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Impaired Mitochondria Promote Parkinson's Disease, Whereas Their Clearance Mitigates Its Progression

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Abstract: Parkinson's disease is the second most common progressive neurodegenerative disorder, after Alzheimer's disease caused by the selective loss of dopaminergic neurons in the substantia nigra region of midrain. Clinical symptoms include resting tremor, bradykinesia, postural instability and rigidity. Although ageing, genetic and environmental factors have been suggested as the putative risk factors for the progression of the disease, the exact molecular mechanisms involved in the pathogenesis of the disease remains elusive. Mitochondria are the power house of the cell where generation of the ATP takes place. Recent studies have shown the importance of the mitochondrial dysfunction in the pathogenesis of the disease. A number of the mitochondrial neurotoxin like MPTP, paraquat, rotenone etc has been shown to induce the PD like features. Dysfunctional mitochondria release the cytochrome c in the cytosol which results in the death of the neurons through the apoptosis. Thus clearance of the dysfunctioned mitochondria can be regarded as a key event in the prevention of the PD. A number of mechanisms including fission, fusion, mitochondrial derived-vesicles formation have been reported in the maintainance of the mitochondrial quality of which mitophagy is most important in the clearance of the defective mitochondria. Mitophagy refers to the removal of the defective mitochondria through autophagy. Parkin and PINK 1 are two proteins function cooperatively in the clearance of the defective mitochondria during autophagy. A strong link of PINK 1/Parkin has been suggested with mitochondrial dysfunction, mitochondrial vesicular trafficking, mitochondrial dynamics, quality control and mitophagy. Pink1 is a ser- thr kinase which fuctions as sensor and detects the dysfunctioned mitochondria, after which it recruits cytosolic Parkin having E3 Ubiquitin ligase activity to depolarized mitochondria. Parkin then ubiquitinates the dysfunctiond mithochondria and directs them towards the autophagy for the clearance. Defects in the lysosomal-autophagy pathway or mutations in the PINK/ Parkin may result in poor clearing of the dysfunctioned mitochondria that ultimately results in the generation of the ROS generation and PD pathogenesis.

Keywords: Parkinson disease, Mitochondria, Autophagy, PINK1, Parkin, Mitochondria, Mitophagy, VDAC1, MDVs, UPS.

I. INTRODUCTION

Parkinson's disease is the second most common progressive neurodegenerative disorder, after Alzheimer's disease caused by the selective loss of dopaminergic neurons in the substantia nigra region of the midbrain. Clinical symptoms includes resting tremor, rigidity, bradykinesia and postural instability (Kashif et al 2024, Daur et al.2003). The disease is further characterized by the presence intra-neuronal cytoplasmic inclusion called Lewy bodies in the brain of the PD patients. Despite first scientific description of the disease in 1817 by James Parkinson, the complete molecular mechanisms involved in the pathogenesis of the disease has yet to be deciphered (Dauer et al., 2003). Age, environmental and genetic factors has been suggested as the putative risk factors in the development of the disease (Di Monte *et. al.,* 2002).

Mitochondria are the dynamic organelle present in the cell which are involved in the generation of the ATP through a tightly regulated process of the oxidative phosphorylation (Lee et al.2025, Cadenas et. al., 2000). The generation of the ATP involves the flows of the electrons over the electron transport chain. But under certain conditions the electrons may leak out over the respiratory chain and may result in the generation of the ROS resulting in the mitochondrial dysfunction (Chance et. al., 1955).

The first link between Parkinsonism and mitochondria became evident in the early 1980s, when it was discovered that MPTP, a neurotoxin that causes Parkinsonian syndrome, also inhibits mitochondrial respiration by inhibiting the complex-I of mitochondrial electron transport chain (Nicklas et.al., 1985). Other complex I inhibitors such as rotenone and paraquat also produce parkinsonian features and these toxin-induced PD models are being used for mechanistic and therapeutic purposes (Kashif et al 2024, Bezard and Przedborski, 2011; and Cannon and Greenamyre, 2011). Interestingly, consumption of fruit and herbal teas from plants of the Annonceae family, containing the complex I

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inhibitor annonacin, has been linked to the high frequency of atypical parkinsonism in Guadeloupe (Lannuzel et al, 2003; Champy et al, 2004), further substantiating a causal role of mitochondrial dysfunction in the pathogenesis of at least some Parkinsonian syndromes. The decreased complex I activity has been reported (in the range of 30%) in the autopsy samples of SNpc and frontal cortex of PD patients (Parker et al, 2008). In mitochondrial preparations from PD frontal cortex samples, complex I subunits derived from both mitochondrial and nuclear genomes were found to be oxidatively damaged as reflected by an increase in protein carbonyls (Keeney et al, 2006). These results clearly show the importance of mitochondrial dysfunction in PD pathogenesis.

Multiple mechanisms have been utilized by mitochondria to maintain their homeostasis. First, mitochondria have their own proteolytic system, allowing them to degrade misfolded proteins that could potentially disrupt mitochondrial function (Almer et al.2001). Second, damaged outer mitochondrial membrane proteins can be degraded by the proteasome (ME Gegg et al.2010). Third, mitochondria can undergo constant fission and fusion to repair damaged components of the mitochondria, which allows for segregation of damaged mitochondria via the fission process and exchange of material between healthy mitochondria via the fusion process (S Ehses et al.2009, Palmer et al.2011). Fourth, a portion of mitochondria can bud off and form mitochondria-derived vesicles(MDV) under oxidative stress conditions, which further fuse with lysosomes to degrade oxidized mitochondrial proteins within MDV (G.McLelland et al.2014). Fifth, damaged mitochondria can form mitochondrial spheroids and acquire lysosomal markers to possibly serve as an alternative pathway for removal of damaged mitochondria . Finally, damaged mitochondria can be enveloped by autophagosomes to trigger their degradation in the lysosome via mitophagy (ME Gegg et al.2010).

Autophagy is the process by which the routine turnover of the organelle takes place. In general autophagy refers to any cellular degradative pathway that involves delivery of the cytoplasmic cargo to the lysosome (He et al.2026, Lin et al.2012). In a cell, three types of autophagy have been recognized: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy initiates with the de novo formation of a cup-shaped isolation double membrane (also called phagophore or preautophagosome) that engulfs a portion of cytoplasm (Levine et al 2011). The isolation membrane then encloses to form a mature vesicle, i.e., autophagosome, that subsequently fuses with a lysosome, leading to the degradation of intra-autophagosomal components by lysosomal hydrolases. Microautophagy involves the engulfment of cytoplasm instantly at the lysosomal membrane by invagination, protrusion, and separation (Cesen et al. 2012). Chaperone-mediated autophagy, on the other hand, is a process of direct transport of unfolded proteins via the lysosomal chaperonin hsc70 and LAMP-2A, a lysosomal membrane receptor (Bandyopadhyay et al.2008). Of these three types, macroautophagy is most prevalent and most frequently referred to as “autophagy,” and it is the macroautophagy only by which the routine degradation of the organelle takes place. While considering the removal of the damaged mitochondria macro-autophagy is most important and a term mitophagy is frequently used for this process. PINK 1 and Parkin are proteins which are involved in the process of the mitophagy (WX Ding et al 2012).

PINK-1 is a serine /threonine kinase that is encoded by the PARK-6 gene. PINK1 gene is composed *of* eight exons, encodes a 581-amino acid protein with a predicted molecular mass of 62.8 KDA (Thayer et al.2026). It contains an N-terminal mitochondrial localization sequence, a putative trans-membrane sequence, a Ser/Thr kinase domain, and a C-terminal regulatory sequence . (Valente et al., 2004). One of the most important role of the PINK1 is mitophagy. Under normal condition level of PINK-1 is present in the undetectable amount as it is degraded by the PARL enzyme in the mitochondria (SM Jin et al 2010). Mitochondrial depolarization results the accumulation of the PINK 1 over the mitochondria which further promote the translocation of the Parkin from the cytosol to mitochondria (Pridgeon et al., 2007). The figure 1 depicts the difference between the molecular events occurring in healthy verses damaged mitochondria.

Parkin is a 465 amino acid enzyme comprising a regulatory Ubl domain (residues 1–76); a RING0 domain (residues 145–215); a RING1 domain (residues 237–292) that binds to an E2; an IBR domain (residues 327–378); and a RING2 domain that mediates the enzyme's catalytic activity (415–465) (Zhao et al., 2026, Shimura et al., 2000). Parkin contains a highly conserved catalytic cysteine (Cys^{431}) within its RING2 domain, which acts as a ubiquitin acceptor that forms an intermediate thioester bond prior to ubiquitylation of its substrate. It plays a important role in Ubiquitin Proteosome System and is a regulator of protein breakdown. It is located in the cytoplasm until depolarization occurs as a result of which it is translocated to mitochondria to induce mitophagy (Narendra et al., 2008). It maintains the mitochondrial integrity. Mitophagy is the process in which the damaged mitochondria are cleared out that cannot withstand the normal cell’s metabolic requirements.

The current review talks about the role of mitochondrial dysfunction in the development of PD,molecular mechanisms involved in the clearance of the defective mitochondria and the emerging strategies in the prevention of the Mitochondrial dysfunction and PD.

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II. ENVIRONMENTAL TOXINS, MITOCHONDRIAL DYSFUNCTION AND DEVELOPMENT OF THE PARKINSON DISEASE.

2.1 MPTP

A group of heroin users in the USA in late 70s developed acute and irreversible parkinsonian features after using illicit drugs intravenously. It was due to the neurotoxic effects of the compound MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a by-product in the synthesis of a meperidine analog (Jiao et al., 2026, Davis et al., 1979, Langston et al., 1983). Patients who died 2 years after the onset of parkinsonian symptoms showed degeneration of dopaminergic neurons in the substantia nigra pars compacta (Davis et al., 1979). Systemic exposure of MPTP in animal models also results in the neurodegeneration of the dopaminergic neurons, PD characterstic. MPTP actively crosses the blood brain barrier due to its lipophilic nature and is oxidized to a toxic molecule, MPP+ (1-methyl-4-phenylpyridinium) by monoamine oxidase in the glial cells (Markey et al., 1984). MPP+ is taken up by dopamine transporter into dopaminergic neurons and accumulates in the mitochondria and inhibits the mitochondrial complex I (Ramsay et al., 1986) in the electron transport chain and thereby disrupts the flow of electrons resulting in decreased ATP production and increased generation of ROS.

2.2 Paraquat

Paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride) is a commonly used herbicide ,structurally very similar to MPTP and has long been linked to human PD (Kocanci et al., 2026, Tanner et al., 2011,). Paraquat has a long half-life following systemic administration caused selective and dose-dependent loss of dopaminergic neurons (McCormack et al., 2002). Paraquat chronic administration resulted in progressive increase in dopaminergic neuronal loss and reduced dopamine levels (Ossowska et al., 2005). Paraquat accumulates in mitochondria (Cocheme and Murphy, 2009) and acts as a potent redox cycler which converts free radicals that further on interacts with molecular oxygen to superoxide and other ROS (Yumino et al., 2002). Paraquat redox cycling is further confirmed by studies showing overexpression of SOD (Thiruchelvam et al., 2005) or compounds that mimic SOD (Mollace et al., 2003) show protection against the adverse effects of paraquat.

2.3 Maneb

Maneb is a manganese-containing ethylene-bis-dithiocarbamate compound used as a fungicide to treat numerous plant diseases results in human Parkinsonism (Meco et al., 1994). It results into an increased risk of developing PD in individuals also exposed to paraquat (Ritz et al., 2009). Maneb administration in mouse models induces deficits in motor behavior (Morato et al., 1989). Combination of paraquat and maneb induces nigrostriatal cell death (Saint-Pierre et al., 2006, Kachroo et al., 2010). Maneb inhibits proteosome activity in vitro (Zhou et al., 2004, Wang et al., 2006). It inhibits mitochondrial complex III of the electron transport chain resulting in ROS production in isolated mitochondria of rat brain (Zhang et al., 2003) and impaired mitochondrial function in primary mesencephalic neuronal culture (Domico et al., 2006). Maneb potentiates mitochondrial ROS production by causing mitochondrial dysfunction and inhibiting mitochondrial complex III. These effects may contribute to its ability to increase PD risk in humans (Ritz et al., 2009.)

2.4 Rotenone.

Rotenone is a naturally occurring organic compound used as a pesticide. It is a specific mitochondrial complex I inhibitor act systemically due to its high lipophilicity, readily cross the blood brain barrier and biological membranes (Nies et al., 2024). It binds to the acceptor end of the enzyme causing an increase in the reduction state of the complex and leads to the leakage of electrons that combine with oxygen to form superoxide (Nicholls, 2008). Rotenone results in increased risk of developing human PD (Tanner et al., 2011). In rats, chronic intravenous administration of rotenone caused selective nigral dopaminergic neuronal loss and a significant reduction in complex I activity (Betarbet et al., 2000). Rotenone pathology closely resembles sporadic PD. Rotenone toxicity results into oxidative damage to proteins, PD-related motor deficits (Fleming et al., 2004) and Lewy body-like inclusions immunostained for α-synuclein and ubiquitin were observed in the substantia nigra and striatum (Sherer et al., 2003).

III. MECHANISMS OF GENERATION OF THE MITOCHONDRIAL ROS

Major biological function of mitochondria is ATP production by oxidative phosphorylation (Cadenas et al. 2000). This process is based on aerobic oxidation of hydrogen in which electron transfer occurs over the mitochondrial respiratory chain. NADH at complex I or succinate at complex II supplies electrons. Electron transfer to complex III mediated by ubiquinone reduces complex IV. Complex IV couples oxygen reduction to water and the proton pump, transporting protons (H+) from the matrix to the inter-membrane space. Respiring mitochondria generate the proton motive force across the inner membrane, which results in a negative charge inside and produces a pH gradient (Chance et al. 1955).

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During the process of the aerobic oxidation, electrons can leak at several sites over the respiratory chain creating superoxide radicals (O2 •−). (Hans et al.2003). The main sources of mitochondrial ROS under physiological conditions are complexes I and II, which produce O2 •− mainly on the matrix side, rapidly dismutated to H2O2 by mitochondrial manganese superoxide dismutase (SOD2) (Hans et al.2001). Other sources of mitochondrial O2 •− may include α-ketoglutarate dehydrogenase, pyruvate dehydrogenase (Starkov et al.2004), glycerol-3- phosphate dehydrogenase, fatty acid β-oxidation (Brand et al.2010), and complex III (Tahara et al. 2009). During the PD development , one of the mitochondrial complexes, particularly complex 1 and complex 3, are inhibited which results in mitochondrial ROS generation.

IV. MECHANISMS BY WHICH THE DYSFUNCTIONED MITOCHONDRIA CAN RESULT IN THE CELL DEATH

Mitochondrial permeability transition (MPT) has been proposed to be responsible for the mitophagy of depolarized mitochondria in mammalian cells (Lemasters et al., 2002). MPT regulates apoptosis and necrosis in mammalian cells, is mediated by the permeability transition (PT) pore, composed of voltage-dependent anion channel (VDAC) in the outer membrane, the adenine nucleotide translocator (ANT) in the inner membrane, and cyclophilin D (CypD) in the matrix space. In addition, creatine kinase (found in the intermembrane space), hexokinase (outer membrane), and Bax (outer membrane) are thought to be associated with PT pores. Mitochondria become permeable to all solutes up to a molecular mass of about 1500 Da after the onset of MPT, which can lead to mitochondrial depolarization. MPT triggers the release of proapoptotic mitochondrial intermembrane space proteins into the cytosol, which include cytochrome c, apoptosis-inducing factor.

V. GENES INVOLVED IN THE MITOCHONDRIAL DYSFUNCTION AND DEVELOPMENTAL OF PARKINSON DISEASE.

5.1 Alpha-synuclein

α-synuclein is a 140-amino acid presynaptic protein expressed in the central nervous system, prone to fibrillar aggregation due to its hydrophobic non-amyloid beta component domain. Three different missense mutations (A530T, A30P and E46K) and duplication or triplication of the α-synuclein gene (PARK1, SNCA) are associated with autosomal dominant PD (Kruger et al., 1998, Zarranz et al., 2004). α-synuclein fibrillar forms are a major component of the Lewy bodies, provides a link between sporadic and familial PD. Mitochondrial toxins administered to rodents and cell cultures leads to the formation of α-synuclein aggregates and inclusions (Fornai et al., 2005). Ubiquitin proteosomal pathway inhibition in vitro causes accumulation of unfolded proteins leading to mitochondrial dysfunction and neuronal cell death (Tanaka et al., 2001). Protein aggregation and mitochondrial dysfunction in PD pathogenesis are interlinked and complementary to each other. Mitochondrial α-synuclein in human brain shows significant accumulation of α-synuclein in the substantia nigra and striatum of PD patients (Devi et al., 2008). A fraction of cytosolic α-synuclein has been found within the mitochondria in specific regions (Nakamura et al., 2008, Shavali et al., 2008) suugesting the role of the α-synuclein in the mitochondrial dysfunction and developmentof the PD.

5.2 PINK-1

PINK1 (PTEN-induced putative kinase; PARK6) gene mutations are the second most common cause of autosomal recessive, early onset PD after Parkin mutations (Valente et al., 2004). PINK1 is a 581 amino acid protein with a highly conserved serine/threonine kinase domain and an N-terminal mitochondrial targeting sequence (Valente et al., 2004, Silvestri et al., 2005). Sub localization of PINK1 in different regions including inner mitochondrial membrane (Pridgeon et al., 2007), intermembrane space (Pridgeon et al., 2007) and outer mitochondrial membrane (Gandhi et al., 2006). PINK1 knockdown in human dopaminergic neurons and in primary neurons derived from PINK1 knockout mice result in widespread mitochondrial dysfunction including abnormalities in mitochondrial morphology, reduced membrane potential, increased ROS generation and high sensitivity to apoptosis (Wood-Kaczmar et al., 2008). Overexpression of PINK1 restored normal mitochondrial morphology and inhibited ROS production indicating the importance of PINK1 in maintaining mitochondrial morphology and protecting neurons from ROS (Wang et al., 2011). These results clearly shows the importance of the PINK in the normal functioning of the mitochondria and in disease prevention.

5.3 Parkin

Mutations in parkin (PARK2) gene have been reported to cause autosomal-recessive juvenile parkinsonism (Abbas et al., 1999). The parkin gene encodes a 465 amino acid protein having E3 ubiquitin ligase activity and is involved in the proteasome mediated degradation of numerous proteins (Shimura et al., 2000) and the clearance of the defective mitochondria. The loss of E3 ligase activity causes accumulation of toxic protein aggregates leading to PD. Parkin is

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localized in the mitochondria and its functions are associated with mitochondria as well. In proliferating SH-SY5Y cells, parkin was found exclusively inside mitochondria where it binds to mitochondrial transcription factor (TFAM) to regulate mitochondrial transcription and replication (Kuroda et al., 2006). Parkin overexpression in differentiated PC12 cell cultures prevented ceramide induced mitochondrial swelling and cytochrome c release (Darios et al., 2003). Overexpression of parkin in mice attenuated dopaminergic cell loss induced by MPTP through protection of mitochondria and reduction of α-synuclein (Bian et al., 2012). Defective mitochondria have been shown in the brain of PD patients having parkin mutations. These results shows the involvement of the parkin in the mitochondrial dysfunction and in the pathogenesis of PD.

5.4 LRKK2

LRRK2 (Leucine-rich repeat kinase 2; PARK8) mutations have been shown to cause autosomal dominant PD. These mutations are associated with a majority of familial PD cases and are also linked to sporadic late-onset PD (Klein and Schlossmacher, 2006). The LRRK2 gene encodes a 2527 amino acid protein which is a serine/threonine kinase containing a conserved mitogen-activated protein kinase kinase kinase (MAPKKK), a Roc domain with Ras/GTPase, a WD40-repeat domain and leucinerich repeats (Biskup and West, 2009, Gandhi et al., 2009). In vitro studies have reported that LRRK2 mutations lead to increase in its kinase activity responsible for the neurotoxicity (Smith et al., 2006). Over-expression of LRRK2 mutated proteins in vitro leads to apoptotic neuronal cell death resulting in mitochondrial dysfunction. In cortical neurons the LRRK2 G2019S mutation results in defects in mitochondrial morphology and dynamics. Expression of LRRK2 also increases ROS production. Endogenous LRRK2 interacts with Dynamin like protein 1 (DLP1) in neurons and LRRK2 expression leads to translocation of DLP1 from the cytosol into the mitochondria suggesting a functional role for LRRK2 (Niu et al., 2012). LRRK2 mutations affect mitochondrial function and morphology (Mortiboys et al., 2010).

5.5 DJ-1

DJ-1 is a multifunctional 189 amino acid protein with antioxidant and transcription modulation properties. Mutations in DJ-1 (PARK7) gene cause rare cases of autosomal recessive, early onset parkinsonism (Bonifati et al., 2003). Under basal conditions DJ-1 is localized in the cytosol and to a lesser extent in nucleus and mitochondria (Zhang et al., 2005). However, in oxidative stress conditions DJ-1 translocates to mitochondria, where it is found in the matrix and intermembrane space, and later to the nucleus. DJ-1 translocation into the mitochondria and nucleus provides neuroprotection (Junn et al., 2009). The translocation of DJ-1 is facilitated by the oxidation of cysteine 106 to cysteinesulfinic acid which is vital for DJ-1 function in the mitochondria (Blackinton et al., 2009). In vitro silencing of DJ-1 using siRNA in neuronal cells showed increased cell death induced by oxidative stress, ER stress and inhibition of proteasome (Taira et al., 2004). DJ-1 null dopaminergic neurons showed deficiency in mitochondrial complex I activity leading to defective supercomplex formation. These defects were reversed by DJ-1 overexpression indicating the specific role of DJ-1 in mitochondrial dysfunction (Heo et al., 2012). These results clearly shows the importance of the DJ-1 in the mitochondrial dysfunction leading to to PD pathgenesis.

VI. MOLECULAR MECHANISMS INVOLVED IN THE MAINTENANCE OF THE MITOCHONDRIAL HOMEOSTASIS AND CLEARANCE OF THE DEFECTIVE MITOCHONDRIA

6.1 Mitochondrial fisssion

Mitochondrial fission in mammals is mediated by dynamin related protein 1(Drp1), a large GTPase. Drp1 is a cytosolic protein that can be recruited to the outer mitochondrial membrane to constrict the mitochondria resulting in eventual division of a mitochondrion into two separate organelles. Drp1 interacts with four mitochondrial receptor proteins: fission 1(Fis1), mitochondria fission factor (Mff), mitochondrial dynamics protein of 49kDa (MID49) and MID51. The interaction between Fis1 and Drp1 has a minor role in regulating mitochondrial fission whereas the interactions of Drp1 with the other three receptor proteins is critical for the fission to occur (Otera e al 2010, Palmer et al.2011, Loson et al.2013) . Drp1can also localize at the endoplasmic reticulum–mitochondria contact site may play a role in the process of mitochondrial fission (Friedman et al 2011) (Figure 2).

6.2 Mitochondrial fusion

Mitochondrial fusion is another mechanism by which mitochondrial homeostasis is maintained. Mitochondrial fusion in mammals is mediated by the fusion proteins mitofusin 1 (Mfn1) and Mfn2 and optic atrophy 1 (OPA1). Mfn1 and Mfn2 are responsible for fusion of outer mitochondrial membranes, OPA1 is involved in the fusion of inner mitochondrial membranes. Presenilin associated rhomboid-like (PARL) (Cipolat et al.2006) and paraplegin (an AAA protease present in the mitochondrial matrix) (Ishihara et al. 2006) induce alternative splicing and alternative processing of OPA1 to generate eight OPA1 isoforms. However, OPA1 processing still occurs in PARL or paraplegin knockout MEF cells, suggesting that other factors may also be involved in OPA1 processing (Caubet et al.2007). Yme

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can further cleave OPA1 under normal conditions to generate Short and Long forms of OPA1 (S-OPA1 and L-OPA1) (Griparic et al.2007), where L-OPA1 is integral in the inner membrane and S-OPA1 is located in the intermembrane space. L-OPA1 is further cleaved by the inducible protease OMA1 when mitochondria are depolarized by the mitochondrial uncoupler carbonyl cyanide m-chloro phenyl hydrazine (CCCP), resulting in mitochondrial fragmentation by preventing mitochondrial fusion (Head et al.2009). The mitochondrial deacetylase SIRT3 is capable of deacetylating OPA1 and elevating its GTPase activity (Samant et al.2014).

6.3 PINK1 -Parkin dependent autophagy

Pink1 level is normally undetectable in most cells because Pink1 is cleaved in the mitochondria by PARL and then degraded by mitochondrial peptidases (Jin et al. 2010). During mitochondrial dysfunction, Pink1 is no longer cleaved and becomes stabilized on the depolarized outer mitochondrial membrane (S.M.Jin et al.2007). Pink1 then promotes Parkin-mediated mitophagy by phosphorylating Parkin at Thr175 and Thr217 residues which promotes the Parkin translocation on the outer mitochondrial membrane (Y. Kim et al.2008). PINK 1 also activates Parkin's E3 ubiquitin ligase activity, enabling it to ubiquitinate mitochondrial proteins (D.Shah et al.2010) (Figure 3).

Parkin functions as the executioner molecule during the mitophagy. Once recruited to the mitochondria, Parkin ubiquitinates several mitochondrial outer membrane proteins including the mitochondrial fusion proteins Mfn1and Mfn2, Miro, Translocase of outer mitochondrial membrane 20 (TOM20) ,and voltage-dependent anion channel (VDAC) to initiate mitophagy. Ubiquitination and proteasomal degradation of Mfn1 and Mfn2 results in mitochondrial fission and fragmentation (Geisler et al 2010, AC.Poole et al.2010). Fragmented mitochondria can fuse together if they have normal membrane potential, but loss of membrane potential prevents fusion and leads to mitochondria segregation and subsequent degradation by mitophagy (Figure 3).

Parkin mediates ubiquitination of outer mitochondrial membrane proteins, the selective autophagy adapter protein p62/SQSTM1 (Sequestosome1) is recruited to mitochondria and thought to play a role in mitophagy.

It directly interacts with LC3 via LC3 interacting region (LIR) (WX.Ding et al.2010, C S Manley et al.2013) . It has been shown that role of p62 in mitophagy is not essential (K. Okatsu et al.2010), due to the presence of other compensatory or similar autophagy receptor proteins. It was recently found that optineurin, another autophagy receptor protein is recruited to ubiquitinated mitochondria via its ubiquitin binding domain after Parkin activation on mitochondria. Optineurin induces autophagosome formation around the damaged mitochondria by recruiting double FYVE-containing protein 1(DFCP1) and LC3 to damaged mitochondria (YC.Wong et al.2014). Parkin also recruits Ambra1 (aBeclin-1interactingprotein) to depolarized mitochondria to initiate engulfment of damaged mitochondria by autophagosomes (C.Van et al.2011). Pink1 and Parkin regulate mitophagy at multiple levels including mitochondrial fragmentation (via Mfn1andMfn2), mitochondrial motility (via Miro), autophagy receptor protein (via p62 oroptineurin), and autophagy machinery (via Ambra1).

6.4 Formation of the mitochondrial spheroids.

Mitochondrial spheroids are structurally unique mitochondria that have a ring or cup-like morphology with squeezed mitochondrial matrix and enwraps the contents of the cytosol such as endoplasmic reticulum, lipid droplets, or other mitochondria. Mitochondrial spheroidsis formation is independent of the canonical autophagy pathway because it occurs in Atg5 orAtg7-deficient MEFs. The formation of mitochondrial spheroids requires the presence of ROS and either Mfn1 or Mfn2 (Ding et al.2012). Parkin negatively regulates the formation of mitochondrial spheroids by inducing proteasomal degradation of Mfn1and Mfn2, suggesting that Parkin prevents mitochondrial spheroid formation in order for mitophagy to occur. Mitochondrial spheroids are detected in CCCP-treated MEFs and in mouse livers exposed to acetaminophen, acute alcohol or high fat diet (HM.NI et al 2013). Mitochondrial spheroids formation may represent general mitochondrial structural remodelling in response to various physiological and pathological stresses and could serve as an alternative mechanism for regulation of mitochondrial homeostasis.

6.5 Formation of the mitochondria derived vesicles.

Mitochondria-derived vesicles (MDVs) is another novel pathway that functions under mitochondrial oxidative stress to regulate mitochondrial protein turnover and mitochondrial quality. This pathway also involves Parkin and Pink1 but it is different from canonical mitophagy because the formation of MDVs is stimulated by ROS production instead of mitochondrial depolarization. Vesicles bud off of damaged mitochondria and are degraded in the lysosome independent of the canonical autophagy pathway (G.McLelland et al.2014). MDVs contain oxidized proteins and regulates mitochondrial quality faster than mitophagyto prevent complete mitochondrial depolarization while preserving mitochondrial function by selectively degrading damaged mitochondrial contents (G.McLelland et al.2014)

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VII. TABLE DEPICTING THE PROTEINS INVOLVED IN MITOCHONDRIAL DYNAMICS

PROTEINS INVOLVED IN MITOCHONDRIAL DYNAMICS	FUNCTION	REFERENCES
Pink-1	Recruitment of Parkin to depolarized mitochondria	Y.Kim et al.2008
Parkin	Ubiquitination of several mitochondrial proteins during mitophagy	M.E.Gegg et al.2010
P62	Autophagy adaptor protein, binds LC3	WX.Ding et al.2010, C Haung et al 2011.
MFN1, MFN2	Fussion of outer mitochondrial membrane	Westermann et al.2010
OPA1	Fussion of inner mitochondrial membrane	S. Ehses et al.2009
VDAC-1	Involved in mitochondria mediated cell death	Geisler et al.2010
MFF mitochondrial fission factor	Recruits Drp1 during mitochondrial fission	Otera et al.2010
Parkin-Pink-1	Regulates mitochondrial quality control	McLelland et al.2014
PARL	Regulation of the level of PINK 1 in healthy mitochondria.	S.M. Jin et al 2010
MiD51 , MiD49	Mitochondrial fission	Palmer et al.2011

VIII. DISCUSSIONS & CONCLUSION

Parkinson disease is the second most common progressive neurodegenerative disorder after Alzheimer's disease caused by the selective loss of the dopaminergic neurons in the substantia nigra. Despite of the description of the disease in very early in 1817 by James Parkinson, no effective therapy is available till date due to the poor Knowledge about the molecular mechanisms involved in the pathogenesis of the disease. The discovery of levodopa revolutionized the treatment of PD, but soon it was found that after several years of treatment most patients develop involuntary movements, termed as "dyskinesia", which are difficult to control and significantly impair the quality of life. Current studies have shown that dysfunction of the mitochondria is the key event involved in the pathogenesis of the. This is further supported by the fact that mitochondrial neutoxins causes dopaminergic cell death both in vitro and in vivo. Thus removal of the dyfunctioned mitochondria or restoration of the mitochondrial function can works as a novel neuro-protective stategy in the prevention of the disease. Identification of suitable targets and development of the targeted drugs that can restore the function of the dysfunctioned mitochondria or increase the removal of the dysfunctioned mitochondria is a new challenge. At present time reseachers has de coded how sensors of the nutrient and energy status (such as AMPK, NAD+ and SIRT1) and their downstream transcriptional effectors govern mitochondrial biogenesis. Other key proteins that are that are involved in the regulation of mitochondrial qulity control and clearance of defective mitochondria such as, fusion, fission, and mitophagy have recently also been identified. Further studies have shown that mitochondrial biogenesis and other processes cannot be seen as separate but they are dependent upon each other. Currently target based drug discovery approaches are being used. It has certain limitations due to the complex nature of the mitochondrial regulatory network. Development of the phenotypic screens for the mitochondrial function is new step in this direction which can lead to the identification of the new targets and development of new drugs towards the prevention of the mitochondrial dysfunction.

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Figure Legends

Figure 1: A diagram depicting the differences in molecular events between healthy and damaged mitochondria.

Figure 2: The flowchart reveals the Parkin and PINK-1 mediated Mitochondrial Fission and Fusion.

Figure 3: The figure reflects Pink-1 – Parkin mediated Mitophagy.

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Figure 1

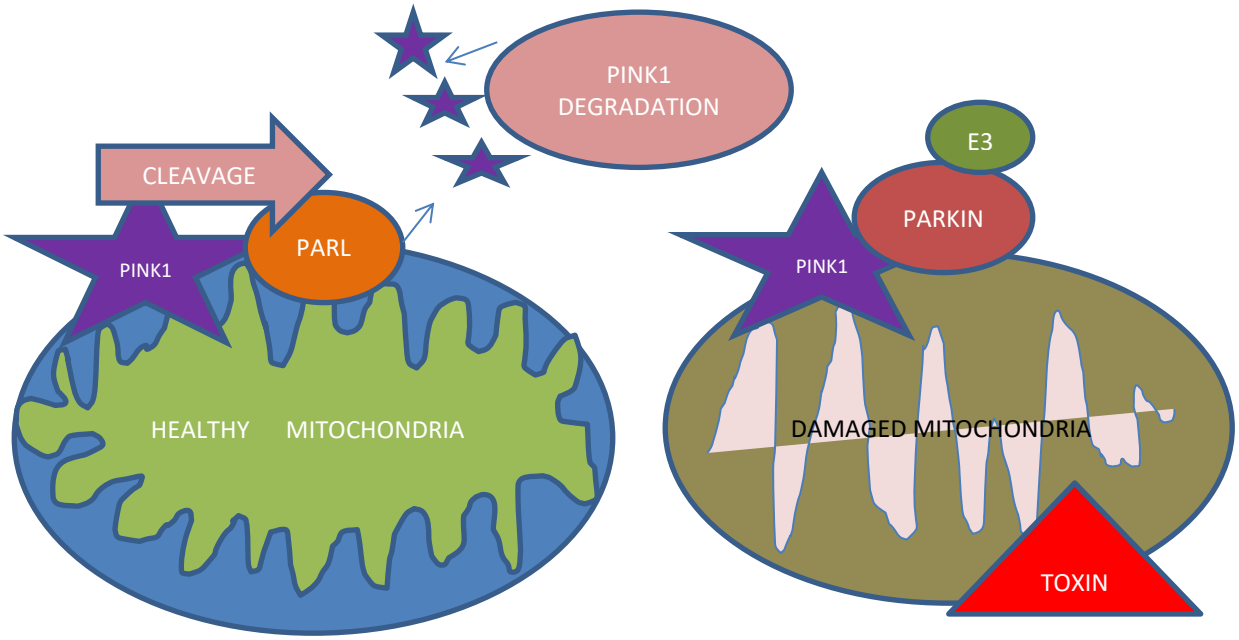

Figure 2

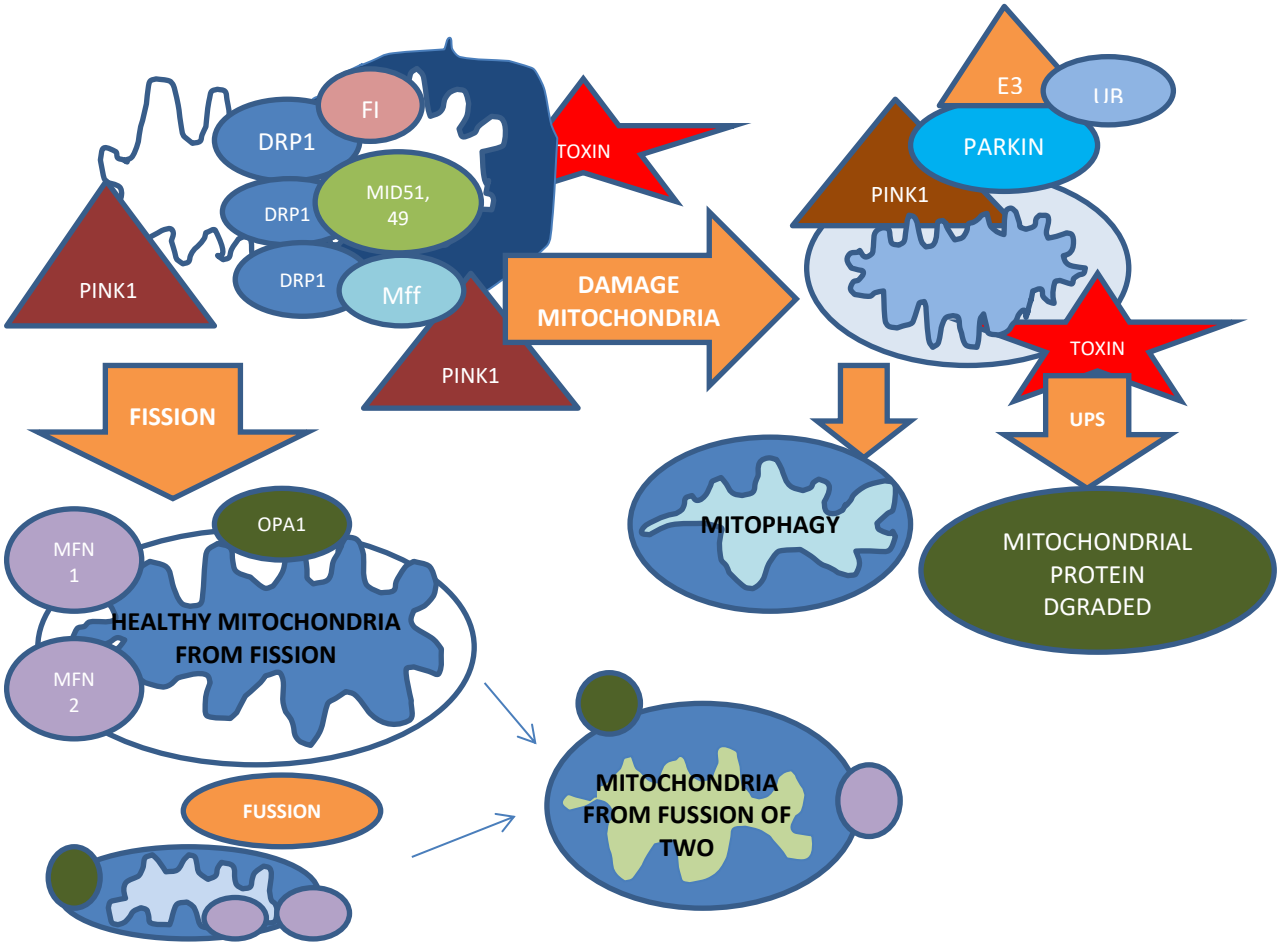

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Figure 3