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Mitochondrial Dysfunction: a Notable Contributor to the Progression of Alzheimer's & Parkinson's Disease

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Abstract

Mitochondrial dysfunctions remained a pivotal mechanism in manifold neurodegenerative diseases. Mitochondrial homeostasis within the cell is an essential aspect of cell biology. Mitochondria which is also known as the power-generating set of the cell, have a dominant role in several processes associated with the genomic integrity and cellular equilibrium maintenance. They are involved in maintaining optimal cells functioning and guidance from possible DNA damage which could lead to mutations and onset of diseases. Conversely, system perturbations which could be due to environmental factors or senescence induce changes in the physiological balance and result in the mitochondrial functions impairment.

The focal point of this review focuses on mitochondrial dysfunction as a significant condition in the onset of neuronal disintegration. We explain the pathways associated with the dysfunction of the mitochondria which are common amongst the most recurring neurodegenerative diseases including Alzheimer's and Parkinson's disease. Do mitochondrial dysfunctions represent an early event in causing a shift towards neuropathological processes?

Keywords- Mitochondrial dysfunction, Alzheimer disease, Parkinson's disease, Neurodegeneration, Amyloid β, Parkin.

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Introduction

Mitochondria is a significant constituent of the cell, sitting at the edge of cellular metabolism, energy production, and cell death. These distinct roles of mitochondria need a host of proteins working both in an inner and outer mitochondrial membrane. Proteomics has mapped over 1,000 constituents to the mitochondria (Hung et al., 2017 and Calvo et al., 2016) even though the mitochondrial genome only encodes for 13 genes. This shows that a major percentage of cellular factors partake in mitochondrial biology.

Classically, mitochondria are known as the powerhouse of the cell, and the active core producing ATP (adenosine triphosphate) for cellular activities. Thorough research on the functions and morphology of mitochondria revealed that they perform numerous roles. Remarkably, mitochondria have their genome, with the mitochondrial DNA (mtDNA) enclosed in the nucleoids in close relationship with the inner membrane of the mitochondria (Brown et al., 2011). Mutations in the mtDNA are responsible for several human diseases generally known as mitochondrial disorders (Steele et al., 2017). Also, mitochondria are dynamic and essential organelles with the capability to change their size and shape to respond to various cellular demands and preserve cellular homeostasis. For the cell homeostasis maintenance, mitochondria play a vital role in determining cell fate due to their involvement in regulating programmed cell death. Mitochondria are very sensitive to all subtle alterations disturbing the cell homeostasis which then alter their number and shape. The mechanisms of fusion and fission are essential, to increase their number or to repair a damaged mitochondrion, as in case of enlarged demand of energy or to enhance their exclusion when damaged to maintain cellular integrity.

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The dysfunction of mitochondria is related to some developmental and age-related diseases, mostly neurodegenerative diseases for example Alzheimer's, Parkinson's, and Huntington's disease, and amyotrophic lateral sclerosis.

Neurodegeneration results in the loss of function and structure of the neuronal system. The hallmarks of most neurodegenerative diseases involve abnormal accumulation and folding of proteins inside the neuronal cell bodies. These alterations in the protein metabolism commonly result in dysfunction and neuronal cell death in the central nervous system (CNS) (Reddy et al., 2017). The consequence of mitochondrial dysfunction in the development of neurodegeneration is captivating. Mitochondrial DNA (MtDNA) carries out numerous metabolic processes including the Krebs cycle and the respiratory chain to generate energy. Most of the time, the circular mitochondrial DNA accumulates mutations as the individual ages and these could result in mitochondrial dysfunction, capable of initiating many complications in the human body, such as the development and progression of neurodegenerative diseases (Kandimalla et al., 2018 and Reddy et al., 2018). The main reason for mitochondrial dysfunction is undecided; although, mtDNA mutation, oxidative damage and, accumulation of mitochondrial proteins resulting in abnormal mitochondrial morphology have been implicated. Since oxidative stress can destroy mitochondrial protein, lipids, and nucleic acid and also involve in the generation of intracellular reactive oxygen species (ROS), which can result in mtDNA mutations (Yin et al., 2016); this makes oxidative stress be a critical factor, responsible for mitochondrial dysfunction (Fig. 1).

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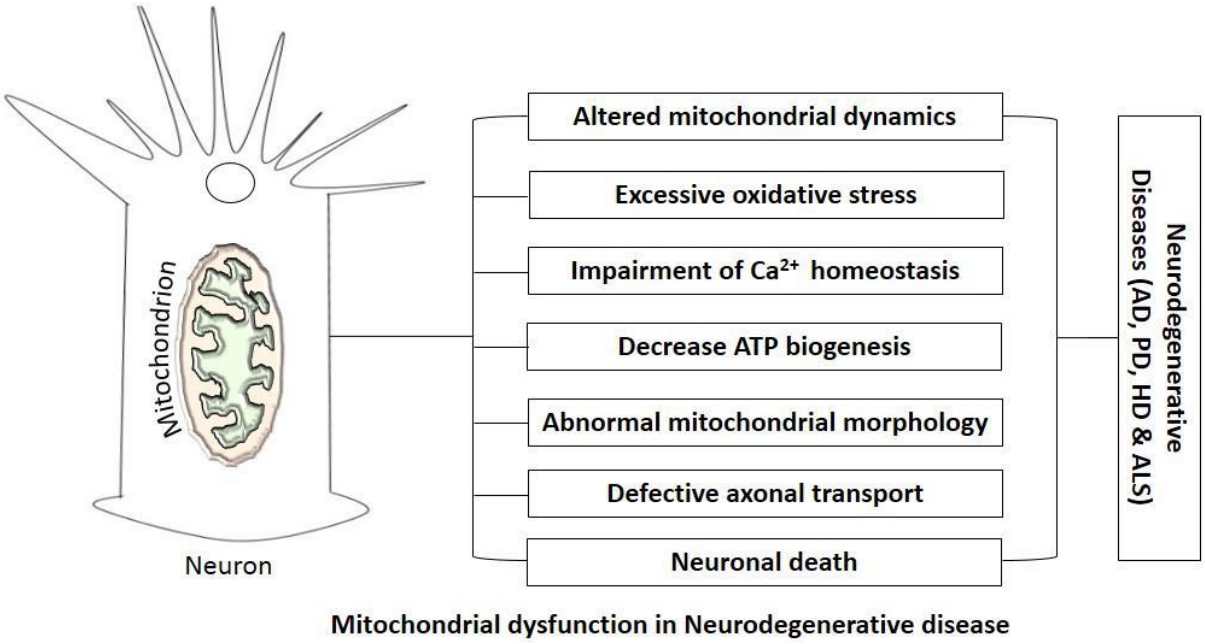

Figure 1- Mitochondrial Dysfunction in Neurodegenerative Disease (Kumar et al., 2018)

General Pathomechanisms of Alzheimer's and Parkinson's Disease

Neurodegenerative diseases comprise of heterogeneous disorders, described by the continuous loss of definite neuronal populaces and circuits in the CNS activated by mitochondrial dysfunctions (Kandimalla et al., 2018 and Yin et al., 2016). Generally, there is a switch in mitochondrial function [Fig. 2] in neurodegenerative diseases contributing significantly to the change to a degenerative condition from a normal physiological one. The aggregation of diverse stresses and the parallel aberration of series of cell-protective processes stimulate neurodegeneration.

The Amyloid hypothesis states that amyloid-β deposition and Tau protein which is an important protein for microtubule assembly is accountable for Alzheimer's disease pathogenesis. Beta (β) and gamma (γ)-secretase act on the Amyloid precursor protein (APP) and then cleave APP in amyloid-β (Aβ) peptides in sizes 38, 40, 42 of amino acids length. Outside the neurons, the largest fragment that is Amyloid-β-42 accumulates and oligomerizes which results in the formation of

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amyloid plaques (Finder 2010). However, through competitive binding, Amyloid-β-40 interacts with Amyloid β-42 in the monomeric and non-toxic states. It was then observed that Amyloid β-40 inhibits Amyloid β-42 fibril formation and also reduced the levels of Amyloid β-40 associated with the formation of plaque in Amyloid precursor protein transgenic mice. Meanwhile, Amyloid β-40 has a protective role in Alzheimer's disease (Yan and Wang 2007). Tau protein becomes phosphorylated in the neurons and then interacts with the other tau protein threads and resulting in the development of neurofibrillary tangles mostly in the pyramidal cells.

Hyper-phosphorylated tau proteins interact with the microtubule, which is responsible for the function and shape of neurons. Hyper-phosphorylation of Tau and aggregation are figured by Amyloid-β accumulation. Therefore, Amyloid-β aggregation was established to start a neurodegenerative cascade resulting in loss of a neuron and dementia known as the amyloid cascade hypothesis. Alzheimer's disease is a result of mutations in the Amyloid precursor protein, Presenilin (PS) -1 or -2 which increases Amyloid-β deposition.

The markers of Parkinson's disease comprise of the presence of intra-neuronal Lewy bodies and dopaminergic neurodegeneration with advanced Parkinson's disease cases showing a neuronal loss in the brainstem, sub-cortex, cortex and, peripheral autonomic sites. Mostly, Parkinson's disease is linked to genetic modifications such as E46K, A30P and, A53T mutations in gamma (γ) -synuclein, triplication of non-mutant gamma (γ)-synuclein resulting in excessive pathological protein buildup. Furthermore, Leucine-rich repeat kinase-2 (LRRK2), protein deglycase (DJ-1), PTEN-induced kinase-1 (PINK1) mutations culminate in mitochondrial dysfunction and also increase oxidative stress which then reduces the level cellular ATP involved in reducing proteasomal activity with low clearance of accumulated proteins. Likewise, parkin and ATP13A2,

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(gene that encodes lysosomal ATPase) mutations also disrupt the cellular protein breakdown machinery (Pan et al., 2008).

The double hit hypothesis affirms that Parkinson's disease progresses as an interaction between environmental factors and mutated genetic. Moreover, excitotoxicity is a fundamental feature for the development of Parkinson's disease. Hence, a combination of the damaging properties of multiple genetic mutations eventually results in pathological protein aggregation, reduced synthesis of ATP and, also dopaminergic neuronal death (Wu et al., 2019).

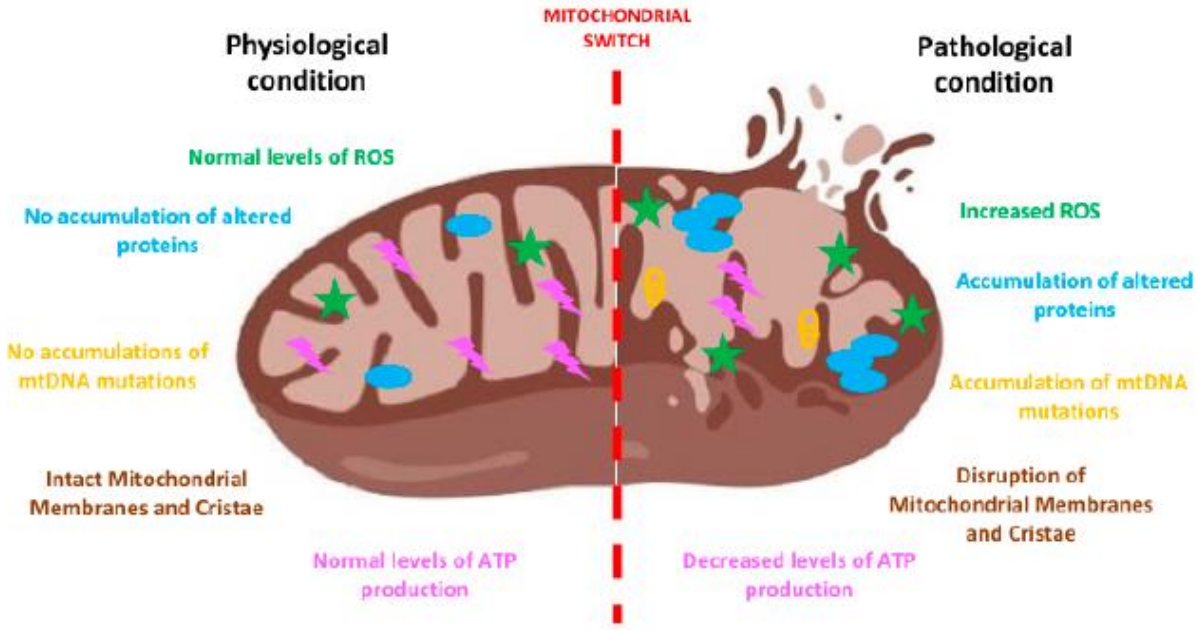

Figure 2- Mitochondrial Switch in Neurodegeneration (Wang et al., 2019)

Alzheimer's Disease (AD) and Mitochondrial Dysfunction

By 2040, Alzheimer's disease (AD) which is the commonest and devastating neurodegenerative disease has been predicted to affect over eighty-one million people globally (Selkoe and Hardy

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2016). AD's pathology is distinguished by senile plaques, mostly comprising of accumulated β-amyloid and intracellular neurofibrillary tangles generated by the aggregation tau protein. In the progression of Alzheimer's disease, two major players are mostly involved and these are – tangles and plaques.

Increased buildup of extra-neuronal amyloid plaques, resulting from the proteolytic processing of the APP (amyloid precursor protein) and NFTs (intra-neuronal neurofibrillary tangles), generated by hyper-phosphorylated tau protein (pTau) are typically examined in the brain cells of Alzheimer's individuals (Reddy and Beal 2008). Plaques consist of amyloid-β fibrils that gather from oligomeric and monomeric intermediates and are prognostic markers of AD. Interestingly, the early stage of Alzheimer's is detected by functionally and morphologically impaired mitochondria susceptible to increase production of reactive oxygen species (ROS), leading to a decrease in brain energy due to the reduction of ATP (Gomes and Santos 2013).

Once Amyloid-β is formed, it is capable of communicating with the mitochondria leading to additional mitochondrial aberrations. Amyloid-β overwhelms complex IV and α-ketoglutarate dehydrogenase and then binds to the mitochondrial matrix protein (Amyloid-β- binding alcohol dehydrogenase- ABAD). When the communication between Amyloid-β and alcohol dehydrogenase-ABAD) is inhibited, it indicates diminished Amyloid-β induced neuronal apoptosis and free radical generation. Amyloid-β prevents two major mitochondrial enzymes (α-ketoglutarate dehydrogenase and cytochrome oxidase) which are observed to be at a low level in the brains of subjects with AD. At the mitochondrial level, cells are more delicate to the apoptotic stimuli formed because of presenilin mutations. Presenilin forms an active gamma (γ)- secretase complex through interaction with Nicastrin (NCT), Anterior pharynx-defective (APH)-1 and, Presenilin enhancer (PEN)-2 and also responsible for breaking β-APP.

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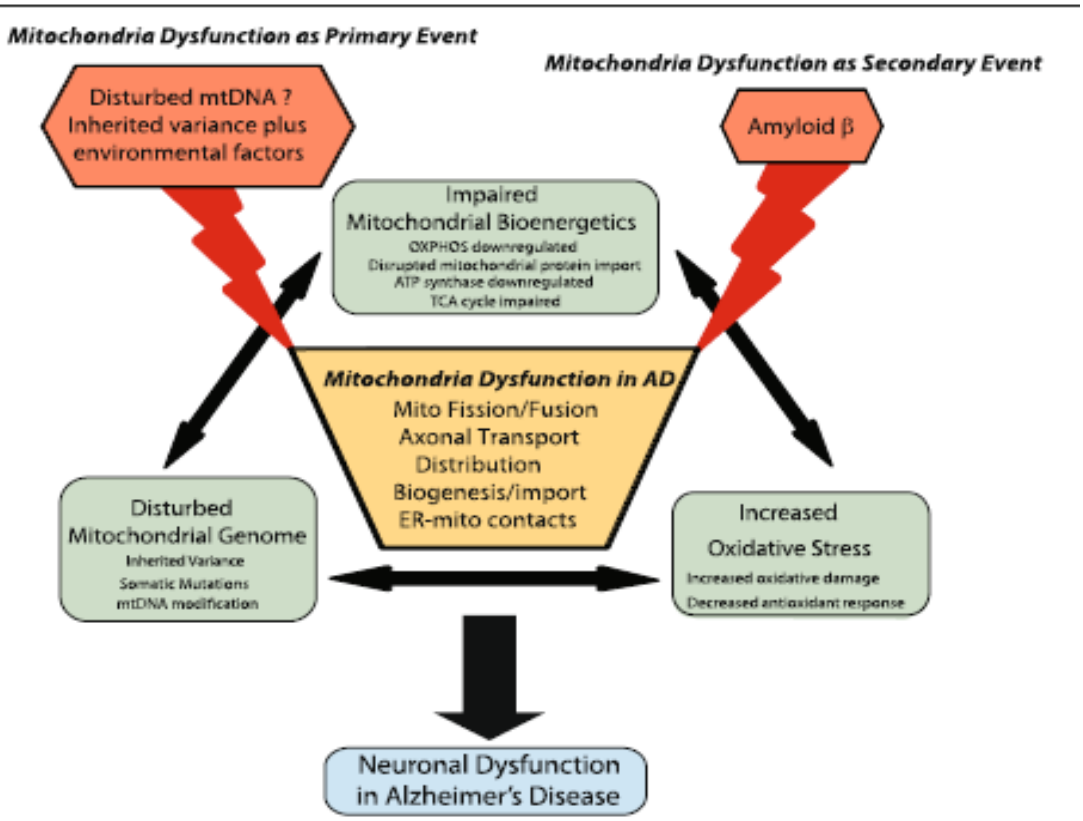

Figure 3- Critical Contribution of Mitochondrial Dysfunction in AD (Wang et al., 2020)

The first proof of the pathogenic mechanisms in AD is the progressive extracellular aggregation of β-amyloid peptide (Aβ) in the brain and neurofibrillary tangles of the hyper-phosphorylated tau proteins inside neurons, influencing the advanced loss of hippocampal and cortical neurons and then initiating brain atrophy, followed by cognitive and memory loss (Herholz 2012). Decrease activity in complex IV has been established in mitochondria from the hippocampus and platelets of Alzheimer's patients and in Alzheimer's disease cybrid cells (Du et al., 2010). A buildup of Amyloid-β results in mitochondrial dysfunction, energy failure and, oxidative stress (Fig. 3), before the progression of plaque pathology. Before amyloid and tau deposition, oxidative stress-induced damage takes place, and mitochondrial dysfunctions are initial events preceding neurodegeneration.

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Mitochondria look functionally and morphologically modified, impacting on many processes for example excess formation of ROS, leading to a reduction in brain energy due to decreased level of ATP, change in calcium homeostasis, and also apoptosis induction (Hroudová et al., 2014 and Kerr et al., 2017).

Parkinson's Disease and Mitochondrial Dysfunction

Parkinson's disease (PD), the second most common neurodegenerative disorder described by loss of dopaminergic neurons progressively in the substantia nigra pars compacta (SNpc), resulting in diminished motor function linked to α-synuclein aggregates (Lewy bodies) (Goedert et al., 2013). PD patients demonstrate a progressive rigidity and tremors of the muscle due to a low level of dopaminergic modulation on striatal neurons modifying motor systems (Hardy et al., 2009). Other markers of this disease include the presence of immuno-reactive α-synuclein and ubiquitin and inclusions of Lewy bodies. With over 680,000 people in North America as of 2010, (Marras et al., 2018) Parkinson's disease represents an increasing condition with an impact on approximately 10 million people globally.

For more than 20 years, studies of human patient mutations and cell biology have shown a surveillance model for mitochondrial through Parkin (E3 ubiquitin ligase) and PINK1 (PTEN-induced kinase 1) vital to support healthy neurons (Jin and Youle 2012). In healthy mitochondria, PINK1 is translated into the outer mitochondrial membrane (OMM) and then translocated into the mitochondria for proteolytic degradation. This shows that in healthy mitochondria, PINK1 levels are usually low. During mitochondrial impairment for instance membrane depolarization, PINK1 is not downgraded but then exists as a membrane-anchored component in the outer mitochondrial membrane (OMM). In its new localization, Parkin is activated through PINK1-mediated phosphorylation. Upon activation, mitophagy is initiated with Parkin-mediated ubiquitination signals, which is the selective degradation of mitochondria through the autophagosome.

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Mitochondrial dysfunctions have been associated with both familial and sporadic PD and are linked to conflicts of mitochondrial dynamics, morphology, and function (Bose and Beal 2016). High levels of reactive oxygen species, owing to the high metabolic call, control the build-up of toxic oxidative species and structural modifications of complex I, altering mitochondria functionality in brains of both human and mouse models (Perier et al., 2010). Furthermore, the accumulation of alpha (α)-synuclein oligomers initiates mitochondrial membrane permeabilization and direct toxicity via increase in the formation of reactive oxygen species and therefore resulting in neuronal death. Instabilities in calcium homeostasis and overload might initiate the of the mitochondrial permeabilization transition pore (MPTP) opening, leading to reactive oxygen species production, cytochrome C release, and induction of apoptosis.

In Parkinson's disease, mitochondrial dysfunctions also result in changes in mitochondria biogenesis due to transcription factors dysregulation for example the peroxisome proliferator-activated receptor (PPAR)- gamma coactivator 1-alpha (PGC1α) (Zheng et al., 2010). Additionally, mitochondrial fragmentation takes place swiftly after the loss of membrane potential was also observed in Parkinson's disease subjects. Also, fission and fusion proteins for example the dynamin-related protein 1 (DRP1) are transformed in familial Parkinson's disease model (Berthet et al., 2014). Remarkably, genes like PINK-1 and Parkin, that are connected with Familial-Parkinson's disease partake in the regulation of mitochondrial dynamics and many other genetic mutations, such as Parkin, PINK-1, LRRK2, DJ-1, and α-Synuclein, have been related to familial Parkinson disease and the resultant gene products also partake in mitophagy (Scarffe et al., 2014).

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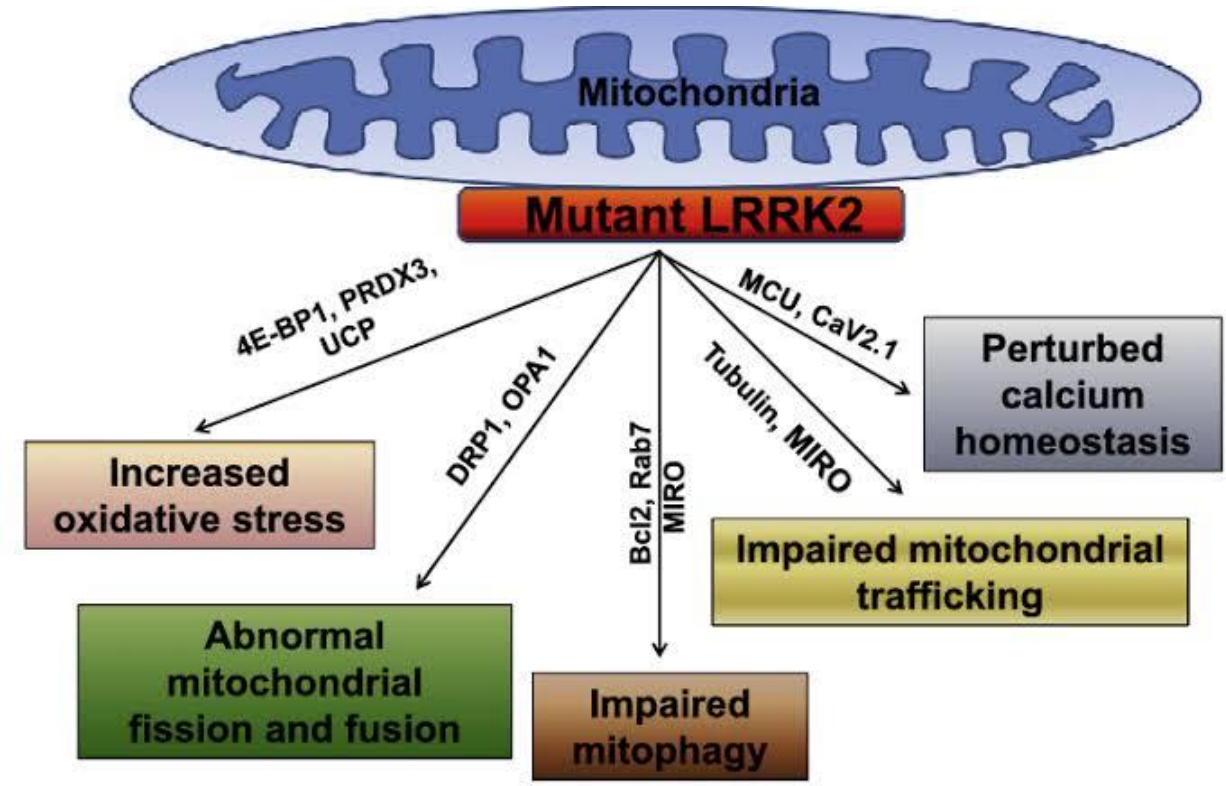

Figure 4- Molecules and pathways affecting the functions of Mitochondria (Singh et al., 2019)

Both Parkinson's and Alzheimer's disease involves modification in the mitochondrial DNA (mtDNA). Alpha-synuclein is the main protein in Parkinson's pathogenesis. Over-expression of the alpha (α)-synuclein leads to mitochondrial dysfunction and oxidative stress. Parkin is connected to the OMM, and then inhibits mitochondrial swelling, cytochrome c release and, caspases activation. In the proliferating cells, Parkin moves inside and with the mitochondrial transcription factor A (TFAM) leading to mitochondrial biogenesis. Parkin acts downstream to the PINK-1 and mutations in these results in excessive mitochondrial fission and reduced fusion. DJ-1 acts as a redox sensor and protects against oxidative stress by acidifying its cysteine residue.

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LRRK2 mutation also leads to excessive mitochondrial fission. Complex activity is reduced resulting in oxidative stress (Fig. 4) (Kumar et al., 2018).

Conclusion

Mitochondrial dysfunction is a common attribute in neurodegeneration. As mitochondria are organelles of the cell, any dysfunction in it results in the pathogenesis of several disorders. Certainly, mitochondrial dysfunctions emerge early in neurodegeneration and, their aggregation induces or exacerbates the degenerative cascade affecting neuronal tissue. Mitochondrial dysfunction and oxidative stress occur early in Alzheimer's and Parkinson's disease. There is testimony that it has a chief role in the pathogenesis of these diseases. Many disease proteins interact with the mitochondria such as Amyloid-β, ABAD, presenilin, DJ-1, PARKIN, PINK-1, alpha-synuclein.

List of Abbreviations

DNA- Deoxyribonucleic acid

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mtDNA- mitochondrial DNA

CNS- Central Nervous System

ROS- Reactive Oxygen Species

APP- Amyloid precursor protein

PS- Presenilin

LRRK2- Leucine-rich repeat kinase-2

DJ-1- protein deglycase

PINK1- PTEN-induced kinase-1

ATP- Adenosine triphosphate

AD- Alzheimer's Disease

PD- Parkinson's Disease

NFT- Neuronal neurofibrillary tangles

pTau- Phosphorylated tau protein

ABAD- Amyloid-β- binding alcohol dehydrogenase

NCT- Nicastrin

APH- Anterior pharynx-defective

PEN- Presenilin enhancer

SNpc- substantia nigra pars compacta

OMM- outer mitochondrial membrane

MPTP- mitochondrial permeabilization transition pore

PPAR- peroxisome proliferator-activated receptor

PGC1α- peroxisome proliferator-activated receptor (PPAR)- gamma coactivator 1-alpha

DRP1- dynamin-related protein 1

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TFAM- Mitochondrial transcription factor A

DECLARATION

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

Not applicable

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study

Competing of Interest

The authors declare that they have no competing interests

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Authors Contribution

All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Conceptualization- ASO Writing-initial draft preparation- ASO, TAO, AAA, BOF, JOT, NQ. Writing- review and editing- SQ, EMA, GEB, OO, Supervision- ASO. All authors read and approved the final manuscript.

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