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Review

Mitochondrial trafficking of APP and alpha synuclein: Relevance to mitochondrial dysfunction in Alzheimer's and Parkinson's diseases

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ABSTRACT

Mitochondrial dysfunction is an important intracellular lesion associated with a wide variety of diseases including neurodegenerative disorders. In addition to aging, oxidative stress and mitochondrial DNA mutations, recent studies have implicated a role for the mitochondrial accumulation of proteins such as plasma membrane associated amyloid precursor protein (APP) and cytosolic alpha synuclein in the pathogenesis of mitochondrial dysfunction in Alzheimer's disease (AD) and Parkinson's disease (PD), respectively. Both of these proteins contain cryptic mitochondrial targeting signals, which drive their transport across mitochondria. In general, mitochondrial entry of nuclear coded proteins is assisted by import receptors situated in both outer and inner mitochondrial membranes. A growing number of evidence suggests that APP and alpha synclein interact with import receptors to gain entry into mitochondrial compartment. Additionally, carboxy terminal cleaved product of APP, ~4 kDa Abeta, is also transported into mitochondria with the help of mitochondrial outer membrane import receptors. This review focuses on the mitochondrial targeting and accumulation of these two structurally different proteins and the mode of mechanism by which they affect the physiological functions of mitochondria.

1. Introduction

Nature of signal sequences required for directing a protein molecule to a specific cellular compartment have been defined [1,2]. Studies for the past several decades on the protein targeting have remarkably contributed to our understanding of mechanisms underlying the transport of protein molecule to a specific cellular compartment (as reviewed in Refs # [1–11]). Recent studies have demonstrated that several physiologically important protein molecules belonging to animal and plant kingdoms also target to more than one compartment suggesting the presence of multiple hidden signals in these proteins [12–26]. Studies have also suggested the need for post translational modifications to activate these hidden signals [13,19,21–25]. Nevertheless, we are still beginning to understand the mechanisms involved in the activation of hidden signals during the targeting of these proteins to multiple compartments and cellular consequences of multiple organelle localization. Mitochondria are vital organelles for various neuronal functions. The mitochondrion, a double-membrane structure organelle, contains machinery for transcription, translation, and five protein complexes involved in the oxidative phosphorylation to generate adenosine triphosphate (ATP). Each mitochondrion contains multiple copies of 16.5 kb DNA that codes for the 13 proteins. Among 13 proteins, seven are part of complex I, one of complex III, three of complex IV and two of complex V. To carry out the cellular commitments, mitochondria need to import a large number of proteins that are coded by nuclear DNA. Recent proteomic studies suggest that over 1500 nuclear encoded proteins are reported to be imported into mammalian mitochondria under physiological conditions [27]. Furthermore, dysfunction of these mitochondrial complexes is well documented during the pathogenesis of neurodegenerative disorders [28–48]. However, the precise cause for dysfunction of these complexes in the neurodegenerative disorders is not well understood. A large body of literature has suggested an important role for a number of factors including oxidative stress, mitochondrial DNA mutations, imbalance in calcium homeostasis and aging in the dysfunction of mitochondrial complexes [28–34,40,46,47]. In addition, recent studies have also implicated a role for targeting and accumulation of plasma membrane APP and cytosolic alpha synuclein to mitochondria in the pathogenesis of mitochondrial dysfunction in Alzheimer's and Parkinson's diseases, respectively [49–66]. It is not clear how APP and alpha synuclein accumulate in the mitochondrial compartment during the pathogenesis of AD and PD respectively. Mitochondrial targeting of alpha synuclein and APP is a challenging and newly emerging field, which may be an important contributor in understanding the mitochondrial dysfunction in neurodegenerative disorders. This review focuses on the role of players involved in the mitochondrial targeting of APP and alpha synuclein and the inhibitory effects of mitochondrial accumulated APP and alpha synuclein on wide varieties of mitochondrial physiological functions resulting in the mitochondrial dysfunction as seen in AD and PD, respectively.

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2. Alpha synuclein and mitochondrial dysfunction in PD models

PD is the second most common progressive neurodegenerative disorder in humans, which is associated with loss of dopaminergic neurons in substantia nigra [67–69]. Clinically, PD is characterized by severe motor dysfunction including uncontrollable resting tremor, muscular rigidity, impaired postural reflexes, and bradykinesia. One of the pathological hallmarks of PD and related synucleinopathies is intracellular inclusions called lewy bodies that consist of aggregated alpha synuclein [67–72]. Although, the physiological functions of alpha synuclein are not clear but several lines of evidence suggest that it may act as a chaperone that plays a role in regulating membrane stability, neuronal plasticity and enzymatic activities [67,68,71–73]. Moreover, constitutive levels of alpha synuclein may be important for maintaining the functional integrity of mitochondria inner membrane complexes I and III [57,74].

Alpha synuclein exhibits dynamic structural changes based on the local cellular conditions. Various triggering factors, either environmental or genetic, can lead to a cascade of events involving misfolding or loss of normal function of alpha synuclein [67–69,71–73,75]. Importantly, two autosomal dominant mutations (A53T), and (A30P) and triplication of the alpha synuclein gene resulting in the increased study state levels of synuclein were linked to familial early onset PD [76–78]. It is thought that mutant alpha synuclein proteins tend to aggregate more rapidly than the wild type human alpha synuclein, to form lewy body-like intraneuronal inclusions [67–69,71,72].

Several groups have shown mitochondrial dysfunction, oxidative stress and impairment of complex I in pathogenesis of PD [34–39]. Complex I is the largest and first of five electron transport linked oxidative phosphorylation complexes of mitochondria and catalyzes the oxidation of NADH, reduction of ubiquinone to generate proton gradient across the membrane. Defect in the function of complex I results in the production of reactive oxygen free radicals. Mammalian complex I is an L shaped structure consisting of 45 subunits. Functionally, the complex I can be subdivided into three distinct fragments. The first part is flavo mononucleotide containing NADH dehydrogenase segment, which is exposed to matrix side of mitochondria. The second part is iron sulfur clusters containing membrane buried portion, which is involved in electron transfer to the electron transporter ubiquinone. The membrane bound transporter segment is the third part of complex I, which is involved in proton translocation. Evidence for impaired complex I mediated mitochondrial dysfunction in PD comes from studies using cybrids that contained mitochondria from PD patients, which showed reduced complex I activity [79,80]. Moreover, chronic administration of rotenone, an inhibitor of mitochondrial complex I, to rat induced the degeneration of tyrosine hydroxylase positive neurons in nigrostriatal region indicating that the perturbation of mitochondrial functions may trigger PD like symptoms [81]. Furthermore, overexpression of either wild type or mutant alpha synuclein forms in cell culture systems as well as in transgenic animal models is associated with mitochondrial abnormalities, oxidative stress, and cell loss [57,59,62–64,66]. These studies clearly demonstrate the possible relationships among increased alpha synuclein levels, mitochondrial defects and PD pathology in human and rodent models

3. Mitochondrial abnormalities and APP in AD models

AD is the fourth leading cause of death in the developed world. Besides dementia, the most prominent clinicopathological features of this disease are extracellular deposition of amyloid plaques, intracellular neurofibrillary tangles, synaptic and progressive neuronal degeneration/loss [82,83]. Amyloid plaques consist of deposits of ~4 kDa peptide called beta amyloid (Abeta), which are derived through proteolytic processing of APP. APP occurs as 3 major isoforms due to alternative splicing of the gene. The shortest form, APP695, lacks the serine protease inhibitor domain and occurs predominantly in neurons while longer non-neuronal forms such as APP770 and APP751 contain the serine protease inhibitor domain [82,53]. However, normal physiological functions of endogenous APP are not thoroughly understood but are thought to be involved in the stabilizing contact points between synapses and maintaining mitochondrial functions [51,82,84].

Decreased energy metabolism, decreased mitochondrial fluidity and decreased activity of mitochondrial cytochrome *c* oxidase, a 13 subunit terminal oxidase in the respiratory chain, leading to mitochondrial dysfunction have been reported in various AD models [33,40–45]. A growing number of studies have reported a possible interconnection among accumulation of full length APP and its cleaved product, especially Abeta, oxidative stress and mitochondrial dysfunction in the cellular, transgenic and human AD models including Down's syndrome patients [85–98]. Upregulation of APP, which is influenced by aging, stress and depletion of tropic factors, is also considered to play an important role in the cellular abnormalities including mitochondrial dysfunction in AD [99–102]. However, the amount of APP expression needed to bring about cellular abnormalities varies from model to model and the presence of familial mutations in and around abeta domain of APP [49,52,85–90,103]. Higher levels of mutations bearing neuronal and non-neuronal forms of APP are reported to bring about mitochondrial abnormalities faster than their wild type counterparts [103]. Using biochemical and electron microscopy techniques, studies have observed that over expression of non-neuronal form APP751 in cultured human muscle-fiber cells and mouse embryonal carcinoma (P19) cells was associated with mitochondrial structural abnormalities and altered mitochondrial membrane potentials [88,89]. Collectively, these studies indirectly suggest the involvement of APP in the mitochondrial dysfunction.

4. Mitochondrial import machinery

The investigations of nature of targeting signals and the interaction with mitochondrial receptors of APP and alpha synuclein are of great importance to understand their direct role in the mitochondrial dysfunction. Mitochondrial targeting signals are rich in basic amino acids, which can form amphipathic α-helices. Majority of mitochondrial proteins have N-terminal mitochondrial targeting signals but in some proteins these signals can either be found at C-terminus or in the internal part of the protein molecule [104–106]. In addition, mitochondrial targeted proteins are required to maintain import competent unfolded confirmation to be recognized by translocases of outer membrane (TOM). The functions of these mitochondrial import receptors are well conserved in prokaryotic and eukaryotic organisms [106]. Mitochondrial import signals are first recognized by a group of major translocases of outer membrane namely TOM 70, TOM 20 and TOM 22 in a sequential manner. Recent study demonstrates that TOM70 can act like a chaperone to keep proteins in import competent confirmation [107,108]. Following the recognition of signals by these surface receptors, proteins are transported through TOM 40, which is a general import pore (GIP) forming protein [109]. Barrel forming outer membrane proteins are further recognized by another group of receptors called SAM (sorting and assembly machinery) complex, which assists the insertion of these proteins in to outer membrane [104–106,110]. Recent study has suggested that mitochondrial translocation of some proteins including the ones with N-terminal chimeric signals may involve by passing of outer membrane receptors such as TOM70, 20 and 22 but not TOM40 [111,112]. Proteins that are passed through TOM40 are further recognized by inner membrane translocases (TIM) namely TIM22 and TIM23. TOM40 channel is thought to be larger than TIM 22 and 23 channels. Importantly, targeting to inner membrane receptors requires ATP as well as mitochondrial membrane potential [104–112]. Polytypic inner membrane proteins are recognized by the TIM22 complex consists of