areas, *Microbiol. Mol. Biol. Rev.*, 2008, vol. 72, no. 4, pp. 590–641. https://doi.org/10.1128/MMBR.00016-08

International Union of Biochemistry and Molecular Biology, Recommendations on biochemical and organic nomenclature, symbols and terminology, Queen Mary University of London. https://www.qmul.ac.uk/sbcs/iubmb. Accessed April 29, 2020.

Itoh, H., Takahashi, A., Adachi, K., et al., Mechanically driven ATP synthesis by F_1-ATPase, *Nature*, 2004, vol. 427, no. 6973, pp. 465–468. https://doi.org/10.1038/nature02212

Jonckheere, A.I., Smeitink, J.A., and Rodenburg, R.J., Mitochondrial ATP synthase: architecture, function and pathology, *J. Inherit. Metab. Dis.*, 2012, vol. 35, no. 2, pp. 211–225. https://doi.org/10.1007/s10545-011-9382-9

Kagawa, Y., Ohta, S., Harada, M., et al., The $\alpha_3\beta_3$ and $\alpha_1\beta_1$ complexes of ATP synthase, *Ann. N. Y. Acad. Sci.*, 1992, vol. 671, pp. 366–376. https://doi.org/10.1111/j.1749-6632.1992.tb43810.x

Kinosita, K. Jr., Yasuda, R., and Noji, H., F_1-ATPase: a highly efficient rotary ATP machine, *Essays Biochem.*, 2000, vol. 35, pp. 3–18. https://doi.org/https://doi.org/10.1042/bse0350003

Kucharczyk, R., Zick, M., Bietenhader, M., et al., Mitochondrial ATP synthase disorders: molecular mechanisms and the quest for curative therapeutic approaches, *Biochim. Biophys. Acta, Mol. Cell Res.*, 2009, vol. 1793, no. 1, pp. 186–199. https://doi.org/10.1016/j.bbamcr.2008.06.012

LaNoue, K.F., Strzelecki, T., Strzelecka, D., and Koch, C., Regulation of the uncoupling protein in brown adipose tissue, *J. Biol. Chem.*, 1986, vol. 261, no. 1, pp. 298–305.

Lapaille, M., Thiry, M., Perez, E., et al., Loss of mitochondrial ATP synthase subunit beta (Atp2) alters mitochondrial and chloroplastic function and morphology in *Chlamydomonas, Biochim. Biophys. Acta, Bioenerg.*, 2010, vol. 1797, no. 8, pp. 1533–1539. https://doi.org/10.1016/j.bbabio.2010.04.013

Lau, W.C., Baker, L.A., and Rubinstein, J.L., Cryo-EM structure of the yeast ATP synthase, *J. Mol. Biol.*, 2008, vol. 382, no. 5, pp. 1256–1264. https://doi.org/10.1016/j.jmb.2008.08.014

Laubinger, W. and Dimroth, P., Characterization of the ATP synthase of *Propionigenium modestum* as a primary sodium pump, *Biochemistry*, 1988, vol. 27, no. 19, pp. 7531–7537. https://doi.org/10.1021/bi00419a053

Lopez-Campistrous, A., Hao, L., Xiang, W., et al., Mitochondrial dysfunction in the hypertensive rat brain: respiratory complexes exhibit assembly defects in hypertension, *Hypertension*, 2008, vol. 51, no. 2, pp. 412–419. https://doi.org/10.1161/HYPERTENSIONAHA.107.102285

Magistretti, P.J. and Pellerin, L., Cellular mechanisms of brain energy metabolism. Relevance to functional brain imaging and to neurodegenerative disorders, *Ann. N. Y. Acad. Sci.*, 1996, vol. 777, no. 1, pp. 380–387. https://doi.org/10.1111/j.1749-6632.1996.tb34449.x

Raichle, M.E. and Gusnard, D.A., Apprising the brain's energy budget, *Proc. Natl. Acad. Sci. U.S.A.*, 2002, vol. 99, no. 16, pp. 10237–10239. https://doi.org/10.1073/pnas.172399499

Meier, T., Yu, J., Raschle, T., et al., Structural evidence for a constant c11 ring stoichiometry in the sodium F-ATP synthase, *FEBS J.*, 2005, vol. 272, no. 21, pp. 5474–5483. https://doi.org/10.1111/j.1742-4658.2005.04940.x

Milne, J.L., Borgnia, M.J., Bartesaghi, A., et al., Cryo-electron microscopy—a primer for the non-microscopist, *FEBS J.*, 2013, vol. 280, no. 1, pp. 28–45. https://doi.org/10.1111/febs.12078

Minauro-Sanmiguel, F., Wilkens, S., and Garcia, J.J., Structure of dimeric mitochondrial ATP synthase: novel F_0 bridging features and the structural basis of mitochondrial cristae biogenesis, *Proc. Natl. Acad. Sci. U.S.A.*, 2005, vol. 102, no. 35, pp. 12356–12358. https://doi.org/10.1073/pnas.0503893102

Mohanty, S., Jobichen, C., Chichili, V.P., et al., Structural basis for a unique ATP synthase core complex from *Nanoarcheaum equitans, J. Biol. Chem.*, 2015, vol. 290, no. 45, pp. 27280–27296. https://doi.org/10.1074/jbc.M115.677492

Morales-Rios, E., Montgomery, M.G., Leslie, A.G., and Walker, J.E., Structure of ATP synthase from *Paracoccus denitrificans* determined by X-ray crystallography at 4.0 A resolution, *Proc. Natl. Acad. Sci. U.S.A.*, 2015, vol. 112, no. 43, pp. 13231–13236. https://doi.org/10.1073/pnas.1517542112

Nannenga, B.L. and Gonen, T., Protein structure determination by MicroED, *Curr. Opin. Struct. Biol.*, 2014, vol. 27, pp. 24–31. https://doi.org/10.1016/j.sbi.2014.03.004

Nelson, N., Evolution of organellar proton-ATPases, *Biochim. Biophys. Acta, Bioenerg.*, 1992, vol. 1100, no. 2, pp. 109–124. https://doi.org/10.1016/0005-2728(92)90072-a

Nelson, N. and Taiz, L., The evolution of H^+-ATPases, *Trends Biochem. Sci.*, 1989, vol. 14, no. 3, pp. 113–116. https://doi.org/10.1016/0968-0004(89)90134-5

Nicholls, D.G., The hunt for the molecular mechanism of brown fat thermogenesis, *Biochimie*, 2017, vol. 134, pp. 9–18. https://doi.org/10.1016/j.biochi.2016.09.003

Nijtmans, L.G., Klement, P., and Houstěk, J., Assembly of mitochondrial ATP synthase in cultured human cells: implications for mitochondrial diseases, *Biochim. Biophys Acta, Mol. Basis Dis.*, 1995, vol. 1272, no. 3, pp. 190–198. https://doi.org/10.1016/0925-4439(95)00087-9

Paumard, P., Vaillier, J., Coulary, B., et al., The ATP synthase is involved in generating mitochondrial cristae morphology, *EMBO J.*, 2002, vol. 21, no. 3, pp. 221–230. https://doi.org/10.1093/emboj/21.3.221

Pecina, P., Nůsková, H., Karbanová, V., et al., Role of the mitochondrial ATP synthase central stalk subunits γ and δ in the activity and assembly of the mammalian enzyme, *Biochim. Biophys. Acta, Bioenerg.*, 2018, vol. 1859, no. 5, pp. 374–381. https://doi.org/10.1016/j.bbabio.2018.02.007

Peters, A., Schweiger, U., Pellerin, L., et al., The selfish brain: competition for energy resources, *Neurosci. Biobehav. Rev.*, 2004, vol. 28, no. 2, pp. 143–180. https://doi.org/10.1016/j.neubiorev.2004.03.002

Magistretti, P.J. and Allaman, I., A cellular perspective on brain energy metabolism and functional imaging, *Neuron*, 2015, vol. 86, no. 4, pp. 883–901. https://doi.org/10.1016/j.neuron.2015.03.035

Pogoryelov, D., Yildiz, O., Faraldo-Gómez, J.D., and Meier, T., High-resolution structure of the rotor ring of a proton-dependent ATP synthase, *Nat. Struct. Mol. Biol.*, 2009, vol. 16, no. 10, pp. 1068–1073. https://doi.org/10.1038/nsmb.1678

Pullman, M.E. and Monroy, G.C., A naturally occurring inhibitor of mitochondrial adenosine triphosphatase, *J. Biol. Chem.*, 1963, vol. 238, no. 11, pp. 3762–3769.

Reed, T., Perluigi, M., Sultana, R., et al., Redox proteomic identification of 4-hydroxy-2-nonenal-modified brain proteins in amnestic mild-cognitive impairment: insight into the role of lipid peroxidation in the progression and pathogenesis of Alzheimer's disease, *Neurobiol. Dis.*, 2008, vol. 30, no. 1, pp. 107–120. https://doi.org/10.1016/j.nbd.2007.12.007

Reidlinger, J. and Müller, V., Purification of ATP synthase from *Acetobacterium woodii* and identification as a Na^+-translocating F_1F_0-type enzyme, *Eur. J. Biochem.*, 1994, vol. 223, no. 1, pp. 275–283. https://doi.org/10.1111/j.1432-1033.1994.tb18992.x

Richter, M.L., Samra, H.S., He, F., Giessel, A.J., and Kuczera, K.K., Coupling proton movement to ATP synthesis in the chloroplast ATP synthase, *J. Bioenerg. Biomembr.*, 2005, vol. 37, no. 6, pp. 467–473. https://doi.org/10.1007/s10863-005-9493-9

Rubinstein, J.L., Walker, J.E., and Henderson, R., Structure of the mitochondrial ATP synthase by electron cryomicroscopy, *EMBO J.*, 2003, vol. 22, no. 23, pp. 6182–6192. https://doi.org/10.1093/emboj/cdg608

Salomon, A.R., Voehringer, D.W., Herzenberg, L.A., and Khosla, C., Apoptolidin, a selective cytotoxic agent, is an inhibitor of F_0F_1-ATPase, *Chem. Biol.*, 2001, vol. 8, no. 1, pp. 71–80. https://doi.org/10.1016/s1074-5521(00)00057-0

Schagger, H. and Pfeiffer, K., Supercomplexes in the respiratory chain of yeasts and mammalian mitochondria, *EMBO J.*, 2000, vol. 19, no. 8, pp. 1777–1783. https://doi.org/10.1093/emboj/19.8.1777

Schapira, A.H., Mitochondrial disease, *Lancet*, 2006, vol. 368, no. 9529, pp. 70–82. https://doi.org/10.1016/S0140-6736(11)61305-6

Scholte, H.R., The biochemical basis of mitochondrial diseases, *J. Bioenerg. Biomembr.*, 1988, vol. 20, no. 2, pp. 161–191. https://doi.org/10.1007/BF00768393

Smith, C.P. and Thorsness, P.E., Formation of an energized inner membrane in mitochondria with a γ-deficient F_1-ATPase, *Eukaryot. Cell*, 2005, vol. 4, no. 12, pp. 2078–2086. https://doi.org/10.1128/EC.4.12.2078-2086.2005

Strauss, M., Hofhaus, G., Schröder, R.R., and Kühlbrandt, W., Dimer ribbons of ATP synthase shape the inner mitochondrial membrane, *EMBO J.*, 2008, vol. 27, no. 7, pp. 1154–1160. https://doi.org/10.1038/emboj.2008.35

Terni, B., Boada, J., Portero-Otin, M., et al., Mitochondrial ATP-synthase in the entorhinal cortex is a target of oxidative stress as stages I/II of Alzheimer's disease pathology, *Brain Pathol.*, 2010, vol. 20, no. 1, pp. 222–233. https://doi.org/10.1111/j.1750-3639.2009.00266.x

van Heeke, G., Deforce, L., Schnizer, R.A., et al., Recombinant bovine heart mitochondrial F1-ATPase inhibitor protein: overproduction in *Escherichia coli*, purification and structural studies, *Biochemistry*, 1993, vol. 32, no. 38, pp. 10140–10149. https://doi.org/10.1021/bi00089a033

Vollmar, M., Schlieper, D., Winn, M., et al., Structure of the c14 rotor ring of the proton translocating chloroplast ATP synthase, *J. Biol. Chem.*, 2009, vol. 284, no. 27, pp. 18228–18235. https://doi.org/10.1074/jbc.M109.006916

Walker, J.E. and Dickson, V.K., The peripheral stalk of the mitochondrial ATP synthase, *Biochim. Biophys. Acta, Bioenerg.*, 2006, vol. 1757, nos. 5–6, pp. 286–296. https://doi.org/10.1016/j.bbabio.2006.01.001

Watt, I.N., Montgomery, M.G., Runswick, M.J., et al., Bioenergetic cost of making an adenosine triphosphate molecule in animal mitochondria, *Proc. Natl. Acad. Sci. U.S.A.*, 2010, vol. 107, no. 39, pp. 16823–16827. https://doi.org/10.1073/pnas.1011099107

Wittig, I. and Schagger, H., Structural organization of mitochondrial ATP synthase, *Biochim. Biophys. Acta, Bioenerg.*, 2008, vol. 1777, nos. 7–8, pp. 592–598. https://doi.org/10.1016/j.bbabio.2008.04.027

Xu, T., Pagadala, V., and Mueller, D.M., Understanding structure, function, and mutations in the mitochondrial ATP synthase, *Microb. Cell*, 2015, vol. 2, no. 4, pp. 105–125. https://doi.org/10.15698/mic2015.04.197

Zeviani, M. and Di Donato, S., Mitochondrial disorders, *Brain*, 2004, vol. 127, no. 10, pp. 2153–2172. https://doi.org/10.1093/emboj/17.24.7170

Zhou, A., Rohou, A., Schep, D.G., et al., Structure and conformational states of the bovine mitochondrial ATP synthase by cryo-EM, *eLife*, 2015, vol. 4, p. e10180. https://doi.org/10.7554/eLife.10180