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Short Communication

Potential Implications of Mitochondrial Unfolded Protein Response in the Pathogenesis and Therapy of Dopaminergic Neuron Degeneration in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. The mitochondria dysfunction has long been appreciated in PD pathogenesis and can be the common pathological pathway contributing to dopaminergic (DA) neuron degeneration in PD. However mitochondria have its own quality control (QC) defensive systems to protect against stresses induced mitochondria impairment and cell degeneration. The mitochondrial QC system includes cellular QC and molecular QC systems. The mitochondrial cellular QC system includes mitophagy, mitofusion and mitofission processes. The mitochondria molecular QC system mainly refers to mitochondria unfolded protein response (mtUPR), including stress induced activation of expression of nucleus encoded mitochondria chaperones and proteases, which can be sent back to mitochondria to counteract against stress induced mitochondria impairment. So far little is known about mtUPR signaling pathway and its relevance to human diseases. The disturbance of mtUPR can be the cause for genetic factors as well as environmental factors induced mitochondria impairment and DA neuron degeneration in PD. The screening and identification of novel small molecular weight neuroprotective mtUPR activators can help develop future anti-PD drugs to alleviate progressive DA neuron degeneration in PD. Furthermore novel molecular targets identified in mtUPR signaling pathway and the potential crosstalk between mtUPR and PD relevant genes can add to PD pathogenesis and therapy. In this short review, these issues will be analyzed and discussed.

INTRODUCTION

Parkinson's disease (PD) is a chronic and incurable neurodegenerative disorder characterized by selective and progressive neurodegeneration of dopaminergic neurons in the *substantia nigra* (SN) , concomitant with Lewy body (LB) formation in affected brain areas [1,2]. PD is a prevalent human neurodegenerative disease whose occurrence crosses geographic, racial and social boundaries, affecting 1-2 % of the population above the age of 65 [3]. Clinically, PD patients demonstrate constellation of motoric deficits that progressively worsen with time, which ultimately contributes to almost total immobility. Although pathological changes can be distributed in the PD brain [4], the major lesion is the progressive loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc) of the midbrain [1,2]. The progressive DA neuronal loss leads to a severe decrease of striatal dopamine (DA) levels and thereby an impaired nigrostriatal function which can otherwise allow an individual to perform coordinated movements. Accordingly, L-DOPA administration to pharmacological up-regulate brain DA level represents an effective symptomatic alleviation therapy for PD patients [5]. However, neither L-DOPA nor any other available therapies can alleviate or terminate the progressive degeneration of DA neurons in the PD brain. To date, PD still remains an incurable human disease. Further understanding of the pathological mechanisms underlying DA neuron degeneration in PD as well as searching for new neuroprotective drug candidates will definitely be significant. Studies on these aspects can provide us novel therapeutic strategies and effective anti-PD drugs to control this formable disease and improve patients' life quality.

Mitochondria dysfunction has long been appreciated in PD pathogenesis [6] and can be the common pathological pathway contributing to neuronal death in human neurodegenerative diseases [7,8]. Mitochondrion is the centre cell organelle to generate ATP as the energy source, which is indispensible for cell proliferation and survival [9]. Furthermore mitochondria are also the major place to generate most of reactive oxygen species (ROS) in cells [9]. The impaired mitochondria will lead

to decreased energy production and increased ROS generation, which can contribute to DA neuron degeneration in PD [7]. However mitochondria have its own quality control (QC) defensive systems to protect against stress induced mitochondria impairment and cell demise [10-13]. The QC defense systems include molecular QC and organellar QC defensive systems respectively [14]. These QC systems can help maintain a steady pool of healthy mitochondrial essential for energy production and beyond. The mitochondrial protective organellar QC system involves mitochondrial fission and fusion as well as mitophagy processes [10]. The mitochondria molecular QC system is mainly referred to mitochondria unfolded protein response (mtUPR), including stress induced enhanced expression of nucleus encoded mitochondria chaperones and proteases, which can be delivered back to mitochondria to counteract against stress induced mitochondria impairment [10,15-17]. It is hypothesized that stress on mitochondria can trigger mtUPR, mitophagy and even apoptosis respectively depending on potency and duration of stress challenges [10]. The mtUPR is the first defensive process to be activated by stress induced disturbance of protein homeostasis in mitochondria prior to mitophagy. In case activation of mtUPR fails to restore protein homeostasis in mitochondria, the mitophagy process will be activated to clear away impaired mitochondria in time. However, if mitochondrial damage is too severe and irreversible, the cell will initiate apoptosis and sentence cells to death [10].

The stress of cells can lead to accumulation of misfolded and destroyed proteins in mitochondria contributing to mitochondria impairment, which can pose a threat to mitochondrial protein homeostasis and mitochondrial integrity [18]. However stress induced protein misfold and aggregation in mitochondria will trigger mtUPR , the primary mitochondria QC defensive response [19]. Briefly, mitochondrial chaperones can promote refolding of misfolded proteins to reduce protein misfold and aggregation in mitochondria [10,17,20]. The increased accumulation of unfolded proteins in mitochondria will also activate mitochondrial proteases [10]. The mitochondria proteases can degrade misfolded proteins and generate peptide fragments, which are supposed to be transported outside of mitochondria via specific transporter in mitochondrial membrane and get into cytosol to activate a potential receptor or a transcriptional factor. The activated factor may enter the nucleus to modulate mtUPR. On the other hand, protein misfolding and aggregation in mitochondrial will activate c-Jun N-terminal kinase (JNK) or dsRNA-activated protein kinase (PKR) via unknown mechanisms, which can up-regulate the expression of transcriptional factors CHOP and C/EBPβ [21,22]. The up-regulated CHOP and C/EBPβ can form dimmer, which binds to CHOP cis-element within the promoters of mitochondrial chaperones and proteases genes. The peptides activated or stress activated unknown factor are supposed to bind to MURE1 and MURE2 cis-elements near CHOP binding site in promoters of mitochondrial chaperones and proteases genes. Finally CHOP, C/EBPβ and the unknown factors work cooperatively to activate the expression of mitochondrial chaperones and proteases. The up-regulated levels of mitochondrial chaperons and proteases can be delivered back into mitochondria to restore protein homeostasis in mitochondria. The JNK kinase activities are indispensable to both cell proliferation and apoptosis [23]. The JNK kinases play a critical role in mitochondrial intrinsic apoptotic pathways [23]. JNK kinase can up-regulate the levels of pro-apoptotic genes via transcriptional modulation. Furthermore JNK kinases can also promote apoptosis via regulation of the activities of mitochondrial pro- and anti-apoptotic proteins through direct phosphorylation [23]. Therefore stress induced mitochondrial impairment and mtUPR protective mechanism seems to form a balance. Mild stresses can damage mitochondria; meanwhile, it can also activate mtUPR via JNK or PKR kinase pathways, which can help restore mitochondrial function and promote cell survival. Thus the balance can be maintained. Under serious stress challenges, the stress of cells can induce activation of mtUPR. However severe challenges of cells will significantly enhance JNK kinase activity, which will activate JNK kinase dependent apoptotic signaling pathway, destroy the balance and lead to cell demise. The proposed mechanisms are illustrated in Figure (1) in details.

The mitochondrial proteases and chaperones are the final executants of mtUPR process [24]. The mitochondrial ATP-dependent proteases and chaperones have 3 types of functions, including: 1), the recognition of inactive or misfolded mitochondrial proteins and promotion of their refolding to native state, 2), the resolubilization of aggregated mitochondrial proteins for either refolding or proteolysis degradation, or 3), the clearance of misfolded and aggregated proteins in mitochondria via protease degradation, if the misfolded protein can be refolded back to active state [10]. Typically, the main function of mitochondrial chaperones is to recognize and bind to unfolded mitochondrial proteins, and promote their stabilization and solubility [25]. The mitochondrial chaperones have various chaperones protein families, including HSP10, HSP70, HSP60, HSP90 and HSP100 protein families [24]. The expression of these HSP family members can be significantly induced under stress conditions. Mutations in Hsp60 are found in patients with an autosomal dominant form of hereditary spastic paraplegia (HSP), a human disease induced by degeneration of the upper motor neurons in the brain [26]. The Trap1, belongs to HSP90 family, is an important candidate with protective roles as a new member of the mitochondrial chaperone network [27]. The CLPX, a mitochondrial HSP100 protein, can bind with Clp protease to form large homo-oligomeric, ring-shaped protein complexes to clear away misfolded protein via Clp protease [28]. On the other hand, there are three classes of organellar proteases belonging to the chambered ATP-dependent mitochondrial proteases, which include the soluble proteases of the Lon protease family and the Clp protease family as well as the membrane-integrated FtsH-type mitochondrial proteases [10,24]. Most of the mitochondrial ATP-dependent proteases also have intrinsic chaperone activities or are functionally and structurally linked to other mitochondrial chaperones. The Lon is a representative of proteases that combine proteolytic and chaperone activities. In human cells, down-regulation of the LON protease can result in significant changes of the mitochondrial morphology and even apoptosis. The Clp protease is a large oligomeric protein complex where its active sites are separated from the environment in the interior of the enzyme, similar to most other mitochondrial proteases. The membrane-integrated FtsH-type mitochondrial proteases contain two sub-members with different membrane topologies (m-AAA and i-AAA proteases). The m-AAA FtsH-type

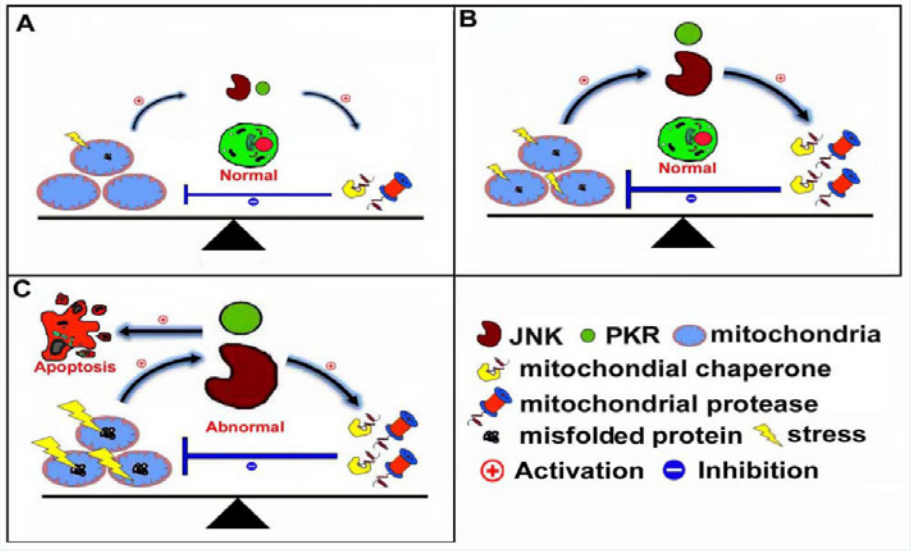

Figure 1 Various stresses induced mtUPR and relevant to cell viability
A, during normal mitochondria oxidation and phosphorylation (OXPHOS) process, ROS generated in mitochondria may cause slight protein misfold and aggregation, which can be controlled well by baseline mtUPR activity. B, under the mild stress challenges, stresses induced enhancement of protein misfold and aggregation in mitochondria can activate JNK and PKR kinase activities, which can increase expression of mitochondrial chaperones and proteases. The up-regulated expression of mitochondrial chaperones and proteases can be delivered back to mitochondria to cope with stress induced disturbance of mitochondrial protein homeostasis. Cells can still survival well under mild stress. C, under persistent and serious stress challenges, JNK and PKR kinase activities can be significantly enhanced. Although mtUPR may still be activated, significantly increased JNK and PKR kinase activities will activate apoptosis and lead to cell demise.

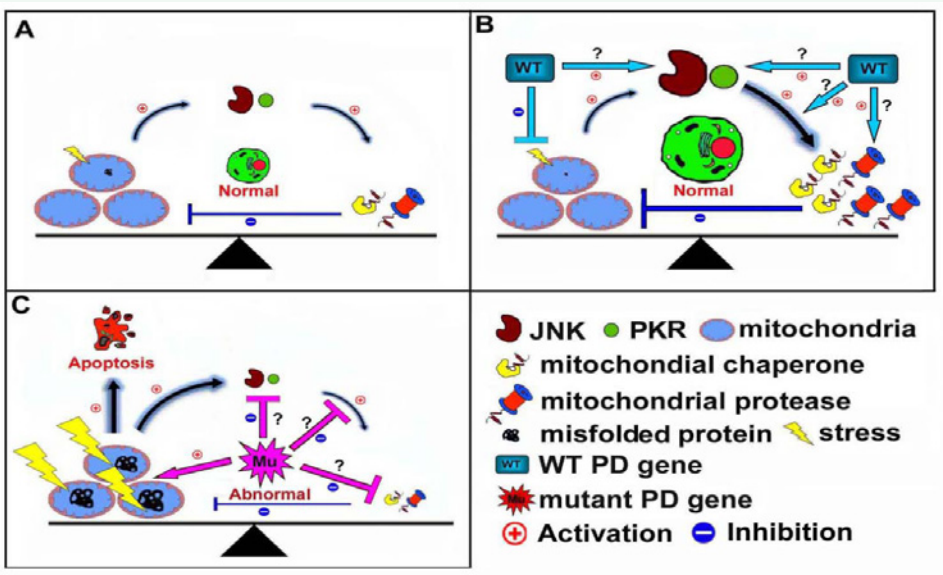

Figure 2 Crosstalk between mtUPR and PD genes, implications in PD gene mutation induced DA neuron degeneration in FPD.
A, under normal conditions, baseline level of mtUPR activities can maintain the mitochondrial protein homeostasis well. B, WT PD genes may play roles to enhance mitochondrial integrity and promote cell proliferation via following mechanisms: 1), WT PD gene can enhance mitochondria quality and reduce ROS levels; 2), WT PD genes may play roles in positively modulation of JNK and PKR kinase activities, therefore can up-regulate the baseline mtUPR activity to promote cell proliferation; 3), WT PD genes may play roles in facilitation of transcriptional modulation of expression of mitochondrial chaperones and proteases, therefore can also up-regulate the baseline mtUPR activity to promote cell proliferation; 4), WT PD genes may directly function on mitochondrial chaperones and proteases to enhance their functions. C, PD gene mutations may lead to impairment of mtUPR activity via following mechanisms: 1), mutations of PD genes can lead to continuous protein aggregates formation in mitochondria, leading to mitochondrial stress; 2), mutations of PD genes may lead to negatively modulation of JNK and PKR kinase activity; 3), mutations of PD genes may lead to inhibition of transcription of mitochondrial chaperones and proteases; 4), mutations of PD genes may lead to inhibition of mitochondrial chaperones and proteases. All these may account for PD gene mutations induced defects of mtUPR, mitochondria impairment and DA neuron degeneration in FPD.

proteases face the matrix compartment, whereas i-AAA FtsH-type protease faces the intermembrane space. Mutations of m-AAA protease subunits have been found in human patients with HSP. Furthermore mammalian mitochondria contain the forth protease family, the HtrA2/OMI proteases, localized in the intermembrane space of mitochondria [29]. The HtrA proteins consist of a serine protease domain and a PDZ domain, which is different from above-mentioned 3 kinds of organellar proteases. Without stress, HtrA2 is proteolytically inactive and the general chaperone function prevails. Under stress condition, the chaperone can be converted into a protease to cope with accumulated misfolded proteins in the mitochondrial intermembrane space. HtrA2 can also be strongly induced under stress conditions. More importantly, HtrA2 has been implicated in neurodegenerative diseases like PD and Alzheimer Disease [29]. As defects of mitochondrial functions have been found to be major culprits to PD and other aging-related diseases, therefore these mitochondrial chaperones and proteases may be highly relevant to the pathogenesis of these human diseases.

Mitochondrial impairment is the common pathway for environmental and genetic factors induced DA neuron degeneration in PD [30]. Mutations of multiple PD genes relevant to early onset and inherent familial form PD (FPD) has been found to be linked to mitochondria impairment [30]. PINK1 is a mitochondrial localized protein and mutations of PINK1 and Parkin can lead to inhibition of mitophagy and mitochondria impairment [31]. Mutation of FBXO7 is found to promote formation of deleterious protein aggregation in mitochondria [18]. CHCHD2 and COQ2 are both mitochondrial localized proteins, mutation of which can be relevant to PD onset [32,33]. The DJ-1 is also vital to mitochondrial functions [34]. In addition, increasing evidence implicates other PD-associated proteins such as α-synuclein (α-syn) and leucine-rich repeat kinase 2 (LRRK2) in mitochondrial dysfunction in genetic cases of PD [35-38]. Therefore, it is highly possible that PD genes may play significant roles in modulation of mtUPR signaling pathway. However, mutations of PD genes may have adverse impacts on mtUPR signaling pathway, which can be implicated in PD gene mutations induced mitochondrial impairment and DA neuron degeneration. It can be hypothesized that WT PD genes may facilitate mtUPR, whereas mutations of PD gene may lead to loss of physiological functions of WT proteins, contributing to mtUPR inhibition. It can be supposed that WT PD gene may facilitate mtUPR via several potential mechanisms, including positive modulation of JNK or PKR kinase activities; enhancement of activities of mitochondrial chaperones and proteases; promotion of activation of the unknown factor for MURE sites binding and transactivation of mtUPR genes. Therefore mutations of PD genes will impair mtUPR signaling pathway and contribute to mitochondrial vulnerability under stress. On the other hand, another possibility may also exist. The WT PD genes may not have significant influences on mtUPR signaling pathway. However mutations of PD genes can lead to protein misfolding and aggregation in mitochondria and this may be true to those mitochondrial localized proteins, such as CHCHD2, COQ2 and PINK1. At early stage, the activated mtUPR can help control the protein misfold in mitochondria and maintain the balance. However persistent presence of protein misfold and aggregation in mitochondria may abnormally activate JNK or PKR kinase activities, especially under increased stress challenges. The abnormal activated JNK or PKR kinase may activate apoptotic signaling pathway, leading to DA neuron degeneration in genetic mutation induced onset of FPD. The potential mechanisms for genetic factors induced impacts on mtUPR and subsequently influences on balance between stresses induced impairment and cell survival are illustrated in Figure (2).

The mtUPR is the primary defensive response for cells to deal with stress induced challenges. However, little is known about the molecular mechanism of mtUPR signaling pathway and relevance to pathogenesis of DA neuron degeneration in PD. More future works are expected. Novel identified neuroprotective mtUPR activators and therapeutic targets in mtUPR signaling pathway as well as crosstalk with PD genes will add to PD pathogenesis and therapy significantly. Considering the centre pathophysiological roles of mitochondria in pathogenesis and therapy of human diseases, new findings on mtUPR signaling pathway will have comprehensive impacts, which can ultimately benefit our patients and improve their life qualities.

AUTHORS' CONTRIBUTIONS

ZZD and CYX contributed to manuscript composition as well as construction of figures. TEK performed final manuscript revising and touching up. All authors read and approved the final manuscript.

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