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Letter to Editor

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The role of domain alterations in F1Fo-ATPase dysfunction associated to neurodegenerative diseases

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Abstract

Mitochondrial dysfunction can lead to degeneration in the central nervous system. F1Fo-ATPase catalyzes most of the intracellular ATP synthesis which plays an essential role in cellular energy supply. The dimerized assembly of F1Fo-ATPase underlies the rotational catalytic function and regulates the mechanisms of oxidative phosphorylation. F1Fo-ATPase dysfunction is involved in a variety of neurological diseases, including epilepsy, Alzheimer's disease, and Parkinson's disease. Dysregulated expression, activity, and localization of F1Fo-ATPase subunits and the interactions with pathogenic proteins result in decreased F1Fo-ATPase activity and ATP production, and aggravated oxidative stress.

Keywords: Mitochondrial energy metabolism, F1 Fo-ATPase, structural assembly, neurodegenerative diseases

INTRODUCTION

Oxidative stress characterized by mitochondrial damage is an important factor affecting the occurrence and development of neurodegenerative diseases[1,2]. Studies suggested that multiple factors leading to disruption of electron transport chain (ETC) play an important role in the pathogenic mechanisms of neurodegeneration. Decreased ATP production is one of the important manifestations of mitochondrial respiratory dysfunction[3].

F1Fo-ATPase, also known as the ETC complex V, participates in the synthesis of cellular ATP[4]. It exists in the cristae and inner membrane of mitochondria. Functional defects or subunit mutations can lead to the occurrence of lactic acidosis, cardiomyopathy, Alzheimer's disease(AD), Leigh syndrome and other human diseases[5,6]. The dimerization structure of F1Fo-ATPase is the basis for maintaining the original power of ATP synthesis[7], so as to regulate the transmembrane potential and participate in the formation of mitochondrial cristae[8]. This article reviews the research progress in the structure and function of F1Fo-ATPase in the nervous system, especially for neurodegenerative diseases.

BIOLOGICAL CHARACTERISTICS OF F1FO-ATPASE

The structure of F1Fo-ATPase

F1Fo-ATPase is located at the inner mitochondrial membrane (IMM). F1Fo-ATPase is a multi-protein complex consisting of 29 subunits[9]. Twenty-seven subunits of F1Fo-ATPase are encoded by nuclear genes and synthesized by cytosolic ribosomes. Another two proteins (subunits 6 and 8) are encoded by mitochondrial DNA (mt-DNA) and synthesized by ribosomes within mitochondria[6,9,10]. F1Fo-ATPase consists of two main domains, called F1 and Fo [Figure 1]. The F1 domain is exposed in the matrix as α3β3γ δε, with alternating α and β subunits forming a barrel protein called the F1 catalytic head, and a centrally asymmetric γ subunit protrudes from the center of the barrel. The δ and ε subunits of the basal surface attached to the Fo c-ring, called the F1 central stalk. Studies suggest that the α and β subunits hexamer interface is the catalytic site for ATP[5,11]. The α and β subunits share about 20% sequence homology with structural similarity[12], though only the β-subunits contribute to catalytic activity[4,5].

F1Fo-ATP synthase includes two domains, called F1 and Fo. The Fo peripheral stalk is on the right. The membrane domain of subunit-b is associated with ATP6 and ATP8, the N-terminal region has a single transmembrane α-helix, and the C-terminal region extends into the peripheral stalk. ATP8 and subunit-b keep ATP6 in contact with the c8 ring. Translocation of a proton between the c8 ring and ATP6 drives the rotation of the ring and the central stalk (γδε). Rotation of the central stalk brings energy into three catalytic sites in the F1 domain (α3β3γδε). The black horizontal line represents the inner mitochondrial membrane.

The Fo domain is subdivided into three parts: the Fo rotor ring, the Fo peripheral stalk, and the Fo other subunits. The Fo rotor ring consists of ATP6 (subunit 6), ATP8 (subunit 8) and a c-ring consisting of 8 identical c-subunits(c8-ring), the size of which varies among species. Other Fo proteins include subunit a and subunit b and other subunits of unknown function, including subunits d, e, f, g, F6, and 8 (A6L). DAPIT (diabetes-associated protein in insulin-sensitive tissue) and 6.8PL are present in vertebrates and assist in the assembly of the Fo component[9,13]. The Fo peripheral stalk includes subunits OSCP, F6, b and d [Figure 1]. Subunit b, which contains two N-terminal transmembrane α-helices, interacts with subunits e, f, g, DAPIT and 6.8PL directly or indirectly. The oligomycin sensitivity conferring protein (OSCP) is encoded by *ATP5O* and contains an N-terminal domain that contains six α-helices and a C-terminal domain consisting of a β-hairpin and two α-helix[14,15]. OSCP is a key part of the peripheral stalk and functions by coupling the F1 and Fo domains together[11]. The intermembrane space (IMS) protons pass through the

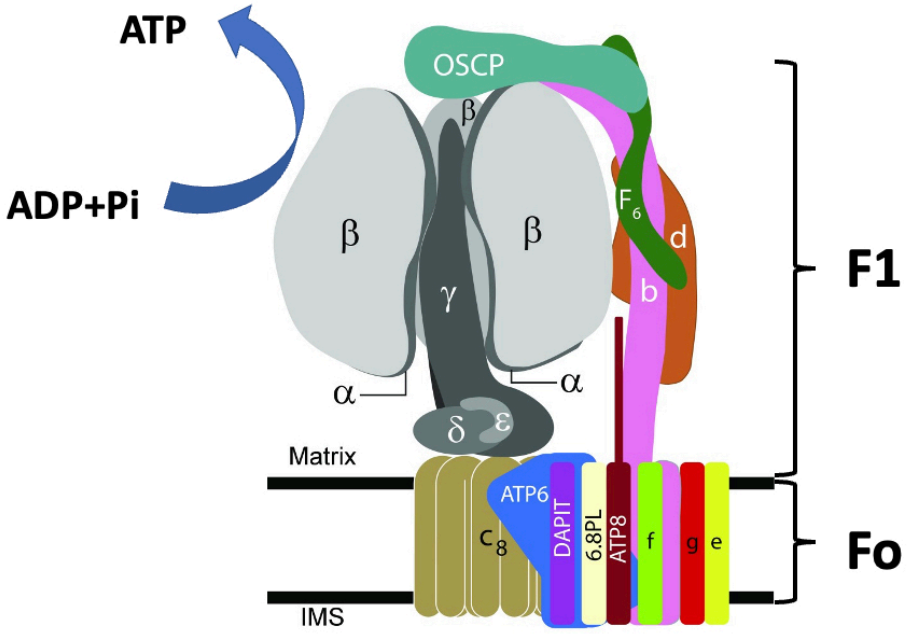

Figure 1. The structure of the F1Fo-ATP synthase subunits[9]. IMS: Intermembrane space; OSCP: oligomycin sensitivity conferring protein.

aqueous hemichannel in subunit-a to the c-ring of Fo domain, where they interact with the c-ring aspartate or glutamate residues[16]. These charged proton-binding sites are hidden by the α-helix rotation in the subunit-c, causing the c-ring to rotate with the central rotation handle subunit-γ[7]. The rotating Fo component transports protons into the matrix through the second aqueous hemichannel on the membrane matrix side, and the asymmetric rotor handle causes a conformational change in F1 that drives the catalytic activity of the β-subunit[17].

The function of F1Fo-ATPase

ATP -hydrolysis and synthesis

F1Fo-ATPase is a membrane multi-protein complex primarily located within the IMM. By utilizing the proton (H^+) gradient produced by ETC activity, F1Fo-ATPase catalyzes ATP synthesis from ADP and inorganic phosphate[4,5]. Proton from the IMS binds to the influx channel between the c-ring and subunit 6, resulting in the protonation of hydrophilic residues and the c-ring counterclockwise rotation. When the protonated subunit-c reaches the outflow channel, the proton is released into the matrix[16]. The c-ring (c8 ring) is an important part of the Fo rotor. Rotation of the c-ring exerts a torque on the F1 central stalk and its rotation within the F1 catalytic head is facilitated by the δ and ε subunits, resulting in a conformational change [Figure 1][7,18]. The F1 catalytic head is held in place by the Fo peripheral stalk and maintains in a specific position relative to the rotating F1 central stalk. The study reports that the catalytic site of the β subunit exists in three unique binding states: β_E (opening), β_{DP} (loose or ADP-bound) and β_{TP} (compact or ATP-bound)[19]. The catalytic site can be occupied by ADP and phosphate (Pi) when it is in the opening state. The Fo domain is not directly involved in ATP synthesis, but supports the functions of F1Fo-ATPase, including structural support[13,20]. On the other hand, F1Fo-ATPase reversely catalyzes the hydrolysis of ATP when the mitochondrial membrane potential (MMP) reduces, that is, the hydrolysis of ATP to ADP and Pi[21].

F1Fo-ATPase is involved in the formation of mitochondrial cristae

Cristae are structures formed by the folding of the IMM towards the matrix, which greatly increase the total surface area of respiratory chain[22,23]. The morphology of cristae varies among species. Oligomerization and dimerization of F1Fo-ATPase is responsible for the cristae organization[24]. Studies suggest that abnormal dimerization causes a block in F1 synthesis and leads to altered cristae morphology with extended onion-like structures and even the disappearance of the cristae in yeast[25]. Human F1Fo-ATPase dimers are linked together back-to-face by DAPIT, forming long oligomers along the edges of the cristae[9]. Mutations in the DAPIT result in defective F1Fo-ATPase dimerization and abnormal cristae structures, resulting in mild Leigh syndrome[13,26]. Knockdown of the subunit-e in HeLa cells manifests as slightly disordered lamellar cristae in the IMM. Another study on yeast mitochondria described that lack of Atp6p resulted in abnormal F1Fo-ATPase structure that affected cristae morphology and altered the overall mitochondrial structure[27]. Several mitochondrial function-related genes, such as *CHCHD2* (Coiled-coil-helix-coiled-coil-helix domain containing protein 2), have been previously reported to be critical in maintaining mitochondrial cristae and stabilizing mitochondrial inner-membrane fusion. CHCHD2 stabilizes the mitochondrial contact site and cristae organizing system (MICOS), holding the formation and stability of cristae[28]. Mic60, a MICOS component involved in cristae membrane curvature, antagonizes with subunit-e or subunit-g, thus inhibiting the oligomerization of the F1Fo-ATPase[29].

The formation and opening of mitochondrial permeability transition pore

F1Fo-ATPase catalyzes ATP synthesis or hydrolysis based on the membrane potential difference. The protons cross the IMM into the matrix following the membrane potential difference and rotate the central stalk counterclockwise (viewed from F1 domain), resulting in the generation of ATP. Conversely, if the membrane potential decreases, ATP is hydrolyzed to ADP and Pi[30]. It can be seen that F1Fo-ATPase is involved in mitochondrial permeability transition (mPT)[31].

The mitochondrial permeability transition pore (mPTP) is composed of mitochondrial outer and inner membrane proteins, regulating the transportation of molecules in or out of the matrix[32,33]. Recent studies suggested that changes in mitochondrial outer and inner membrane structure and function regulate the open state of mPTP and cell death[32,34]. The role of F1Fo-ATPase in the formation of mPTP has been confirmed in mammals, yeast, drosophila melanogaster and other eukaryotes in recent years[35-37]. Giorgio *et al.* reported that the binding of Ca^{2+} to the subunit-β can trigger the opening of mPTP[38]. The c-ring acts as an uncoupling channel for mPTP and participates in mPTP formation[39,40]. Karch *et al.* reported that Bcl-2 protein family members Bax and Bak promote changes in outer membrane permeability involved in mPTP[41]. The features of Ca^{2+}-dependent currents generated by dimers of ATP synthase are indistinguishable from those of the mPTP[14], which suggests that F1Fo-ATPase is directly involved in mPTP formation[38,42]. Walker's study shows that the phenomenon of mPT persists despite the absence of Fo subunits[8,43]. Therefore, the characteristic composition is the basis for stable functional coordination among components, so as to ensure the dynamic balance of proton electrochemical gradient and the normal ATP supply in eukaryotic mitochondria[5-7].

F1FO-ATPASE AND NERVOUSE SYSTEM DISEASES

F1Fo-ATPase dysfunction is involved in a variety of neurological diseases[44]. It has been reported that α and β subunits are present in isolated fractions of plasma membrane and biotin-labelled surface protein from primary cultured neurons of rat brain. It suggests the involvement of this enzyme in the mechanism of extracellular ATP generation and pH(i) homoeostasis[45]. There is substantial evidence that ETC complex and energy metabolism-related proteins responsible for oxidative phosphorylation are particularly affected during aging[46]. As a target of lipoxidation-derived damage in human brain aging[47], F1Fo-ATPase affects

the α and β subunits first accompanied by loss of enzymatic activity rather than a decrease in the protein expression[48,49]. The loss of the activity of F1Fo-ATPase induces ETC dysfunction and reactive oxygen species (ROS) production, leading to oxidative stress based neuronal damage.

In status epilepticus, calcium accumulation leads to mitochondrial membrane depolarization, resulting in ATP reduction and cellular energy exhaustion[44,50]. Excessive calcium and ROS production lead to the opening of mPTP, which is permeable to pro-apoptotic proteins and leads to further depolarization of the MMP, exacerbating reduced ATP production, disturbance of ion homeostasis and matrix swelling[37]. ROS can further promote mPTP opening and initiate mitochondria-mediated programmed cell death by activating ryanodine receptors and inhibiting sarcoplasmic reticulum calcium-ATPase from releasing calcium from internal stores[32].

Studies have established a link between F1Fo-ATPase dysfunction and the loss of dendritic spines, which have been reported in neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP), Alzheimer's Disease (AD) and many other neurological diseases as well[51-54]. Alterations in oxidative phosphorylation mechanisms are associated with myelin and axonal degeneration[55]. F1Fo-ATPase protein expression level is decreased, and subcellular localization exhibits alterations in C-fiber and A-δ fiber neurons of L4-L5 dorsal root ganglia following sciatic nerve injury. Thermal and mechanical hypersensitivity was significantly improved by intrathecal injection of ATP, suggesting a potential role in the treatment of neuropathic pain[56].

F1Fo-ATPase and Alzheimer's disease

AD is characterized by accumulation of extracellular amyloid-β (Aβ) plaques and intracellular aggregation of tau protein in neurofibrillary tangles (NFTs). ETC dysfunction contributes to the development of the AD mitochondrial cascade hypothesis. Blue native polyacrylamide gel electrophoresis (BN-PAGE) analysis shows that the expression of F1Fo-ATPase complex subunits is reduced in the hippocampus of AD patients[25,57,58]. A study by the usage of iPSC-derived neuronal stem cells (NSCs) found a decreased expression of the F1Fo-ATPase in familial AD associated mutation PS1(M146L), even though PS1 expression was maintained[59]. In a study of sporadic AD, N2a neuroblastoma cells expressing the *ApoE4* allele were found to have reduced levels of all F1Fo-ATPase subunits when compared with *ApoE3* controls[60].

Another earlier study on AD and F1Fo-ATPase found that the catalytic activity was not significantly reduced in mitochondria isolated from AD patients' hippocampus and motor cortex[61]. Localization of F1Fo-ATPase on neuronal membranes and its extracellular activity is inhibited by amyloid precursor protein (APP) and Aβ[25,62,63]. The α subunit of F1Fo-ATPase is modified by 4-hydroxynonenal(HNE) in the hippocampus of mild cognitive impairment (MCI) individuals, which has 35% lower enzyme activity than controls[64]. NFT formation depends on stages of AD progression, which appears to be associated with the lip-oxidation of the α subunit[49]. In primary cultures of hippocampal neurons, inhibition of F1Fo-ATPase function *via* oligomycin A induces mitochondrial deficits[65]. The Bcl-x(L) protein directly interacts with the subunit-β, increasing H^+ pumped by F1Fo-ATPase complex ducring activation and improving the efficiency of energy metabolism. Recombined Bcl-x(L) directly increases the activity of the purified synthase complex, and inhibition of endogenous Bcl-x(L) reduces the activity[66].

The expression levels of various subunits encoding genes and proteins in brain regions were significantly reduced in entorhinal cortex, medial frontal gyrus, and temporal lobe of AD patients[67]. Meanwhile, the expression of ATP5H in hippocampal tissue in 3xTg AD mice has been found significantly decreased[68].

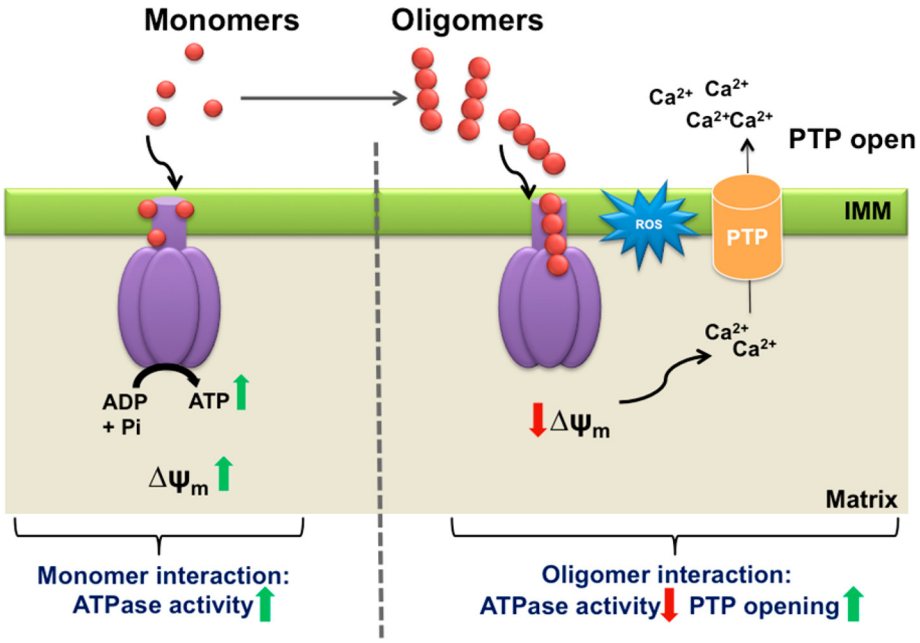

Figure 2. Effects of α-syn oligomers on mitochondria[74]. IMM: Inner mitochondrial membrane; PTP: permeability transition pore.

The expression of the OSCP was also significantly reduced in synaptic mitochondria from young and old 5xFAD mice compared to controls as well as in non-synaptic mitochondria from aged 5xFAD mice. Similarly, downregulation of MMP and ATP production have been found in the primary neurons of the OSCP knock-down mice[15]. Interestingly, Beck *et al.* found that the interaction between Aβ and OSCP reduces the ATP synthase activity[51]. Restoration of OSCP ameliorates Aβ-mediated mitochondrial damage[69]. Therefore, F1Fo-ATPase dysfunction may prevent AD progression by modulating the functions of OSCP[51].

F1Fo-ATPase and Parkinson's disease

The role of mitochondria dysfunction in Parkinson's disease (PD) is supported by a growing body of evidence[3,23,70]. Another study observed a significant reduction of F1Fo-ATPase in the substantia nigra of PD patients[71,72]. In addition, the F1Fo-ATPase levels in the frontal cortex are decreased in PD patients[73]. Superoxide dismutase 2 (SOD2) is also increased in the frontal cortex of PD. These findings indicate the disease-specific alterations in mitochondrial-associated protein expression in the frontal cortex[3] and demonstrate that the presence of mitochondrial modifications is prior to the appearance of the histological features[2].

Monomeric α-syn binds to the IMM and can improve F1Fo-ATPase efficiency and mitochondrial metabolic function in physiological conditions[74,75]. Studies by Ludtmann *et al.* revealed that monomeric α-syn directly interacts with the subunit-α of F1Fo-ATPase and positively regulates the activity of F1Fo-ATPase[76]. Brain mitochondria from α-syn, β-syn, and γ-syn knockout mice are characterized by decreased MMP, F1Fo-ATPase activity and ATP levels[76].

Another study showed co-localization of aggregated α-syn with F1Fo-ATPase in rodent and human neurons[77]. However, studies suggest an antagonistic relationship between α-syn oligomers and F1Fo-ATPase. β-sheet α-syn oligomers interact with F1Fo-ATPase and induce mitochondrial dysfunction in PD[75]. Oligomeric α-synuclein induces selective oxidation of the F1Fo-ATPase subunit-β and mitochondrial

lipid peroxidation, increasing the probability of mPTP opening, triggering mitochondrial swelling, and ultimately cell death [Figure 2][74]. Studies in isolated mitochondria also suggest a direct effect of F1Fo-ATPase on α-syn oligomers preventing the pathological opening of mPTP. When α-syn undergoes misfolding and aggregation in PD, the ability of monomeric α-syn to enhance ATP synthase efficiency may be important for the development of PD[76]. Whether α-syn aggregates damage the structure directly or through any target to affect the function of F1Fo-ATPase still needs to be determined.

Monomeric α-syn interacts with F1Fo-ATPase, which is helpful for increasing the efficiency of ATP synthesis. α-syn oligomers lead to respiration injury and mitochondrial depolarization. In addition, oligomers-induced ROS leads to essential protein oxidation, lipid peroxidation and mPTP opening in mitochondria.

Recently, two missense mutations (T61I and R145Q) and one splice site mutation (c.300 + 5G > A) in *CHCHD2* have been identified in autosomal dominant familial PD[78]. The mechanism of function in MICOS complex includes the regulation of mitochondrial apoptosis and mitophagy[79]. Based on the structural characteristics of cristae, the functional regulation of F1Fo-ATPase may become an important direction to explore the pathological mechanism of PD pathogenic genes.

CONCLUSION

Previously, the mitochondrial hypothesis for neurodegenerative diseases has poorly focused on F1Fo-ATPase. This work presents evidence for the role of F1Fo-ATPase structure and dysfunction in neurological disorders, which strengthens the argument that F1Fo-ATPase dysfunction plays a role in neuro-energy metabolism disorders. Further study of F1Fo-ATPase related mitochondrial metabolic function and mechanism in neurodegenerative diseases is crucial to better understanding the pathological characteristics.

DECLARATIONS

Authors' contributions

Made the most contributions to conception and writing the draft: Zhou M

Performed data acquisition, as well as collected all the literature: Lin Y, Zhang Z, Tang Y, Zhang W, Liu H, Peng G, Qiu J, Guo W

Conceived the project and modified the manuscript: Chen X, Xu P

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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