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Review article

New insights into the complex role of mitochondria in Parkinson's disease

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ABSTRACT

New discoveries providing insights into mitochondrial bioenergetics, their dynamic interactions as well as their role in cellular homeostasis have dramatically advanced our understanding of the neurodegenerative process of Parkinson's disease (PD). Respiratory chain impairment is a key feature in sporadic PD patients and there is growing evidence that links proteins encoded by PD-associated genes to disturbances in mitochondrial function. Against the backdrop of latest advances in the development of PD treatments that target mitochondria, we aim to give an overview of the literature published in the last three decades on the significance of mitochondria in the pathogenesis of PD. We describe the contribution of mitochondrial genome alterations and PD-associated genes to mitochondrial maintenance. We highlight mitophagy as a key mechanism in neurodegeneration. Moreover, we focus on the reciprocal interaction between alpha-synuclein aggregation and mitochondrial dysfunction. We discuss a novel trafficking pathway involving mitochondrial-derived vesicles within the context of PD and provide a synopsis of the most recently emerging topics in PD research with respect to mitochondria. This includes the relationship between mitochondria and cell-mediated immunity, the ER-mitochondria axis, sirtuin-mediated mitochondrial stress response and the role of micro RNAs in the aetiology of PD. In addition, recent studies have challenged the neuro-centric view of PD pathology, moving microglia and astrocytes into the research spotlight. Greater insights into these mechanisms may hold the key for the development of novel targeted therapies, addressing the need for a disease-modifying treatment, which has remained elusive to date.

1. Introduction

Mitochondria are known to play key roles in cellular signalling processes using the cell's bioenergetics status to determine whether the cell survives or undergoes degeneration. As such, mitochondria have a fundamental role in the neurodegenerative process of Parkinson's disease (PD), the most common neurodegenerative movement disorder in the world. PD affects about 1% of people over the age of 60 years (de

Abbreviations: ATP, adenosine triphosphate; ATP13A2, ATPase 13A2; CD, cluster of differentiation; COS, CV-1 in origin with SV40 genes; COX, cytochrome c oxidase; DAT, dopamine transporter; D-loop, displacement loop; DMF, dimethylfumarate; DNA, deoxyribonucleic acid; ERK2, extracellular signal-regulated kinase 2; FOXO3a, forkhead box protein O3; GSH, reduced glutathione; HSP, heat shock protein; iNOS, inducible nitric oxide synthase; IPD, idiopathic Parkinson's disease; iPSC, induced pluripotent stem cell; LRRK2, leucine-rich repeat kinase 2; MAM, mitochondria-associated endoplasmic reticulum membrane; MB, methylene blue; MDV, mitochondrial-derived vesicle; MFN1/2, mitofusin1/2; MHC, major histocompatibility complex; MitAP, mitochondrial antigen presentation; MMF, monomethylfumarate; MPP+, 1-methyl-4-phenyl-4propionoxy-piperine, 1-methyl-4-phenylpyridinium; MPPP, 1-methyl-4-phenyl-4propionoxy-piperine; MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mtDNA, mitochondrial DNA; MVBs, multi-vesicular bodies; NAC, N-acetylcysteine; NdufA10, NADH: ubiquinone oxidoreductase subunit A10; Nrf2, nuclear factor erythroid 2-related factor 2; 6-OHDA, 6-hydroxydopamine; OPA1, optic atrophy 1; OPTN, optineurin; p62, sequestosome 1; PD, Parkinson's disease; PFF, preformed alpha-synuclein fibrils; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PINK1, PTEN-induced putative kinase 1; POLG, mitochondrial polymerase gamma; PTPIP51, protein tyrosine phosphatase-interacting protein 51; RNS, reactive nitrogen species; ROS, reactive oxygen species; SDH, succinate dehydrogenase; SIRT, sirtuin; SN, substantia nigra; SOD, superoxide dismutase; TFAM, mitochondrial transcription factor A; TFB2M, mitochondrial transcription factor B2; TH, tyrosine hydroxylase; TIM, translocase of inner membrane; TNT, tunnelling nanotube; TOM, translocase of outer membrane; Ub, ubiquitin; UPR^{mt}, mitochondrial unfolded protein response; VAPB, vesicle-associated membrane protein-associated protein B; VDAC1, voltage-dependent anion-selective channel 1; VPS35, vacuolar protein sorting-associated protein 35

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Lau and Breteler, 2006; Mehta et al., 2007) and is characterised by cardinal motor manifestations of bradykinesia, tremor, rigidity and postural instability, as well as non-motor features. Pathological findings include loss of dopaminergic neurons in the substantia nigra (SN) pars compacta and the intraneuronal presence of Lewy bodies. Lewy bodies contain aggregates of alpha-synuclein, neurofilaments, ubiquitin, and other compounds (Spillantini et al., 1997).

Although most cases of PD are sporadic, about 5–10% of affected patients have a monogenic form of the disease with Mendelian inheritance (Deng et al., 2018; Kumar et al., 2011, 2012a).

Major insights from recent genetic discoveries have underpinned the importance of mitochondria in the neurodegenerative process of PD, as multiple genes unequivocally linked to the disease encode proteins that are relevant for mitochondrial homeostasis. Among this subset are the presynaptic protein alpha-synuclein, the E3 ubiquitin ligase Parkin, PTEN-induced putative kinase 1 (PINK1), the protein deglycase DJ-1, Leucine-rich repeat kinase 2 (LRRK2), ATPase 13A2 (ATP13A2) and vacuolar protein sorting-associated protein 35 (VPS35) (Larsen et al., 2018). In the following, we will highlight the relationship between the afore-mentioned proteins and mitochondria in the context of (accelerated) neurodegeneration and PD.

2. Respiratory chain complex dysfunction as a key feature of PD

2.1. Respiratory impairment in IPD

Mitochondria initially became the focus of PD research when Drs Langston, Ballard, Tetrud and Irwin from California reported two incidents of drug abuse in an article published in Science in 1983 (Langston et al., 1983). Within a week of exposure, four patients showed typical signs of L-dopa-responsive Parkinsonism after injecting what they believed to be a new “synthetic heroin”. The compound that was injected intravenously contained the mitochondrial toxin 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Langston et al. linked their findings to an earlier case report (Davis et al., 1979), which described the onset of similar symptoms in a 23-year old student who had injected a “sloppy batch” of self-synthesized 1-methyl-4-phenyl-4propionoxy-piperine (MPPP). Autopsy material of this patient revealed typical Lewy body pathology in the SN (Davis et al., 1979).

MPTP can pass the blood brain barrier and is converted into the cation 1-methyl-4-phenylpyridinium (MPP +) by monoamine oxidase B - an enzyme highly abundant in glial cells (Levitt et al., 1982). Via the dopamine transporter (DAT), MPP + selectively enters dopaminergic neurons (Storch et al., 2004) where it inhibits respiratory chain complexes I, III and IV (Desai et al., 1996; Nicklas et al., 1985). The assumption that PD can be triggered by mitochondrial impairment was corroborated when, 6 years later, reduced activities of complexes I, II and IV were determined in post-mortem SN homogenates of PD patients (Bindoff et al., 1989; Schapira et al., 1990a,b, 1989). These publications initiated vigorous research endeavours worldwide exploring the contribution of mitochondria to the pathology of PD. Entering the search terms “mitochondria” and “Parkinson’s disease” into the literature database PubMed retrieved more than 2500 articles linked to the topic. In comparison, “lysosomes” or “lysosome” and “Parkinson’s disease” only linked about 500 publications over a similar timeframe.

Because of its effects on the respiratory chain, which results in a loss of bioenergetic function, oxidative stress and impaired calcium homeostasis (Desai et al., 1996; Langston, 2017), MPTP is now considered the “gold standard” for modelling PD in animals (Francardo, 2018; Jackson-Lewis et al., 2012). Like in the above-described patient, MPTP mediates the preferential degeneration of SN dopaminergic neurons in mice and non-human primates, causing motor symptoms in the latter model. By contrast, the occurrence of Lewy bodies, the neuropathological hallmark of PD, in these animals is inconsistent (Dauer and Przedborski, 2003). Due to this limitation, paraquat and rotenone are used as alternatives to induce parkinsonian phenotypes in animals. While paraquat ingestion generates reactive oxygen species (ROS) by redox cycling, rotenone’s primary site of action is respiratory chain complex I. Contrary to MPTP, both pesticides cause alpha-synuclein aggregation and Lewy body-like inclusions but less reliably reproduce the PD-associated loss of dopamine in the nigrostriatal pathway (Jackson-Lewis et al., 2012).

The quest for a prodromal disease marker and an accurate cellular system, which allowed studying the molecular causes of PD, motivated the analysis of more accessible peripheral patient tissues. Enzyme kinetic analysis in mitochondria isolated from platelets (Benecke et al., 1993; Krige et al., 1992; Parker et al., 1989) and skeletal muscle (Bindoff et al., 1991; Cardellach et al., 1993) confirmed reduced complex I and IV activity as a more widespread phenomenon in IPD. The first two reports in which IPD patient fibroblasts were used to explore mitochondrial function *in vitro* also described a complex I phenotype (Mytilineou et al., 1994; Winkler-Stuck et al., 2004) (Table 1). In a subset of patient-derived cultures, treatment with the antioxidant coenzyme Q10 was sufficient to reverse the complex I deficit (Winkler-Stuck et al., 2004) (Table 1). In line with a key role for complex I in IPD, oxygen consumption profiles determined with an extracellular flux analyser showed reduced rotenone-sensitive respiration (Ambrosi et al., 2014). In contrast, a study comprising the largest collection of IPD patient (n = 20) and control (n = 19) fibroblasts to date showed no abnormalities for complexes I–IV, only a mild (but significant) reduction in the activity of complex V (Table 1) (del Hoyo et al., 2010). A comparison of the average disease durations in the studied cohorts (Mytilineou et al.: n/a; Winkler-Stuck et al.: 4.2 + / − 3.1 years; Ambrosi et al.: 12.1 + / − 6.0 years; and del Hoyo et al.: 8.1 + /4.2 years) did not explain this discrepancy. Given that none of the patients had mutations in PD-associated genes excluded, it is possible that the observed variability is (at least in part) due to genetic heterogeneity. An attempt to define homogeneous subpopulations of sporadic patients by stratification according to valinomycin sensitivity did not result in distinct respiratory chain complex phenotypes between the two groups. However, in the “high sensitivity” IPD group, fewer mitochondrial-lysosomal co-localization events were found together with increased nitric oxide and mitochondrial superoxide generation (Smith et al., 2016).

Primary or toxin-induced respiratory chain complex dysfunction in PD is tightly interlinked with the generation of ROS. ROS develop when electrons prematurely escape from the electron transport chain. The main sites for such events are located at respiratory chain complexes I and III (Quinlan et al., 2013). In addition, mitochondria possess a specific nitric oxide synthase which catalyses nitric oxide formation from L-arginine and O_2 (Nisoli and Carruba, 2006). Reactive nitrogen species (RNS) are produced via the interaction of superoxide with nitric oxide (Al Shahrani et al., 2017). ROS and RNS are important for normal cellular physiology and their intracellular levels are regulated by antioxidants such as superoxide dismutase (SOD) and glutathione (GSH) (Puspita et al., 2017). In PD, this equilibrium was shown to be disturbed (Bosco et al., 2006) with the exact cause still being elusive. However, multiple lines of evidence suggest that mitochondrial oxidative stress is mediated by dopamine metabolism (Blesa et al., 2015). Dopamine can undergo auto-oxidation producing free radicals and active quinones (LaVoie and Hastings, 1999) which interact with ROS scavengers (Belluzzi et al., 2012; Jana et al., 2007), respiratory chain complexes (Jana et al., 2007) or proteins of the mitophagy pathway (LaVoie et al., 2005). A study using induced pluripotent stem cell (iPSC)-derived neurons from human and mice with mutant or depleted DJ-1 demonstrated a species-specific relationship between dopamine oxidation mitochondrial dysfunction and lysosomal dysfunction in PD (Burbulla et al., 2017). Given that DJ-1 functions in ROS defence, neurons lacking DJ-1 may serve as model of primary mitochondrial oxidative stress (Guzman et al., 2010). The experiments revealed a pathogenic cascade from mitochondrial via lysosomal to neuronal dysfunction, which was exacerbated in the presence of high cytosolic dopamine levels. It was postulated that higher dopamine concentrations resulted in the

Table 1
Endogenous mitochondrial function studies in PD patient fibroblasts.

Gene	Study	Control samples: n total	Mutant samples: n total	Mutations	Respiratory chain function	Oxidative stress	mtDNA levels/integrity	Mitochondrial morphology	Mitophagy	Other mitochondria-related	Knockdown/overexpression	Rescue with treatments	Type of treatment
IPD	(Mytilineou *et al.*, 1994)	4	6	Not sequenced	B								
	(Winkler-Stuck *et al.*, 2004)	15	18	Not sequenced	B							B	Coenzyme Q10
	(Hoepken *et al.*, 2008)	5	5	Not sequenced						B			
	(del Hoyo *et al.*, 2010)	19	20	Not sequenced	B	B							
	(Ambrosi *et al.*, 2014)	7	11	Not sequenced	B	B/S			B/S	S			
	(Smith *et al.*, 2016)	14	10	No mutations in LRRK2 or GBA1	S	B/S		B/S	B/S	S		B/S	LRRK2-in-1 (LRRK2 kinase inhibitor)
	(Hsieh *et al.*, 2016)	**4**	5	No mutations in known PD genes					S				
Parkin	(Mortiboys *et al.*, 2008)	6	5	c.255delA/delEx5; c.202-203delAG/c.202-203delAG; c.202-203delAG/delEx2; c.202-203delAG/delEx4; c.202-203delAG/c.1289G>A	B/S			B			KD		
	(Rothfuss *et al.*, 2009)	1	1	c.101delAG/delEx3-4			B/S						
	(Grunewald *et al.*, 2010)	**5**	6	c.1072delT/delEx7; c.1072delT/1072delT; delEx7/delEx7; delEx3-4/duplEx7-12; c.924C>T/delEx4; c.924C>T/delEx1	B/S	B/S		S					
	(Pacelli *et al.*, 2011)	1	2	delEx2-3/delEx3	B/S	B		B	B	B			
	(Rakovic *et al.*, 2011a)	**2**	2	c.1072delT/c.1072delT; delEx7/delEx7				S	S		OE		
	(Mortiboys *et al.*, 2013)	4	4	c.255delA/delEx5; c.202-203delAG/c.202-203delAG; c.202-203delAG/delEx2; c.202-203delAG/delEx4	B							B	Ursocholanic acid, dehydro(11,12) ursolic acid, ursolic acid, urso-deoxycholic acid lactone (activators of glucocorticoid receptor, GR)
	(Ferretta *et al.*, 2014)	1	2	delEx2-3/delEx3; delEx7-9/c.1326G>T	B/S	B	B	B	B/S	B	KD		
	(van der Merwe *et al.*, 2014)	**2**	3	delEx3-4/delEx3-4; delEx4/delEx4 (n=2)	B			B	B				
	(Zanellati *et al.*, 2015)	**4**	4	c.815C>G/c.924C>T; c.202-203delAG/c.202-203delAG; delEx1/c.924C>T; duplEx2/delEx3-5	B/S			B		B			
	(Gautier *et al.*, 2016)	**8**	7	delEx1-2/c.202-203delAG; delEx8-9/c.226G>C (n=3); delEx4/c.255delA; del ex3-6/delEx3-4; delEx5/c.1422T>C						B	OE (Parkin)/KD (MFN2)		
	(Hsieh *et al.*, 2016)	**4**	3	delEx3-4/c.255delA; c.226G>C/c.226G>C; c.924C>T/c.924C>T	B				S				
	(Haylett *et al.*, 2016)	**3**	3	delEx3-4/delEx3-4; delEx4/delEx4 (n=2)	B/S			B					
	(Lobasso *et al.*, 2017)	2	2	delEx7-9/c.1326G>T; delEx2-3/delEx3						B			
	(Zanon *et al.*, 2017)	**2**	2	c.1072delT/c.1072delT; delEx7/c.1072delT						S			
Parkin (het)	(Ferretta *et al.*, 2014)	1	1	delEx2-3*	B/S	B	B	B	B/S	B			
	(van der Merwe *et al.*, 2014)	**2**	2	delEx2-3*; delEx4*	B			B	B				
PINK1	(Hoepken *et al.*, 2007)	2	3	c.926G>A/c.926G>A (n=3)	B	B							
	(Piccoli *et al.*, 2008b)	1	1	c.1311G>A/c.1311G>A	B/S	B		B				B	Dyphenylene iodinium (nitric oxide synthetase inhibitor)
	(Piccoli *et al.*, 2008a)	1	1	c.1311G>A/c.1311G>A	B	B	B						
	(Hoepken *et al.*, 2008)	5	3	c.926G>A/c.926G>A (n=3)						B	KD		
	(Grunewald *et al.*, 2009)	8	5	c.1366C>T/c.1366C>T (n=4); c.509T>G/c.509T>G	B	B/S	B	B/S					
	(Klinkenberg *et al.*, 2010)	4	3	c.926G>A/c.926G>A (n=3)						B/S	KD		
	(Rakovic *et al.*, 2010)	**4**	4	c.1366C>T/c.1366C>T (n=3); c.509T>G/c.509T>G					S		OE (Parkin)		
	(Rakovic *et al.*, 2011a)	**2**	2	c.1366C>T/c.1366C>T; c.509T>G/c.509T>G				S	S		OE		

(*continued on next page*)

Table 1 (*continued*)

PINK1	(Rakovic *et al.*, 2011b)	**2**	3	c.1366C>T/c.1366C>T (n=3)						B			
	(Abramov *et al.*, 2011)	**2**	5	c.1366C>T/c.1366C>T (n=4); c.509T>G/c.509T>G	B/S	B							
	(Rakovic *et al.*, 2013)	≥1	1	c.509T>G/c.509T>G					S		OE (Parkin)		
	(Azkona *et al.*, 2018)	**5**	4	c.1488+1G>A/delEx7; c.1488+1G>A/delEx7; c.926G>A/c.926G>A (n=2)	B			B		B	OE		
	(Hsieh *et al.*, 2016)	**4**	2	c.1103T>A/c.1103T>A (n=2)	B				S				
	(Vos *et al.*, 2017)	**2**	2	c.1366C>T/c.1366C>T; c.509T>G/c.509T>G	B					B		B	Cerulenin (FASN inhibitor)
	(Lopez-Fabuel *et al.*, 2017)	**3**	3	c.1488+1G>A/delEx7; c.1488+1G>A/delEx7; c.926G>A/c.926G>A	B								
PINK1 (het)	(Hoepken *et al.*, 2007)	2	3	c.926G>A (n=3)*		B							
	(Hoepken *et al.*, 2008)	5	3	c.926G>A (n=3)*						B			
	(Klinkenberg *et al.*, 2010)	4	3	c.926G>A (n=3)*						B/S			
	(Azkona *et al.*, 2018)	**5**	3	c.1488+1G>A* (n=2); c.926G>A*	B			B		B	OE		
DJ-1	(Krebiehl *et al.*, 2010)	1	1	c.926G>A/c.926G>A					S				
	(Di Nottia *et al.*, 2017)	≥1	1	c.461C>A/c.461C>A	B	B/S	B						
DJ-1 (het)	(Krebiehl *et al.*, 2010)	1	2	c.926G>A (n=2)*					S				
LRRK2 G2019S	(Mortiboys *et al.*, 2010)	8	5	c.6055G>A (n=5)	B			B					
	(Papkovskaia *et al.*, 2012)	**7**	8	c.6055G>A (n=8)	B/S	B	B					B	Genipin (inhibitor of UCP activity)
	(Su and Qi, 2013)	1	3	c.6055G>A (n=3)	B	B		B	S		OE (DRP1)	B/S	P110 (Drp1 inhibitor)
	(Mortiboys *et al.*, 2013)	3	3	c.6055G>A (n=3)	B							B	Ursocholanic acid, ursodeoxycholic acid (activators of GR)
	(Grunewald *et al.*, 2014a)	**4**	5	c.6055G>A (n=5)	B/S	B	B	B	B				
	(Grunewald *et al.*, 2014a)	**4**	3	c.6055G>A (n=3)*	B/S	B	B	B	B				
	(Hsieh *et al.*, 2016)	**4**	3	c.6055G>A (n=3)	B				S	S	OE (Parkin)	S	LRRK2-IN-1 (LRRK2 kinase inhibitor)
	(Verma *et al.*, 2017)	1	1	c.6055G>A						B		B	U0126 (MEK inhibitor)
LRRK2 Other	(Hsieh *et al.*, 2016)	**4**	3	c.5096A>G; c.4321C>G; c.4321C>T					S				
	(Verma *et al.*, 2017)	1	1	c.4321C>G						B		B	U0126 (MEK inhibitor)
ATP 13A2	(Grunewald *et al.*, 2012)	**4**	3	c.1550C>T/c.1550C>T; c.3176T>G/c.3253delC; c.3057delC/IVS13+5:G>A	B/S		B	B			OE		
VPS35	(Wang *et al.*, 2016)	4	1	c.1858G>A	B/S			B				B/S	mdivi-1 (mitochondrial fission inhibitor)
	(Wang *et al.*, 2017)	1	1	c.1858G>A				B				B	Decoy peptide targeting FLV motif in C-terminal of DLP1

Notes: Controls screened for mutations in respective PD gene highlighted in bold. Number of isogenic control or mutant samples in brackets. Shading: Green - normal function, grey - altered function, blue - successful rescue, red - failed rescue attempt. Abbreviations: B - under basal conditions; KD - knockdown; OE - overexpression; S - under stress conditions; *Cells from unaffected individuals.
(Abramov et al., 2011; Azkona et al., 2018; Di Nottia et al., 2017; Ferretta et al., 2014; Grunewald et al., 2010; Grunewald et al., 2014a; Haylett et al., 2016; Hoepken et al., 2007; Hoepken et al., 2008; Klinkenberg et al., 2010; Lobasso et al., 2017; Mortiboys et al., 2008; Mortiboys et al., 2010; Mortiboys et al., 2013; Pacelli et al., 2011; Papkovskaia et al., 2012; Piccoli et al., 2008a; Piccoli et al., 2008b; Rakovic et al., 2011b; Su and Qi, 2013; van der Merwe et al., 2014; Vos et al., 2017; Verma et al., 2017; Wang et al., 2016; Wang et al., 2017; Zanellati et al., 2015).

increased vulnerability of human neurons when compared to mouse nigral neurons (Burbulla et al., 2017). Notably, administration of inorganic nitrite can disrupt this vicious circle in various animal and cellular models of PD. In the presence of nitrate, the antioxidant Nrf2 pathway is activated and S-nitrosation of complex I is favoured over other types of oxidation which leads to improved mitochondrial efficiency and neuroprotection (Milanese et al., 2018)

While iPSC-derived neurons from genetic PD patients are widely used to explore the cellular pathways that underlie mitochondrial dysfunction, oxidative stress and neurodegeneration, the potential of iPSC technology for research into IPD has not been fully exploited yet. Contrary to all previous IPD models, iPSC-derived neurons enable analyses against the biological environment of the original patient genotype. To date, there are no reports that comprehensively study the involvement of respiratory chain deficiency in the pathogenesis of IPD using iPSC-derived patient neurons (Table 2). Additional studies employing iPSC technology may be beneficial for elucidating further mechanistic insights into this condition.

2.2. PD-associated proteins with links to the respiratory chain

In 1997, the first gene mutation underlying a familial form of PD was discovered. In three Greek kindreds, Polymeropoulos and co-authors identified the Ala53Thr substitution in the alpha-synuclein protein (Polymeropoulos et al., 1997) - known now to be a component of the Lewy body (Spillantini et al., 1997). Another report of a German family harbouring an Ala30Pro mutation in alpha-synuclein (Kruger et al., 1998) swiftly followed. Overexpression of Ala30Pro alpha-synuclein in PC12 cells brought the first evidence of a mitochondrial contribution in familial PD. Compared to wild-type, mutant lines showed significantly increased mitochondrial depolarization (Tanaka et al., 2001). Remaining doubts as to the significance of mitochondria in the pathogenesis of PD were subsequently dispelled when PINK1, the protein encoded by the PARK6 gene, was located in the mitochondria of transfected COS-7 cells (Valente et al., 2004).

Among the proteins unequivocally linked to familial forms of PD, PINK1 remains the best example with the strongest evidence for a direct

Table 2
Endogenous mitochondrial function studies in iPSC-derived PD patient neurons.

Gene	Study	Control samples: n_{total} ($n_{isogenic}$)	Mutant samples: n_{total} ($n_{isogenic}$)	Mutations	Respiratory chain function	Oxidative stress	mtDNA levels/integrity	Mitochondrial morphology/motility	Mitophagy	Other mitochondria-related	Knockdown/overexpression	Rescue with treatments	Type of treatment
IPD	(Sanchez-Danes *et al.*, 2012)	**4**	7	No mutations in known PD genes					B/S	B			
	(Hsieh *et al.*, 2016)	3	2	Not sequenced				S	S				
	(Burbulla *et al.*, 2017)	**2**	2	No mutations in known PD genes		B				B			
SNCA	(Schwab and Ebert, 2015)	3	1	Gene triplication					B	B			
	(Paillusson *et al.*, 2017)	**1**	1	Gene triplication						B			
	(Arias-Fuenzalida *et al.*, 2017)[§]	**1**	**2 (2)**	c.209G>A*[#]; c.88G>C*[#]	B/S								
	(Burbulla *et al.*, 2017)	**2**	1	Gene triplication		B							
Parkin	(Jiang *et al.*, 2011)	2	2	delEx3/delEx5; delEx3/delEx3		S	B/S		B/S	B/S	OE		
	(Imaizumi *et al.*, 2012)	2	2	delEx2-4/delEx2-4; delEx6/delEx7	B/S	B		B	S	B			
	(Shaltouki *et al.*, 2015)	1	4	c.924C>T/c.924C>T; delEx3-4/c.255delA; delEx3/c.226G>C; c.226G>C/c.226G>C	B		B			B			
	(Chung *et al.*, 2016)	2	1	c.1072delT/c.1072delT	S	B		B		B			
	(Gautier *et al.*, 2016)	**2**	1	delEx8-9/c.226G>C						B			
	(Suzuki *et al.*, 2017)	3	2	delEx2-4/delEx2-4; delEx6/delEx7		B			S	S			
	(Zanon *et al.*, 2017)	**4**	2	c.1072delT/c.1072delT; delEx1/c.924C>T	B			B			OE (SLP-2)		
	(Shiba-Fukushima *et al.*, 2017)	2	2	delEx2-4/delEx2-4; delEx6/delEx7	B/S			B	B/S				
	(Burbulla *et al.*, 2017)	**2**	1	c.1072delT/c.1072delT		B				B			
PINK1	(Seibler *et al.*, 2011)	**1**	1	c.1366C>T/c.1366C>T			B/S		S	S	OE		
	(Cooper *et al.*, 2012)	**2**	2	c.1366C>T/c.1366C>T (n=2)	B/S	S		B		S		S	Coenzyme Q10, GW5074 (LRRK2 kinase inhibitor)
	(Rakovic *et al.*, 2013)	≥1	1	c.509T>G/c.509T>G				S			OE (Parkin)		
	(Chung *et al.*, 2016)	2	1	c.1366C>T/c.1366C>T	S	B		B		B	OE	B	MnTBAT, EUK134 (SOD mimetics); N-acetyl-L-cysteine (antioxidant)
	(Vos *et al.*, 2017)	**2**	2	c.1366C>T/c.1366C>T; c.509T>G/c.509T>G	B							B	Cerulenin (FASN inhibitor)
	(Shiba-Fukushima *et al.*, 2017)	2	1	c.1162T>C/c.1162T>C				B	B/S				
	(Burbulla *et al.*, 2017)	**2**	1	c.1366C>T/c.1366C>T		B							
DJ-1	(Burbulla *et al.*, 2017)	**2**	2	c.192G>C/c.192G>C (n=2)	B	B				B	KD (isogenic)	B	mito-TEMPO, NAC (antioxidants); isradipine, FK506 (inhibitors of calcium import), AMPT (TH inhibitor)
DJ-1 (het)	(Burbulla *et al.*, 2017)	**2**	1	c.192G>C		B				B		B	Isradipine, FK506 (inhibitors of calcium import)
LRRK2 G2019S	(Sanchez-Danes *et al.*, 2012)	**4**	4	c.6055G>A (n=4)					B/S	B			
	(Cooper *et al.*, 2012)	**2**	1	c.6055G>A/c.6055G>A	B/S	S		B		S		S	Coenzyme Q10, rapamycin (mTOR kinase inhibitor), GW5074 (LRRK2 kinase inhibitor)
	(Reinhardt *et al.*, 2013)	**3 (2)**	**3 (1)**	c.6055G>A (n=2); c.6055G>A/c.6055G>A*[#]					B/S				
	(Sanders *et al.*, 2014)	**4 (1)**	4	c.6055G>A (n=3); c.6055G>A/c.6055G>A			B						
	(Schwab and Ebert, 2015)[$]	3	3	c.6055G>A; c.6055G>A/c.6055G>A (n=2)					B	B		B	GSK2578215A (LRRK2 kinase inhibitor)
	(Hsieh *et al.*, 2016)	3 **(1)**	3	c.6055G>A; c.6055G>A/c.6055G>A (n=2)	B			B/S	B/S		KD (Miro)		
	(Schwab *et al.*, 2017)	3	3	c.6055G>A; c.6055G>A/c.6055G>A (n=2)	B/S			B		B		B	GSK2578215A (LRRK2 kinase inhibitor)
LRRK2 Other	(Cooper *et al.*, 2012)	**2**	2	c.4321C>T (n=2)	B/S	S		B		S		S	Coenzyme Q10, rapamycin (mTOR kinase inhibitor), GW5074 (LRRK2 kinase inhibitor)
	(Sanders *et al.*, 2014)	**4**	2	c.4321C>T (n=2)			B						

Notes: Controls screened for mutations in respective PD gene highlighted in bold. Number of isogenic control or mutant samples in brackets. Shading: Green - normal function, grey - altered function, blue - successful rescue, red - failed rescue attempt. Abbreviations: B - under basal conditions; KD - knockdown; OE - overexpression; S - under stress conditions; [§]study performed in neuroepithelial stem cells, *cells from unaffected individual; [#]isogenic mutant; [$]study performed in sensory neurons.
(Chung et al., 2016; Cooper et al., 2012; Imaizumi et al., 2012; Schwab and Ebert, 2015; Sanders et al., 2014; Sanchez-Danes et al., 2012; Schwab and Ebert, 2015; Shiba-Fukushima et al., 2017; Suzuki et al., 2017; Reinhardt et al., 2013).

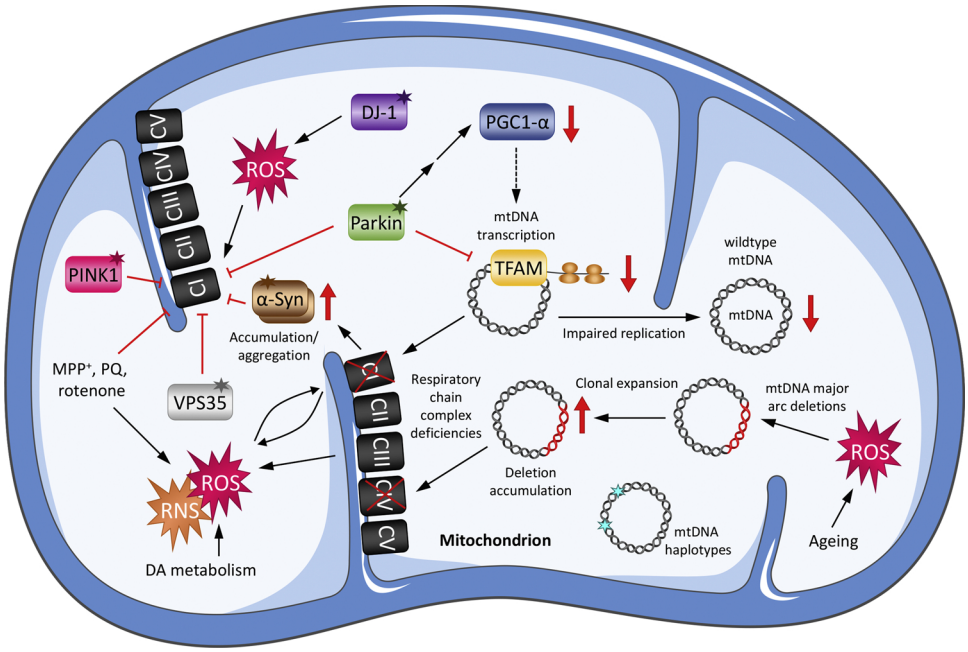

Fig. 1. Respiratory chain dysfunction and mtDNA alterations in Parkinson's disease (PD). Respiratory chain dysfunction primarily involving complexes I and IV are often identified in idiopathic PD. As a consequence of impaired oxidative phosphorylation, the cellular levels of reactive oxygen (ROS) and nitrogen species (RNS) rise. This initiates a viscous cycle, which is exacerbated in the presence of dopamine. Toxins such as MPTP, paraquat (PQ) and rotenone can mirror the clinical phenotypes of idiopathic PD by inhibiting complex I or through the generation of ROS and RNS. Oxidative stress and replication errors occurring during ageing and PD are the cause of major arc deletion in the mitochondrial genome (mtDNA). Clonal expansion of these deleted mtDNA molecules results in a complex IV deficit. While, in aging, the accumulation of deleted species is compensated by an increase in copy number, in IPD, the level of wild-type mtDNA molecules recedes. This coincides with an impairment of mitochondrial transcription and replication. Regarding PD-associated proteins, mutations in the ROS scavenger DJ-1 enhance mitochondrial oxidative stress, which acts on complex I. Similarly, mutant forms of PINK1, VPS35, alpha-synuclein and Parkin interfere with complex I function. The interplay between mitochondrial dysfunction and alpha-synuclein is bidirectional, i.e. respiratory chain impairment can also induce alpha-synuclein accumulation and aggregation. Furthermore, Parkin can either modulate mtDNA transcription via ubiquitination of the PGC-1α repressor Paris (in the cytosol) or via direct interaction with TFAM at the mitochondrial genome. Fig. 1 was created using elements from Servier Medical Art, which is licensed under a Creative Common Attribution 3.0 Generic License (http://smart.servier.com/).

interaction with the mitochondrial respiratory chain. PINK1-knockout mice show a loss of phosphorylation at serine 250 of the complex I subunit NdufA10 in brain tissue (Morais et al., 2014). Phosphorylation at this site is a prerequisite for ubiquinone reduction. Overexpression of a phosphomimetic version of NdufA10 was sufficient to rescue respiratory chain function in PINK1-knockout mouse embryonic fibroblasts or pink1-null mutant drosophila (Morais et al., 2014). By contrast, NdufA10 overexpression in parkin-null mutant flies failed to rescue mitochondrial morphology and locomotor phenotypes implicating that PINK1 acts on complex I via a mechanism independent of mitophagy (Pogson et al., 2014). Such mechanisms may involve the drosophila homolog of UBIAD. UBIAD/Heix is a modifier of the pink1-null phenotype and mediates the conversion of vitamin K1 into vitamin K2 (Vos et al., 2012). Feeding pink1-null flies with vitamin K2 supplemented media was sufficient to improve cellular ATP levels and mitochondrial membrane potential (Vos et al., 2012).

Regarding human endogenous models, respiratory chain dysfunction is the most frequently identified mitochondrial phenotype in fibroblasts from patients with PINK1 mutations (Table 1). For example, analysis of the 3D structure of complex I revealed a shift from free to supercomplex-assembled complex I and complex III and an overall depletion of complex IV in skin cells from PINK1 patients (Lopez-Fabuel et al., 2017). These changes have implications for mitochondrial bioenergetics and ROS production (Lopez-Fabuel et al., 2016).

Although the above-described results from drosophila studies may give the impression that Parkin's impact on the respiratory chain is only via the PINK1/Parkin mitophagy pathway, the protein's actions in humans are manifold. Applying co-immunoprecipitation and proximity ligation assays to SH-SY5Y cells, Parkin was demonstrated to interact with mitochondrial Stomatin-like protein 2 (SLP-2), which is required for the assembly of respiratory chain proteins (Zanon et al., 2017). The significance of this finding was emphasised when overexpression of SLP-2 successfully recovered complex I deficiency in iPSC-derived patient neurons with Parkin mutations (Zanon et al., 2017). The molecular theme of impaired respiratory chain complex assembly in genetic PD also extends to DJ-1 (Heo et al., 2012) and VPS35 (Zhou et al., 2017). In DJ-1-knockout mouse neurons and VPS35-mutant patient fibroblasts, abnormal complex I formation was observed using blue-native PAGE (Heo et al., 2012; Zhou et al., 2017) (Fig. 1).

3. Mitochondrial genome involvement in PD

3.1. Inherited and somatic mtDNA variation in IPD

Evidence for a role of maternally inherited mitochondrial DNA (mtDNA) alterations in the pathogenesis of IPD was provided by studies employing transmitochondrial cytoplasmic hybrids (or "cybrids"). To generate cybrids, control cells with "wild-type" nuclear background are deprived of their own mtDNA by incubation with ethidium bromide. The resulting Rho° cells are then fused with cytoplasts or enucleated cells derived from patient cells only containing the patient mtDNA (Taylor and Turnbull, 2005). Rather than using enucleated cells, Parker et al. (Parker et al., 1989) and Krige et al. (Krige et al., 1992) used anucleate platelets from IPD patients as an ideal source of mtDNA for such transmission experiments (Gu et al., 1998; Swerdlow et al., 1996). Cybrids obtained in this fashion were more susceptible to MPP + and recapitulated the original complex I defects, indicating that mtDNA from affected patients contributed to the aetiology of IPD (Gu et al., 1998; Swerdlow et al., 1996) (Fig. 1). In contrast, a study investigating the association between maternal transmission and risk of PD in 168 affected families failed to demonstrate a maternal bias in the inheritance of the disease. Moreover, common mtDNA haplogroups or the mitochondrial 10,398 G variant located in the ND3 subunit of complex I did not define the risk to develop PD (Mehta et al., 2009; Simon et al., 2010), thus challenging previous, presumably underpowered reports, ascribing a higher disease risk to the mitochondrial haplotype groups J (van der Walt et al., 2003), K (Ghezzi et al., 2005; van der Walt et al., 2003), UK (Khusnutdinova et al., 2008) or UKJT (Pyle et al., 2005). Despite increasing sample numbers and, therefore, enhancing power (Hudson et al., 2013), the significance of mtDNA association analyses remains limited due to a lack of studies which underpin the genetic results on a cellular level (Giannoccaro et al., 2017). To date, only two

reports have used cybrid technology to uncover differences in mtDNA copy number, transcription, protein synthesis, and respiratory chain function between haplogroups UK, J and H (Giannoccaro et al., 2017; Gomez-Duran et al., 2010, 2012).

In any case, considering that ageing is the strongest factor influencing PD risk, somatic mutations are likely to outweigh the effect of mtDNA polymorphisms over time (Giannoccaro et al., 2017). In agreement with this hypothesis, Alper's disease patients, who accumulate somatic mtDNA mutations throughout life due to an error-prone version of polymerase gamma (POLG), show more severe neuronal loss in the SN than patients with inherited mtDNA mutations (Reeve et al., 2013). The most common mtDNA change occurring during ageing is a 4977bp deletion in the mitochondrial genome (Soong et al., 1992). This large deletion is especially abundant in brain regions with high dopamine metabolism and auto-oxidation, such as the caudate, putamen and the SN (Soong et al., 1992). A combination of immunohistochemistry, laser capture microdissection and single-neuron (Bender et al., 2006) or single-molecule (Kraytsberg et al., 2006) mtDNA analysis of SN sections from aged individuals revealed that cytochrome c oxidase (COX)-negative dopaminergic neurons harbour higher deletion levels than those with normal activity. This phenomenon was even more pronounced in IPD patients (Bender et al., 2006), providing a first molecular explanation for the long-established respiratory phenotype in IPD (Fig. 1). When single-cell technology was applied to non-catecholaminergic and catecholaminergic nigral neurons with or without neuromelanin, highest deletion levels were found in pigmented tyrosine hydroxylase (TH)-positive cells highlighting their specific vulnerability (Elstner et al., 2011). By contrast, more recent research shows that respiratory chain dysfunction in IPD does not exclusively stem from sporadically formed and clonally expanded large-scale mtDNA deletions (Nido et al., 2018). In an attempt to explore the contribution of the mitochondrial genome to complex I rather than complex IV deficiency, we substituted COX/succinate dehydrogenase (SDH) histochemistry as mitochondrial function readout by quantitative immunofluorescence labelling of various respiratory chain subunits (Grunewald et al., 2014b). Surprisingly, complex I abundance in pigmented SN neurons from IPD patients was not determined by the extent of deletion accumulation but by the number of mtDNA copies per cell (Grunewald et al., 2016). Implicating mito-nuclear signalling in IPD, neuronal complex I levels tightly correlated with the abundance of mitochondrial transcription factor A (TFAM). In concordance with impaired mtDNA maintenance in dopaminergic patient neurons, triplex real-time PCR analysis indicated fewer mtDNA molecules with associated 7S DNA strands (Grunewald et al., 2016), which are required for the initiation of mitochondrial transcription and replication (Nicholls and Minczuk, 2014). Finally, besides complex I, mtDNA, TFAM, and TFB2M depletion, we detected a slight but significant reduction in the abundance of the entirely nuclear-encoded respiratory chain complex II in patient neurons (Grunewald et al., 2016). This result additionally emphasized that a disturbance in the communication between nucleus and mitochondria is part of the complex landscape of PD pathology (Fig. 1). In two studies from the Tzoulis laboratory, the relationship between mtDNA major arc deletions, copy number and respiratory chain deficiency in ageing and IPD was further examined. While in SN neurons of healthy aged individuals the occurrence of major arc mtDNA deletions coincided with an increase in copy number thereby maintaining a constant pool of wild-type mtDNA molecules, this compensatory mechanism was not present in IPD patients (Dolle et al., 2016). Moreover, the dependence of complex I on mtDNA copy number is restricted to the SN, albeit IPD patient neurons in the prefrontal cortex, the hippocampus and putamen also show a significant loss of complex I (Flones et al., 2018). This finding could indicate that (i) very subtle changes in mtDNA (deletion) levels below the current detection limit are sufficient to cause a significant impact on complex I; (ii) disturbances in the regulation of nuclear genes coding for respiratory chain subunits precede mtDNA disintegration, or that (iii) complex I dysfunction and mtDNA disintegration are the result of two distinct processes, i.e. impaired mitophagy and dopamine-induced oxidative stress, respectively. To disentangle these three scenarios, patient-derived cellular models may be useful despite their limitations (Kang et al., 2016). By contrast, we could not identify a single publication employing fibroblasts or, more sensibly, post-mitotic iPSC-derived dopaminergic neurons from sporadic patients with a focus on mtDNA involvement in IPD (Tables 1 and 2).

3.2. PD-associated proteins involved in mtDNA maintenance

Regarding PD-associated proteins, Parkin has the strongest links to mtDNA maintenance. Firstly, via the degradation of PARIS, a repressor of PPARGC1A expression, Parkin regulates the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)-mediated transcription of nuclear genes encoding for e.g. TFAM, TFB2M and the majority of complex subunits (Shin et al., 2011). Secondly, chromatin immunoprecipitation and co-immunoprecipitation studies suggest a direct interaction between Parkin and TFAM at the mtDNA D-loop (Kuroda et al., 2006; Rothfuss et al., 2009). In SH-SY5Y cells (Rothfuss et al., 2009) and mouse cortical neurons (Zheng et al., 2017), overexpression of wild-type Parkin enhanced mtDNA transcription and replication. By contrast, in patient fibroblasts with Parkin mutations, mtDNA transcription is severely suppressed (Rothfuss et al., 2009). Supporting these *in vitro* studies, mutator Parkin-knockout mice, which combine parkin depletion with POLG proofreading deficiency, showed enhanced loss of TH-positive SN neurons. The concomitant lack of dopamine caused motor phenotypes, which were reversible by L-DOPA (Pickrell et al., 2015). Furthermore, knocking-out parkin in the genetic mutator background accelerated the accumulation of pathogenic mtDNA mutations in these animals (Pickrell et al., 2015). In line with these findings, crossing PD-mito-PstI mice, which express mitochondrial-targeted endonuclease PstI under control of a DAT promotor leading to dopaminergic neuron-specific mtDNA depletion (Pickrell et al., 2011), with Parkin-knockout mice accelerated the neurodegenerative phenotype and precipitated the onset of motor symptoms (Pinto et al., 2018). Interestingly, the lack of Parkin in the resulting animals caused a rise in mtDNA copy number, which was not associated with an increase in mitochondrial mass or clearance (Pinto et al., 2018). This further highlights the possibility of a role for Parkin in mtDNA maintenance independent from mitophagy (see Section 5 for details on Parkin's involvement in mitophagy).

Apart from the above-mentioned study in endogenous Parkin-mutant cells, mtDNA integrity data in fibroblasts and neurons from genetic PD patients are sparse or, as in case of Parkin and LRRK2, inconsistent (Tables 1 and 2). Conversely, the only two publications, which assessed mtDNA features in neurons with Parkin mutations, did not detected differences between patient and control cultures (Jiang et al., 2011; Shaltouki et al., 2015).

4. Impact of alpha-synuclein aggregation on mitochondrial function: a reciprocal interaction

4.1. Alpha-synuclein interferes with mitochondrial function

The mechanism by which alpha-synuclein accumulation contributes to the death of dopaminergic neurons in PD is currently unclear, but there is growing evidence that mitochondrial dysfunction may play a role. Alpha-synuclein has been shown to accumulate in mitochondria thereby impairing various functions of the organelles (Chinta et al., 2010; Devi et al., 2008). The N-terminal domain of alpha-synuclein is important for mitochondrial targeting where it may be associated with complex I (Devi et al., 2008) (Fig. 1). Disruption of this N-terminal domain results in elongation of mitochondria, implicating alpha-synuclein in the maintenance of mitochondrial size (Pozo Devoto et al., 2017). Further data supporting a link between alpha-synuclein and respiratory chain dysfunction was collected in endogenous PD models

(Table 2). A technique known as 'FACS-assisted CRISPR-Cas9 editing' was used to generate isogenic lines of PD-associated mutations (Arias-Fuenzalida et al., 2017). In alpha-synuclein p.A53T-mutant neuroepithelial stem cells, the maximal respiration capacity was reduced. Additionally, both the p.A30 P and p.A53 T mutation in alpha-synuclein lowered the energy performance as demonstrated by a reduction in basal, ATP-linked and non-mitochondrial respiration (Arias-Fuenzalida et al., 2017).

In addition, a disease mechanism involving toxic species of wild-type alpha-synuclein was identified by Di Maio and colleagues (Di Maio et al., 2016). Alpha-synuclein has the ability to assemble into fibrils thereby accepting amyloid-like structures as present in Lewy bodies (Crowther et al., 1998). During this conformational change, alpha-synuclein transitions from monomers to mature fibrils via protofibrillar oligomers. These short elongated oligomers are composed of more than 15 monomers and it has been reported that these aggregates can spread from cell to cell in a prion-like fashion (Luk et al., 2012). While monomeric and fibrillar forms of the protein do not interact, oligomeric and dopamine-modified forms of alpha-synuclein can bind to the TOM20 (translocase of outer membrane 20) receptor of the mitochondrial protein import machinery (Di Maio et al., 2016). As a result of this interaction, TOM20 can no longer bind to its co-receptor TOM22, resulting in impaired mitochondrial protein import. The consequences of this include reduced mitochondrial respiration with increased production of ROS and a loss of mitochondrial membrane potential. Notably, this process was confirmed in nigrostriatal neurons from post-mortem brains of individuals with IPD (Di Maio et al., 2016). Nigrostrial neurons are particularly vulnerable because they are long, feature numerous synapses (Bolam and Pissadaki, 2012; Surmeier et al., 2017) and have high energy requirements to match the elevated electrical excitability, thereby resulting in increased levels of mitochondrial oxidative stress (Faustini et al., 2017; Surmeier et al., 2017).

Oxidative stress and apoptosis may be of particular importance in the relationship between alpha-synuclein and mitochondria. In both SH-SY5Y cells and isolated rat brain mitochondria, cytochrome c release is caused by an interaction between alpha-synuclein and mitochondria, and is associated with an increase of mitochondrial calcium and nitric oxide, and oxidative modification of mitochondrial components (Parihar et al., 2008). More recently, synthetic human preformed alpha-synuclein fibrils (PFFs) were shown to induce respiratory chain impairment, oxidative stress, and inflammation in rat ventral midbrain dopamine neurons (Tapias et al., 2017). Interestingly, when the investigators blocked the expression of inducible nitric oxide synthase (iNOS), a reduction in protein nitration levels and protection against PFFs-induced dopaminergic neuron death was detected, indicating a role for iNOS-derived nitrogen oxide in the pathogenicity of PFFs.

Further evidence for mitochondrial dysfunction occurring secondary to alpha-synuclein pathology comes from MPTP models of PD. In alpha-synuclein A30P transgenic mice, MPTP treatment led to enhanced degeneration of the nigrostriatal dopaminergic system when compared to non-transgenic controls (Nieto et al., 2006). This suggests that overexpression of A30P-mutant alpha-synuclein enhances the neuronal susceptibility to MPTP. In keeping with this concept, mice that are deficient of alpha-synuclein have been shown to be more resistant to the effects of MPTP on dopaminergic neurons (Dauer et al., 2002). These findings have been confirmed in MPTP-treated SH-SY5Y cells. Suppression of alpha-synuclein reduced the transport of dopamine in human cells, thereby altering dopamine homeostasis and increasing cellular survival in the presence of MPTP (Fountaine and Wade-Martins, 2007).

Controversially, there is also data in the literature that suggests a neuro-protective role for alpha-synuclein (Sidhu et al., 2004). Mice lacking alpha-synuclein have altered mitochondrial membrane composition and structure as well as complex I/III defects in the brain (Ellis et al., 2005). Furthermore, unfolded, monomeric alpha-synuclein was shown to interact with ATP synthase subunit alpha to improve ATP synthase efficiency in mice. Alpha-synuclein deficiency increased respiration and caused lower mitochondrial membrane potential and ATP levels (Ludtmann et al., 2016). Alpha-synuclein may also be required for endoplasmic reticulum (ER)-mitochondrial signalling. The impact of mutations in alpha-synuclein on mitochondria-associated endoplasmic reticulum membrane (MAM) function is summarized in Section 7.2 below.

4.2. Mitochondrial dysfunction mediates alpha-synuclein accumulation

Evidence in support of the hypothesis that mitochondrial dysfunction precedes alpha-synuclein accumulation comes from studies exploring the role of pesticides such as paraquat and rotenone in the pathogenesis of PD. Exposure of rodent models to these agents led to an increase in alpha-synuclein aggregation (Nistico et al., 2011; Tieu, 2011). By contrast, paraquat and rotenone neither directly interact with alpha-synuclein nor alter fibrillation of the protein (Maturana et al., 2015). This implies that the observed alpha-synuclein phenotype in these animal models occurs downstream of mitochondrial impairment. Similarly, chronic administration of MPTP increased the number of alpha-synuclein-positive nigral neurons in mice (Vila et al., 2000).

Further data in support of alpha-synuclein accumulation as an event occurring secondary to mitochondrial dysfunction was collected in studies of genetic PD. Mutations in *ATP13A2* cause a complicated form of autosomal recessive PD (Kufor Rakeb syndrome) (Ramirez et al., 2006). *ATP13A2* codes for a lysosomal type 5 P-type ATPase which is believed to function as a cation pump (Park et al., 2014). In fibroblasts from patients with Kufor Rakeb syndrome, altered respiratory chain function, increased mtDNA copy numbers and deletion levels have been reported (Grunewald et al., 2012) (Table 1). Moreover, in patient-derived human olfactory neurosphere cultures, zinc dyshomeostasis due to mutations in ATP13A2 was shown to provoke mitochondrial depolarization, fragmentation, ATP depletion, and cell death (Park et al., 2014). ATP13A2 mutations also cause lysosomal dysfunction in patient-derived fibroblasts, reduced proteolytic processing of lysosomal enzymes, decreased degradation of the substrates of lysosomes, and diminished clearance of autophagosomes by lysosomes (Dehay et al., 2012) (Table 1). In this context, ATP13A2 has been shown to localize to multi-vesicular bodies (MVBs), which can serve as a link between the autophagic and endosomal pathways. MVBs may function as exosomes to release intracellular cargoes including zinc and alpha-synuclein (Kong et al., 2014). While ATP13A2 overexpression reduced intracellular alpha-synuclein levels due to enhanced exocytosis, this exosomal release of alpha-synuclein was compromised in ATP13A2-deficient cells (Kong et al., 2014). Given that, ATP13A2 depletion was previously associated with impaired bioenergetics (Grunewald et al., 2012; Park et al., 2014), these experiments place mitochondrial dysfunction upstream of intracellular alpha-synuclein accumulation.

Taken together, these studies suggest that the relationship between alpha-synuclein and the mitochondria is reciprocated and tightly regulated. Disturbances in the dynamics of this interaction may result in a shift of the properties of alpha-synuclein from neuro-protective to neuro-toxic.

5. Mitochondrial homeostasis: mitophagy maintains mitochondrial function

5.1. PINK1/Parkin-mediated mitophagy selectively degrades damaged mitochondria

Mitochondrial homeostasis is dependent on the continued turnover of mitochondria to maintain their optimal function. Key to the maintenance of mitochondrial health is the process of "mitophagy" or the selective degradation of mitochondria via autophagy (Gao et al., 2017; Lemasters, 2005). There are several forms of autophagy including microautophagy and endosomal microautophagy, chaperone-mediated

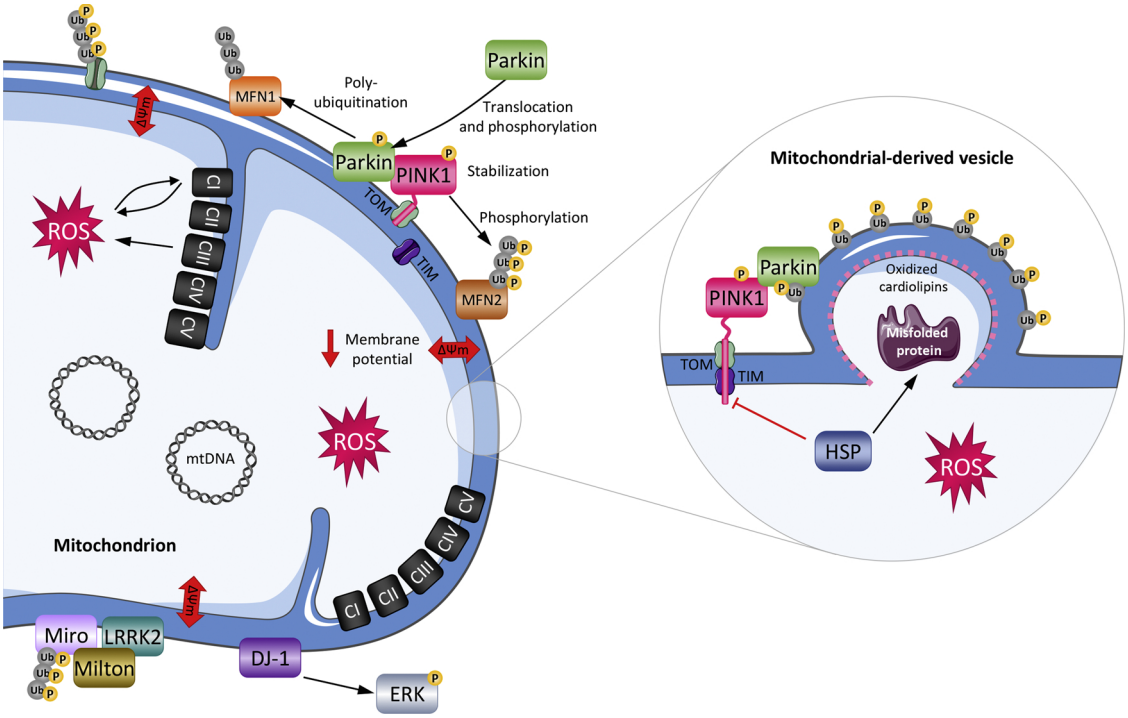

Fig. 2. Mitophagy and mitochondrial-derived vesicle formation in Parkinson's disease (PD). PINK1 is targeted to the mitochondria, where its transmembrane domain enters the TOM/TIM complex and undergoes cleavage mediated by PARL. When mitochondria are uncoupled under the impact of oxidative stress, the processing of PINK1 is prohibited, causing the protein to accumulate at the outer mitochondrial membrane. Here, PINK1 activates the E3 ubiquitin ligase Parkin, which ubiquitinates outer mitochondrial membrane proteins e.g. mitofusins and TOM. PINK1 stabilizes Parkin at the mitochondria by phosphorylation of Ser65 in the ubiquitin-like domain, which promotes ubiquitin chain assembly. Moreover, ubiquitin itself can be phosphorylated by PINK1 on Ser65. Jointly, these events at the outer mitochondrial membrane activate mitophagy receptors, which promote sequestration of mitochondria by autophagosomes. Additionally, ERK signalling can regulate mitophagy. DJ-1 can activate ERK2 independently of the PINK1/Parkin pathway. To facilitate clearance of damaged mitochondria, Miro is removed from the outer mitochondrial membrane thereby disrupting the connection with Milton and kinesin heavy chain (KHC, not shown). Mitochondria are attached via Milton and KHC to the microtubule during mitochondrial transport. Mutations in LRRK2 can delay the removal of the PINK1/Parkin target Miro. Consequently, in the presence of mutant LRRK2, mitochondrial arrest and the initiation of mitophagy is stalled. PINK1 and Parkin are also involved in the formation of mitochondrial-derived vesicles, which serve to remove small-scale damaged cargo from the mitochondria. The current working hypothesis assumes that contact with oxidized proteins will alter the lipid composition and change the curvature of the inner mitochondrial membrane. When the capacity of chaperones to counteract misfolding is reached, mitochondrial proteins, including PINK1, can no longer be imported. Under these circumstances, Parkin is stabilized and activated at the mitochondria by PINK1-mediated phosphorylation. Parkin-mediated ubiquitination of targets at the outer mitochondrial membrane is a requisite for the formation of vesicles, which travel to the lysosome for degradation. Fig. 2 was partially adapted from a publication by Sugiura and colleagues (Sugiura et al., 2014) and elements from Servier Medical Art (http://smart.servier.com/) were used.

autophagy and macroautophagy (Galluzzi et al., 2017; Gao et al., 2017). Mitophagy is a well-characterised form of a macroautophagy that occurs in mammalian cells (Galluzzi et al., 2017). Important PD-related genes have been shown to play pivotal roles in the process of mitophagy.

PINK1/Parkin-mediated mitophagy is the most investigated mechanism for the homeostatic quality control of mitochondria. PINK1 senses mitochondrial depolarisation, ROS, or protein misfolding (Shirihai et al., 2015) (Fig. 2) and triggers mitophagy. The mitochondrial-targeting sequence of PINK1 guides the protein to the mitochondria. Under basal conditions, PINK1 is rapidly degraded as its transmembrane domain enters the translocase of outer membrane (TOM)/translocase of inner membrane (TIM) complex and is cleaved by presenilins-associated rhomboid-like protein (PARL) (Harper et al., 2018). The degradation of PINK1 after import is disrupted when mitochondria become depolarised, leading to a build-up of PINK1 and the recruitment of the E3 ubiquitin ligase Parkin (Gao et al., 2017). There are differing views on the how Parkin is translocated from the cytosol (Shirihai et al., 2015). By contrast, it has been confirmed that the PINK1-mediated phosphorylation of Ser65 in the ubiquitin-like domain stabilizes and activates Parkin at the mitochondria (Harper et al., 2018). This is highlighted by a study showing that the recruitment of Parkin to mitochondria is dependent upon PINK1 expression, and that the overexpression of wild-type but not mutant forms of PINK1 causes relocation of Parkin to mitochondria (Vives-Bauza et al., 2010). Parkin ubiquitinates various outer mitochondrial membrane proteins including Mitofusin1/2 (MFN1/2) and voltage-dependent anion-selective channel 1 (VDAC1) (Karbowski and Youle, 2011). In turn, the resulting poly-ubiquitin chains are phosphorylated by PINK1 (Fig. 2). These damage signals recruit ubiquitin-binding autophagy receptors such as p62 (sequestosome 1) and optineurin (OPTN) to the mitochondria. Finally, the depolarized organelles are engulfed by LC3-positive phagophores (the precursors to autophagosomes) and eventually degraded by lysosomal hydrolases (Harper et al., 2018).

The PINK1/Parkin mitophagy pathway has been confirmed in PD patient-derived fibroblasts (Rakovic et al., 2011a, 2010) and iPSC-derived neurons (Rakovic et al., 2013; Seibler et al., 2011) (Tables 1 and 2). Fibroblasts from individuals with PINK1 mutations were used to show that PINK1 regulates the stress-induced decrease in endogenous Parkin as well as the translocation of Parkin, that endogenous PINK1 is stabilised on mitochondria that are depolarised, and that mitochondrial accumulation of PINK1 is sufficient but not a prerequisite for the loss of Parkin signal and Parkin mitochondrial translocation induced by stress (Rakovic et al., 2010). Thus, primary human dermal fibroblasts originating from PD patients with various PINK1 mutations were used to show the requirement of introducing an environmental factor such as stress to detect the differences in the interaction of PINK1 and Parkin in mutants compared to controls (Rakovic et al., 2010). PD patient-

derived fibroblasts were also used to show that PINK1 and Parkin mutations impair ubiquitination of Mitofusins (Rakovic et al., 2011a). A study compared human primary fibroblasts and iPSC-derived neurons from controls and PINK1 mutation carriers. The investigators demonstrated that mitophagy differs between human non-neuronal versus neuronal cells, and between "endogenous" cellular models in comparison to models using Parkin overexpression (Rakovic et al., 2013). Another study used iPSC-derived neurons from individuals with PD and PINK1 mutations to demonstrate evidence of impaired recruitment of Parkin to mitochondria, increased mitochondrial copy number, and upregulation of PGC-1α (Seibler et al., 2011). These changes could be corrected via lentiviral expression of wild-type PINK1, using a patient-derived, biologically relevant cell model.

PINK1 and Parkin, both also play a role in mitochondrial homeostasis through their effect on mitochondrial fission and fusion (Gao et al., 2017). PINK1 inhibits the fusion of damaged mitochondria, which may serve the purpose of preventing contamination of healthy mitochondria by those that are damaged (Shirihai et al., 2015). Excessive fission can be countered by the mitochondrial fusion proteins MFN2 and protein optic atrophy 1 (OPA1) or by a dominant negative mutation of the Drp1 fission protein (Giannoccaro et al., 2017).

5.2. Mutations in DJ-1 may contribute to impaired mitophagy

Mutations in *DJ-1* are a rare cause of autosomal recessive PD (Bonifati et al., 2003). A study investigated the mechanisms underlying *DJ-1*-associated PD by using knockout mice and human carriers of *DJ-1* mutations (Krebiehl et al., 2010). DJ-1 depletion led to disturbed mitochondrial respiration, an increase in ROS, decreased mitochondrial membrane potential and altered mitochondrial morphology. Furthermore, the basal autophagic degradation was reduced and there was an accumulation of defective mitochondria in DJ-1-knockout cells coinciding with a decrease in phospho-activated ERK2 (Fig. 2). The ERK1/2 pathway has been identified as an alternative regulator of mitophagy (Hirota et al., 2015). This suggests that DJ-1 loss results in impaired autophagy and an accumulation of dysfunctional mitochondria (Krebiehl et al., 2010) (Table 1). Interestingly, DJ-1 can regulate ERK signalling in parallel to the PINK1/Parkin mitophagy pathway. The mitochondria-protective effects of DJ-1 are independent of PINK1 and size exclusion chromatography revealed that the three proteins do not complex together (Thomas et al., 2011).

5.3. Potential role of LRRK2 in mitophagy

Mutations in *LRRK2* are a cause of autosomal dominant PD (Paisan-Ruiz et al., 2004; Zimprich et al., 2004). LRRK2, a member of the leucine-rich kinase family, has also been reported to have a role in mitophagy. Overall, the common G2019S mutation in LRRK2 is the most intensively studied mutation in iPSC-derived neurons regarding mitochondrial function (Table 2). A study using human iPSC-derived neurons showed that LRRK2 promotes the removal of Miro by forming a complex with this protein (Hsieh et al., 2016) (Table 2). Miro is an outer mitochondrial membrane protein, which serves to anchor mitochondria to microtubule motors. Miro is removed to prevent mitochondrial motility in the early stages of clearing dysfunctional mitochondria and has been previously linked with PINK1 and Parkin (Liu et al., 2012; Wang et al., 2011) (Fig. 2). Hsieh and colleagues showed that the G2019S mutation in LRRK2 delays the arrest of dysfunctional mitochondria and slows the initiation of mitophagy. In iPSC-derived sensory neurons from PD patients, the G2019S mutation led to increased levels of the autophagy markers p62 and LC3 (Schwab et al., 2017). Moreover, sensory neurons showed neurite aggregations and abnormal calcium dynamics. Theses defects were distinct from changes observed in dopaminergic neurons (see Section 7.3 for details on a study by the same group on dopaminergic neurons with G2019S mutation) and may explain some of the non-motor symptoms in LRRK2-associated PD (Schwab et al., 2017).

6. Mitochondrial quality control via mitochondrial-derived vesicles (MDVs)

6.1. PINK1 and Parkin are required for MDV transport

MDVs are a trafficking pathway generated through the selective incorporation of protein cargo, which is targeted to the late endosome/multivesicular body, or to a subpopulation of peroxisomes (Neuspiel et al., 2008; Soubannier et al., 2012a; Sugiura et al., 2014). MDVs are stimulated by mitochondrial stress and the identification of their cargo is dependent upon the nature of the mitochondrial stress (Soubannier et al., 2012b). In particular, stress-induced MDVs are enriched for oxidised proteins, suggesting they have a role in mitochondrial quality control (Soubannier et al., 2012b).

It has been shown that Parkin and PINK1 are involved in the vesicular trafficking pathway (McLelland et al., 2014). Following oxidative stress, wild-type but not mutant Parkin promotes the biogenesis of MDVs, which bud off from the mitochondria and contain specific cargo proteins. The MDVs are dependent upon the expression of PINK1, and eventually will target lysosomes for degradation. An interruption to this parkin or PINK1-dependent pathway may affect the ability of mitochondria to clear oxidised proteins, potentially adding to the mitochondrial dysfunction seen in PD (McLelland et al., 2014) (Fig. 2).

Sugiura and colleagues have formulated a 4-step hypothesis to explain the mechanism of MDV generation by PINK1 and Parkin (Sugiura et al., 2014). In 'Step 1', ROS or failure of proteins to assemble results in an aggregation of unfolded, oxidised proteins within the matrix. Cardiolipin oxidation creates phosphatidic acid, which modulates the curvature of the membrane. In 'Step 2', chaperones are saturated by protein aggregates. This leads to a 'very localised failure' of importation at an individual channel. The channels are also affected by local oxidation of cardiolipin. For 'Step 3', phosphorylation of ubiquitin as well as the ubiquitin-like domain of Parkin by PINK1 leads to the recruitment of activated Parkin. This ubiquitination activity of Parkin facilitates the creation of MDVs. Finally, in 'Step 4', an MDV is formed and released.

Regardless of the exact mechanisms responsible for the generation of MDVs, it is clear that PINK1 and Parkin are involved (Sugiura et al., 2014). This suggests that PINK1 and Parkin have dual roles in mitophagy and trafficking/degradation of specific oxidised cargo from mitochondria (Sugiura et al., 2014) (Fig. 2).

6.2. Vesicle transport to peroxisomes

The purpose of vesicle delivery to the peroxisomes is unclear and the only protein known to traffic to peroxisomes is MAPL (Braschi et al., 2009; Mohanty and McBride, 2013). It has been shown that the retromer complex, which is involved in transporting cargo from the endosome to the Golgi apparatus, is a regulator of the transport of MAPL from mitochondria to peroxisomes (Braschi et al., 2010). VPS35 and VPS26 are in complex with MAPL and silencing of VPS35 or VPS26A results in diminished delivery of MAPL to peroxisomes. VPS35 is recruited to mitochondrial vesicles, and notably, mutations in *VPS35* can cause autosomal dominant PD (Kumar et al., 2012b; Vilarino-Guell et al., 2011; Zimprich et al., 2011), underpinning the role of the retromer complex in the aetiology of PD.

7. Newly emerging roles for mitochondria in the pathogenesis of PD

7.1. Mitochondria and cell-mediated immunity

Recent research shows that by regulating MDV formation, PINK1 and Parkin may also link PD to the immune system (Matheoud et al., 2016). While PINK1 and Parkin are required for the budding of ROS-induced MDVs from the mitochondria (McLelland et al., 2014), they repress the generation of heat-shock and liposaccharide-induced MDVs thereby preventing mitochondrial antigen presentation (MitAP) (Matheoud et al., 2016). Under inflammatory conditions, MitAP is induced by the recruitment of the cytosolic proteins Rab9 and Snx9 to the mitochondria. Once MDVs have been formed, the GTPase Rab7 likely enables their fusion with late endosomes where the mitochondrial antigens are enzymatically processed (Matheoud et al., 2016). Before being mounted onto and displayed by major histocompatibility complex I (MHC-I) molecules, the peptides are proteolytically cleaved in the cytosol and finally trimmed to 8–10 amino acids-long fragments in the ER. The presence of mitochondrial antigens at the cell surface may then activate specific cytotoxic T cells (Lazaro et al., 2015). This process is kept in check by the PINK1/Parkin pathway. Stress-induced translocation of Parkin to the mitochondria ensures that the mitochondrial concentration of Snx9 is regulated in a proteasome-dependent manner (Matheoud et al., 2016). It is important to note that while the presentation of exogenous antigens on MHC II molecules can only be performed by specialized immune cells, the MHC I pathway for endogenous peptide presentation exists in all nucleated cells, including dopaminergic neurons (Cebrian et al., 2014; Matheoud et al., 2016). In the absence of Parkin, the activation of MitAP may trigger a response by cytotoxic T cells, which eventually causes neuronal demise. MHC I presentation in dopaminergic neurons may alternatively be induced by cytokine release from microglia that have been activated by neuromelanin or alpha-synuclein. The latter protein has been shown to elicit an immune response in mice (Benner et al., 2008; Theodore et al., 2008). By contrast, MHC II-deficient mice are protected against neuronal death due to alpha-synuclein overexpression (Harms et al., 2013). In PD patients, peptides from two different regions within alpha-synuclein produce a response by CD4+ or CD8 + T cells. These are the Y39 antigenic region, which is situated in close proximity to known alpha-synuclein point mutations, and the S129 antigenic region, which requires phosphorylation as typically found in Lewy bodies (Sulzer et al., 2017). Finally, mitochondrial stress provoked by a partial depletion of TFAM can cause the mtDNA to escape from mitochondria into the cytosol where it engages innate immune signalling in mouse embryonic fibroblasts (West et al., 2015). Taken together, these studies suggest that the mitochondrial, mtDNA maintenance and lysosomal disease mechanisms in PD may converge at the level of cell-mediated immunity.

7.2. Links between astrocyte and neuronal mitochondrial dysfunction in PD

Research into the role of alpha-synuclein in glial cells is not limited to the above-described studies in microglia. In a recent series of publications by the Erlandsson lab, uptake, degradation and toxicity of oligomeric alpha-synuclein were tested in a co-culture system of mouse primary neurons, astrocytes and oligodendrocytes (Lindstrom et al., 2017). Astrocytes were shown to engulf alpha-synuclein from the extracellular space and to degrade the protein via the lysosomal pathway. However, at large alpha-synuclein concentrations, the digestion capacity of astrocytes was reached and intracellular deposits formed and interfered with mitochondrial function (Lindstrom et al., 2017). In a study using iPSC-derived human astrocytes, it was further demonstrated that overburdened astrocytes connect with nearby healthy astrocytes via tunnelling nanotubes (TNTs). Through the TNTs, stressed cells can release oligomeric alpha-synuclein and obtain functional mitochondria in return. This intercellular rescue mechanism was abolished by treatment with the F-actin depolymerization drug latrunculin B (Rostami et al., 2017). In another study from the same group, the therapeutic effect of alpha-synuclein oligomer-selective antibodies was tested in a murine co-culture system. Indeed, in the presence of these antibodies, extracellular alpha-synuclein was cleared more efficiently and the intracellular digestion of the protein was enhanced. Moreover, previously observed mitochondrial phenotypes in alpha-synuclein-ingesting astrocytes were reversed after treatment (Gustafsson et al., 2017). However, astrocyte dysfunction in PD is not exclusively linked to alpha-synuclein. Astrocytes cultivated from Parkin-knockout mice exhibited an increased number of morphologically altered mitochondria and an upregulation of the mitochondrial proteins PINK1, Drp1 and SOD2 upon oxidative stress (Schmidt et al., 2011). Furthermore, in astrocytes derived from PINK1-knockout mice, proliferation defects were associated with a decrease in mitochondrial mass, membrane potential and ATP production as well as an increase in cellular ROS. Treatment of wildtype astrocytes with the ATP synthase inhibitor oligomycin was sufficient to mimic the proliferation phenotype observed in PINK1-deficient murine cells (Choi et al., 2013). It is conceivable that impaired mitochondrial metabolism in astrocytes constrains their neuron support function.

7.3. ER-mitochondria axis

Between 5 to 20% of the mitochondrial surface is situated opposite of the ER. ER-mitochondria signalling is crucial for lipid biosynthesis, inflammasome formation, cellular calcium handling and mitochondrial homeostasis (Gomez-Suaga et al., 2018). Especially within the context of the two latter functions, MAMs have been linked to PD. Characteristics in their calcium handling properties, may explain the specific vulnerability of nigral dopaminergic neurons in PD. A study from Surmeier's laboratory found that these neurons heavily rely on L-type Ca(v)1.3 Ca^{2+} channels for rhythmic pacemaking (Chan et al., 2007). This dependency is age-associated as juvenile dopamine neurons in the SN use pacemaking mechanisms similar to neuron types not affected by PD (Chan et al., 2007). Considering these findings, it is conceivable that even slight disturbances of ER-mitochondria contacts would have detrimental consequences for the survival of dopaminergic neurons (Gomez-Suaga et al., 2018). One such interfering factor is alpha-synuclein, which was identified at the MAM in mouse and human brain tissue. This association with the MAM is weakened by pathogenic mutations in alpha-synuclein coinciding with fewer areas of ER-mitochondria apposition, impaired MAM function and increased mitochondrial fragmentation (Guardia-Laguarta et al., 2014). While overexpression of wild-type alpha-synuclein successfully recovered the mitochondrial morphology phenotype, rescue experiments with MFN2 and DRP1 had no impact on the mitochondrial network. These analyses place alpha-synuclein downstream of the mitochondrial fusion and fission machinery (Guardia-Laguarta et al., 2014). The connection between mitochondria and the ER is stabilized by tethering complexes. In humans, this includes an interaction between the outer mitochondrial membrane protein, protein tyrosine phosphatase-interacting protein 51 (PTPIP51) and the ER protein, vesicle-associated membrane protein-associated protein B (VAPB) (Gomez-Suaga et al., 2018). Alpha-synuclein can bind to VAPB and overexpression of wild-type or mutant forms of alpha-synuclein disrupts the VAPB-PTPIP51 tethers. This finding could be recapitulated in iPSC-derived neurons from a PD patient with an alpha-synuclein triplication (Table 2). Loosening of the mitochondria-ER contacts impairs calcium exchange between the two organelles, which in turn lowers ATP production (Paillusson et al., 2017). In addition to alpha-synuclein, also PINK1 and Parkin seem to be required for ER-mitochondria cross talk (Gomez-Suaga et al., 2018). Both proteins are targeted to MAMs upon mitochondrial depolarization, where they recruit autophagy factors (Gelmetti et al., 2017; Yang and Yang, 2013). Confocal and electron microscopy analyses showed closer

interactions between ER and mitochondria in fibroblasts from patients with mutations in Parkin than in control cells. Functionally, Parkin mutations led to enhanced inter-organelle calcium transfer not only in patient fibroblasts but also in thereof-derived patient neurons (Gautier et al., 2016). The Parkin substrate MFN2, which forms mitochondria-ER tethers with MFN1 (Gomez-Suaga et al., 2018), was considerably more abundant in MAMs of Parkin-knockout than control mouse tissue. Moreover, MFN downregulation and Parkin overexpression rescued the calcium dyshomeostasis in Parkin-mutant patient fibroblasts. Finally, also DJ-1 was found to modulate mitochondrial calcium transients via its effect on ER-mitochondria coupling in HeLa cells. Even under p53-induced stress, which causes reduced mitochondrial calcium buffering capacity and ER-mitochondria contact sites, DJ-1 overexpression sufficed to re-establish normal ER-mitochondria tethering (Ottolini et al., 2013).

7.4. Sirtuin-mediated mitochondrial stress response

Sirtuin proteins are nicotinamide adenine dinucleotide-dependent deacetylases, which mediate the cellular response to mitochondrial stress. This includes the mitochondrial unfolded protein response (UPR^{mt}), ROS scavenging and events of mitochondrial maintenance such as fusion, fission and mitophagy (Lin et al., 2018). Especially, SIRT1 and SIRT3 have recently received much attention in PD research with respect to the PINK1/Parkin mitophagy pathway. Genetic depletion of SIRT1 led to diminished deacetylation and a decrease in activity of the mitochondrial superoxide dismutase 2 (SOD) in mice. In turn, higher ROS levels in SIRT1-knockout cells accelerated the mitochondrial translocation of Parkin (Di Sante et al., 2015). Given the distinct cellular localization of SIRT1 (cytosolic) and SOD2 (mitochondrial) (Lin et al., 2018), the authors of the respective study speculate that the uncovered cellular mechanism may, in fact, include mitochondrial SIRT3 (Di Sante et al., 2015). Strengthening this hypothesis, SIRT3-null mice exposed to MPTP exhibited reduced SOD2 and glutathione peroxidase protein levels compared with wild-type animals (Liu et al., 2015). Moreover, SIRT3 was previously found to act on PINK1 gene expression and mitophagy via the activation of Forkhead box protein O3 (FOXO3A) (Mei et al., 2009). The existence of a SIRT3-FOXO3A-PINK1-Parkin axis was recently confirmed in mice (Yu et al., 2017). Zhang and colleagues further studied the pathway, which is now also thought to include PGC-1α and estrogen-related receptor alpha (ERRα). The two proteins directly interact at the SIRT3 promoter regulating the gene's expression and SOD2 acetylation, which influences dopaminergic neuron survival (Zhang et al., 2016). Lysine 68 in SOD2 was identified as the acetylation site for SIRT3 (Shi et al., 2017a). Additionally introducing a knockout of the antioxidant protein DJ-1, which can directly bind and activate SIRT1 (Takahashi-Niki et al., 2016), further exacerbated the oxidative stress and neuronal degeneration phenotypes in SIRT3-null mice (Shi et al., 2017a). The effect of SIRT3 on the viability of dopaminergic neurons has also been observed in an adeno-associated virus-expressing mutant (A53 T) alpha-synuclein rat model of Parkinsonism (Gleave et al., 2017).

With regard to endogenous PD models, Schwab and colleagues determined the protein levels of SIRT1-3 in iPSC-derived neurons from patients with the G2019S mutation in LRRK2. Western blotting analyses revealed elevated levels of all three proteins. To test if this increase was due to excessive kinase activity, the authors performed a rescue experiment using the LRRK2 kinase inhibitor GSK2578215 A (Table 2). However, while the treatment reduced mitochondrial velocity, it had no effect on SIRT1, SIRT2, or SIRT3 expression levels or any other mitochondrial function phenotypes observed in the cells (Schwab et al., 2017). In conclusion, an age-associated decline in the capacity of sirtuins to act upon mitochondrial stress may also play a role in the dopaminergic neuron loss in PD.

7.5. MicroRNA and mitochondrial anomalies in PD

With respect to mitochondrial function in PD, micro RNAs (miRNA) are the most intensively studied small non-coding RNAs (which also include Piwi-interacting RNAs and small nucleolar RNAs) (Leggio et al., 2017). MiRNAs are typically 21–22 nt long and they modulate the expression of specific targets by interfering with mRNA. This interaction destabilizes the mRNA or prevents its translation (Leggio et al., 2017). MiRNA profiling in different post-mortem brain tissue from IPD patients revealed widespread dysregulation, including expression changes in the cingulate gyri, cerebellum, putamen, midbrain, SN, prefrontal and frontal cortex, amygdala and striatum (Martinez and Peplow, 2017). Some of these miRNAs specifically target PD genes that have been associated with mitochondrial function. MiR-7, which is highly abundant in TH-positive nigral neurons (Choi et al., 2014), was found to interfere with alpha-synuclein gene expression and to protect against oxidative stress as early as in 2009 (Junn et al., 2009). Recent data in (MPP +)-treated HEK293 cells underlined that miR-7, together with miR-153, regulates the ROS-mediated *de novo* synthesis of alpha-synuclein (Je and Kim, 2017). Reduced levels of miR-34b and miR-34c in human brain samples correlated with lower abundances of the proteins DJ-1 and Parkin. SH-SY5Y cells depleted of miR-34b or miR-34c showed reduced mitochondrial membrane potential, decreased ATP levels and more fragmented mitochondria (Minones-Moyano et al., 2011). Additionally, DJ-1 mRNA was identified as a direct target of miR-4639-5p (Chen et al., 2017). With regard to PINK1, miR-27a and miR-27b were demonstrated to supress the gene's expression thereby inhibiting clearance of damaged mitochondria (Kim et al., 2016). An inverse relationship was also reported between miR-205 and LRRK2 protein expression. Induction of miR-205 in neurons overexpressing LRRK2 R1441 G sufficed to rescue a neurite outgrowth phenotype (Cho et al., 2013). Evidence for a role of miRNAs in modulating mitochondrial-lysosomal cross talk in PD comes from a 6-hydroxydopamine (6-OHDA) stress model. Treatment of SH-SY5Y cells with the neurotoxin led to a significant downregulation of miR-5701. Expression of a miR-5701 mimic caused a reduction in complex I activity, ATP and NADH levels. Moreover, the levels of the autophagy marker LC3-II were increased in the presence of miR-5701, whereas the turnover of p62 was decreased. These results indicated that miR-5701 is crucial for mitochondrial energetics and the maturation of autophagolysosomes as well as lysosomal function (Prajapati et al., 2018). MiRNAs have potential as therapeutic targets in PD warranting further studies into the cellular pathways regulating gene expression.

8. Therapeutic approaches targeting mitochondria in PD

PD is a slowly progressive, disabling condition. There is a pressing need to develop neuroprotective therapy to modify the natural history of this disorder. Multiple strategies have been employed to address this need, and many target mitochondrial function. Key studies involving preclinical studies and clinical trials are outlined below.

8.1. Antioxidant therapies

There is a range of preclinical studies that suggest that antioxidants may address mitochondrial dysfunction in PD. However, these promising investigations have not yet translated into a beneficial effect in clinical trials.

Methylene blue (MB) is a renewable electron cycler in the mitochondrial electron transport chain, with antioxidant and cell energetic enhancing properties (Biju et al., 2018). Investigators have used acute toxin models of PD to demonstrate that MB has beneficial effects on nigrostriatal dopaminergic cell loss and motor impairment (Rojas et al., 2009; Smith et al., 2017; Wen et al., 2011). In a chronic MPTP/probenecid mouse model it was shown that olfactory dysfunction

improved with MB treatment, in comparison to currently available anti-parkinsonian medication, which had no benefit (Biju et al., 2018). These results indicate that MB is a promising neuroprotective agent with potential beneficial effects for, both, motor and non-motor manifestations of PD (Biju et al., 2018).

There is evidence that the mitochondrially targeted antioxidant, mito-apocynin (Mito-Apo), has neuroprotective effects on pre-clinical PD (Ghosh et al., 2016; Langley et al., 2017). In a recent study, mitochondrial transcription factor A was selectively knocked out to create MitoPark mice, an animal model of PD (Langley et al., 2017). It was shown that Mito-Apo attenuated severe nigrostriatal degeneration, improved mitochondrial function, and inhibited NOX2 activation, oxidative damage and neuroinflammation (Langley et al., 2017). These results support a clinical application of a Mito-Apo as neuroprotective and anti-neuroinflammatory agent in PD therapy (Langley et al., 2017).

The monoamine oxidase-B (MAO-B) inhibitor, N-Methyl, N-propynyl-2-phenylethylamine (MPPE), is a selegeline analogue, and has been shown to attenuate dopaminergic damage induced by MPTP (Shin et al., 2016). The effect of MPPE depends on inhibition of mitochondrial oxidative stress, mitochondrial translocation of p53, and pro-apoptotic change (Shin et al., 2016). The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) Trial suggested that deprenyl (selegeline), but not tocopherol, delayed the onset of disability in early, untreated PD (Parkinson Study Group, 1993). However, it was unclear whether this was a symptomatic effect or a slowing of the underlying disease process (Parkinson Study Group, 1993). A trial of a newer MAO-B inhibitor, rasagaline, showed a benefit consistent with a disease modifying effect with a dose of 1 mg, but not with a higher dose of 2 mg (Olanow et al., 2009). Given these mixed results, no definitive recommendations regarding rasagaline can be made (Mehta et al., 2010).

Pramipexole exists in two isomers, the S(−) enantiomer, which is a potent D3/D2 receptor agonist used extensively in the management of PD, and the R(+) enantiomer, which has little dopamine agonist effects (Ferrari-Toninelli et al., 2010). Using differentiated SH-SY5Y neuroblastoma cells, investigators showed that, both, S(−) and R(+) pramipexole have equipotent effects of preventing cell death induced by H_2O_2 and inhibiting mitochondrial reactive oxygen species generation (Ferrari-Toninelli et al., 2010). This suggests that pramipexole has an anti-oxidant and neuroprotective activity, which is independent of its role as a dopamine receptor agonist.

It has been reported that MitoQ, a mitochondrial targeted antioxidant, can protect dopaminergic neurons in a 6-OHDA-induced model of PD (Xi et al., 2018). The mechanism involves activation of PGC-1α to augment Mfn2-dependent mitochondrial fusion (Xi et al., 2018). A double-blind, placebo-controlled study assessed MitoQ as a potential therapy for disease modification in PD patients (Snow et al., 2010). Unfortunately, this study showed no benefit of MitoQ for disease progression (Snow et al., 2010).

Coenzyme Q10 (CoQ10) is an antioxidant that supports the function of mitochondria. The effect of CoQ10 on disease progression was investigated in a large phase III randomized, placebo-controlled, double-blind clinical trial with a change in total unified Parkinson's disease rating scale (UPDRS) score (Parts I-III) as the primary outcome measure (Parkinson Study Group QE3 Investigators et al., 2014a). While Coenzyme Q10 was safe and well tolerated, the study showed no evidence of clinical benefit.

A triple-blinded, randomised, placebo-controlled trial to investigate the efficacy and safety of ViNeuro in PD has been completed (NCT00517842), but the results are currently not available. The action of ViNeuro includes a mitochondrial antioxidant effect.

The drug EPI-589, which modifies cellular GSH levels and has an antioxidant effect, was developed to treat mitochondrial disease in children. It is currently the subject of a phase 2 study (NCT02462603) with primary outcome being safety and secondary outcomes of clinical and biomarker parameters.

N-acetylcysteine (NAC), a GSH precursor, is currently used to treat acetaminophen overdose and for its mucolytic properties in cystic fibrosis (Ammal Kaidery and Thomas, 2018). NAC has antioxidant properties by fortifying GSH and has also shown benefits in preclinical models of PD (Ammal Kaidery and Thomas, 2018; Berman et al., 2011; Clark et al., 2010; Martinez Banaclocha, 2000; Rahimmi et al., 2015). A cell line study of NAC showed an increase in midbrain dopaminergic neurons surviving after exposure to rotenone in comparison to no NAC (Monti et al., 2016). This was combined with a preliminary clinical study, which showed significantly increased DAT binding in the caudate and putamen on DaTscan and improved UPDRS scores in the NAC group (Monti et al., 2016). This study suggests that a large-scale clinical trial is necessary to investigate the therapeutic effect of NAC for PD.

The ability to selectively induce a range of cytoprotective and antioxidative enzymes under the control of a single transcription factor such as Nrf2 is a promising strategy (Ammal Kaidery and Thomas, 2018). Compounds including synthetic triterpenoids and fumaric acid esters can activate the Nrf2 pathway and have a neuroprotective effect in animal models of PD (Ahuja et al., 2016; Ammal Kaidery and Thomas, 2018; Kaidery et al., 2013; Lastres-Becker et al., 2016). A drug used to treat multiple sclerosis, Tecfidera, has been repurposed to explore its potential to treat PD (Lastres-Becker et al., 2016). Tecfidera is a putative Nrf2 activator and is the oral formulation of dimethylfumarate (DMF) (Ahuja et al., 2016). Ahuja and colleagues compared the effects of DMF and its metabolite monomethylfumarate (MMF) on Nrf2 signalling and ability to block MPTP-induced experimental PD (Ahuja et al., 2016). Both DMF and MMF were neuroprotective against MPTP neurotoxicity through Nrf2-mediated antioxidant, anti-inflammatory, and mitochondrial functional/biogenetic effects, but MMF does so without depleting GSH and inhibiting mitochondrial and glycolytic functions. The results suggest that MMF, rather than DMF, is a promising therapeutic intervention in PD while keeping side effects to a minimum.

Uric acid is an antioxidant, which has neuroprotective effects in preclinical models by activating the Nrf2 pathway (Ammal Kaidery and Thomas, 2018; Zhang et al., 2014). Further evidence of the relationship between uric acid and PD include the finding that there is a decreased incidence of PD in individuals with higher serum urate levels/gout (Cortese et al., 2018; Davis et al., 1996; Weisskopf et al., 2007). While a diet rich in urate could be neuroprotective in PD, this has to be balanced by the expected adverse effects including gout and cardiovascular disease (Ammal Kaidery and Thomas, 2018). The Safety of Urate Elevation in PD (SURE-PD) demonstrated that the urate precursor inosine was safe, well tolerated and effective at raising urate levels in early PD (Parkinson Study Group SURE-PD Investigators et al., 2014b). Currently, a phase 3 clinical trial (SURE-PD3 trial; NCT02642393) is underway to determine whether oral inosine can slow clinical progression in early PD (Crotty et al., 2017).

8.2. Creatine supplementation

Creatine is a natural compound, which plays a critical role in cellular energy homeostasis (Mo et al., 2017). Oral creatine supplementation has been shown to have a protective effect on MPTP mouse models (Klivenyi et al., 2003; Matthews et al., 1999). However, for patients with early and treated PD, creatine monohydrate therapy did not result in an improvement in clinical outcomes (Writing Group for the NINDS Exploratory Trials in Parkinson *Disease* (NET-PD) Investigators et al., 2015). A recent meta-analysis of five randomized control trials showed no observed benefit of creatine in PD (Mo et al., 2017).

8.3. Ursodeoxycholic acid treatment

Ursodeoxycholic acid (UDCA) is used for the treatment of primary biliary cirrhosis, but preclinical studies have shown a protective effect for, both, toxic-induced and genetic forms of PD by improving

mitochondrial function (Abdelkader et al., 2016; Ammal Kaidery and Thomas, 2018; Mortiboys et al., 2015). A phase 1 trial is currently underway measuring plasma UDCA before and after oral UDCA dosing, as well as the effects of oral UDCA on brain bioenergetics derived from magnetic resonance spectroscopy measurements (NCT02967250).

8.4. Modifying the interaction with alpha-synuclein

Alpha-synuclein is a major target for the development of novel therapies in PD. This would be expected to influence mitochondrial function, given the reciprocal interaction between alpha-synuclein aggregation and mitochondrial impairment as described in Section 4.

Alpha-synuclein antibodies may have a therapeutic effect by enhancing clearance, reducing cellular toxicity and spread of pathology (Lang and Espay, 2018). Monoclonal antibodies to different parts of alpha-synuclein have shown promise in preclinical trials paving the way for phase 2 randomised control trials (the PASADENA trial; RO7046015, the SPARK trial; BIIB054) (Lang and Espay, 2018).

A recent study used aptamers to reduce alpha-synuclein aggregation *in vitro* and in cells and to induce alpha-synuclein degradation via the lysosomal pathway (Zheng et al., 2018). These effects were able to rescue mitochondrial dysfunction due to alpha-synuclein overexpression.

Decreased levels of the master regulator of mitochondrial biogenesis, PGC-1α, may also indirectly induce alpha-synuclein toxicity and mitochondrial dysfunction. For example, down-regulation of PGC-1α in PGC-1α reference gene (RG-PGC-1α)-deficient mice induces alpha-synuclein oligomerization and toxicity (Eschbach et al., 2015). Additionally, pharmacological activation or genetic overexpression of RG-PGC-1α lowers alpha-synuclein oligomerization and rescues alpha-synuclein-mediated toxicity (Eschbach et al., 2015). This is in keeping with the concept that PGC-1α downregulation and alpha-synuclein oligomerization can form a 'vicious circle'. This suggests that restoration of PGC-1α could be a therapeutic strategy for PD (Eschbach et al., 2015).

8.5. Enhancement of mitophagy

Mitophagy is thought to be impaired in PD as outlined previously (Section 5). Enhancement of mitophagy is therefore an appealing strategy for the treatment of PD. However, this strategy is limited by the lack of pharmacological agents that selectively enhance mitophagy (Moors et al., 2017). Compounds that are used to trigger mitophagy *in vitro*, such as trifluorocarbonylcyanide phenylhydrazone and antimycin/oligomycin combinations, are toxic, non-specific, and trigger non-physiological levels of mitophagy, and so they are not considered suitable to be used for therapeutic applications (East and Campanella, 2016; Moors et al., 2017). The p62-mediated mitophagy inducer is thought to enhance mitophagy but has not been applied to preclinical PD models (Moors et al., 2017). Other options for enhancing mitophagy include induction of alternative mitophagy pathways (Koentjoro et al., 2017) or specific gene therapy approaches as outlined below (Section 8.11).

8.6. Modulating calcium homeostasis

The dihydropyridine calcium channel antagonist, isradipine, has been demonstrated to be neuroprotective in animal models of PD (Ilijic et al., 2011). A recent study administered the Cav1 channel inhibitor isradipine to mice to assess for benefit of SN dopaminergic neurons (Guzman et al., 2018). This treatment reduced cytosolic Ca^{2+} oscillations in nigral dopaminergic neurons without changing autonomous spiking or expression of Ca^{2+} channels. The effect was mimicked by knocking down expression of Cav1.3 channel subunits. Moreover, the treatment led to lower mitochondrial oxidant stress, a reduction of a high basal rate of mitophagy, and normalized mitochondrial mass. This demonstrated that Cav1 channels increase mitochondrial oxidant stress and turnover *in vivo*. Therefore, chronic isradipine treatment remodelled SN dopaminergic neurons in a manner that protected against mitochondrial challenges and autophagic stress. A Phase II safety, tolerability, and dose selection study of isradipine has been completed (Parkinson Study Group, 2013), and a phase III clinical trial for early PD is underway (NCT02168842).

8.7. Neuroprotection from hormones involved in glucose metabolism

Hormones involved in glucose metabolism such as ghrelin and glucagon-like-peptide-1 (GLP-1) may also modulate mitochondrial function (Wilkins and Morris, 2017). For example, ghrelin has been shown to be protective against rotenone and MPTP in preclinical models (Wilkins and Morris, 2017). A novel GLP-1/GIP dual agonist (DA-JC1) had a neuroprotective effect in a MPTP mouse model and enhanced levels of the neuroprotective brain-derived neurotropic factor (BDNF) (Ji et al., 2016).

Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, was investigated in a single-centre, randomised, double-blind, placebo-controlled trial, in patients with moderate PD (Athauda et al., 2017). Exenatide showed beneficial effects on off-medication motor scores in PD beyond the period of exposure to the drug. However, it is unclear whether this result was due to modification of the underlying disease process, or a long-lasting symptomatic effect (Ammal Kaidery and Thomas, 2018).

8.8. Proliferator-activated receptor gamma agonists

The thiazolidinediones, including rosiglitazone and pioglitazone, activate proliferator-activated receptor gamma (PPAR-γ) and are used to treat type 2 diabetes mellitus but have also shown promise in treating PD (Wilkins and Morris, 2017). There is evidence that the PPAR-γ agonists protect mitochondrial membrane potential and prevent apoptosis (Wu et al., 2009). Pioglitazone and rosiglitazone have been shown to be neuroprotective in preclinical models of PD (Barbiero et al., 2014; Carta et al., 2011; Schintu et al., 2009; Wilkins and Morris, 2017). However, a clinical study of early PD did not show any benefit from pioglitazone in terms of disease progression or biomarker levels (NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators, 2015; Simon et al., 2015; Wilkins and Morris, 2017).

8.9. Mitochondrial replacement

Replacement of dysfunctional mitochondria with functional exogenous mitochondria is an innovative strategy for treating PD. In an experimental PD mouse model induced by MPTP, mitochondrial replacement halted PD progress by increasing ATP production, reducing reactive oxygen species, and preventing cell apoptosis and necrosis (Shi et al., 2017b).

8.10. Exercise

Preclinical models of PD suggest that exercise could be neuroprotective (Wilkins and Morris, 2017). A recent study showed that treadmill exercise improved gait speed and balance, decreased oxidative stress, improved mitochondrial fusion and fission, increased mitochondrial amounts, and possibly attenuated dopaminergic neuron degeneration in a unilateral 6-OHDA rat model of PD (Chuang et al., 2017).

A number of studies have evaluated the benefit of exercise in PD (Wilkins and Morris, 2017). A systematic review and meta-analysis of randomized controlled trials found strong evidence that resistance training can improve muscle strength in PD and that endurance training can improve cardio-respiratory fitness in PD (Uhrbrand et al., 2015).

8.11. Gene therapy

Genes involved in recessive forms of PD, such as *Parkin* and *PINK1*, may be particularly amenable to treatment with gene therapy, since loss of function mutations may be rescued by the overexpression of functional protein (Valdes and Schneider, 2016). However, individuals with *Parkin* mutations have atypical forms of PD with slow progression and early onset and, in the majority of cases, there is absence of typical alpha-synuclein-containing Lewy bodies in the SN (Bruggemann and Klein, 1993; Valdes and Schneider, 2016). It is not clear, if enhancing the Parkin-PINK1 pathway will be beneficial in idiopathic PD. In fact, there may be adverse effects given that overexpression of both mutant and wildtype Parkin has been show to induce dopaminergic cell death (Valdes and Schneider, 2016; Van Rompuy et al., 2014).

A recent study suggested that induction of NIX can restore mitophagy in PINK1- and Parkin-related PD patient cell lines (Koentjoro et al., 2017). Furthermore, overexpression of NIX can improve mitochondrial ATP production in patient cells (Koentjoro et al., 2017). These findings suggest that NIX may also be a target for gene therapy.

9. Summary and future perspectives

Within the framework of this article, we have reviewed studies on mitochondria and PD published in the last three decades. Recent developments have added to a large body of evidence supporting the role of mitochondrial dysfunction in the pathophysiology of both familial and sporadic forms of PD. The current research suggests that this role is complex and multifaceted, with an interplay of elements involving the mitochondrial respiratory chain, mitochondrial genome, interactions with alpha-synuclein, mitophagy/mitochondrial homeostasis, mitochondrial vesicular trafficking and newly emerging mechanisms such as a role for inflammation. The molecular pathways involved appear to overlap at multiple points. The next challenge will be to better characterize these molecular interactions as they may emerge as targets for PD therapy across different subtypes of the disease. For such approaches to be successful, movement away from studies using isolated cell types and towards those assessing PD neurons against the backdrop of their supporting tissue should be made. IPSC technology holds the key for the development of two or three dimensional co-culture systems. When preparing this synopsis, a particular focus was placed on mitochondrial phenotyping in iPSC-derived PD models. This analysis revealed that the potential of iPSC technology to investigate the mitochondrial component in idiopathic and very rare PD types such as DJ-1, ATP13A2- or VPS35-associated PD has successfully identified important contributions to biologically relevant pathogenic disease mechanisms but has not been fully exploited. For the genetic forms of PD, this is most likely explained by the limited number of patient iPSC cultures currently available worldwide. Regarding IPD, the phenotypic heterogeneity of sporadic cases still represents a significant challenge in PD research as it impedes the identification of disease mechanisms. However, by applying high-throughput omics methods to stratified endogenous neuronal cell models (which recapitulate the exact genotype underlying the disease in a specific IPD patient) this obstacle may be overcome in the near future. Moreover, protocols for the culture of multicellular PD models, such as midbrain organoids, have only recently been published and are not yet widely used in the PD field (Monzel et al., 2017). Studies in co-culture systems will help understand how mitochondrial dysfunction in neurons and glia cells mutually influence each other.

Targeting mitochondrial defects may open new avenues for the development of PD therapies. This concept is supported by numerous preclinical studies. However, multiple drug trials targeting mitochondrial impairment have failed to show benefit, particularly those employing antioxidant therapies. The lack of success in clinical trials can be attributed to an incomplete understanding of the molecular pathways and targets, heterogeneity of the patient population, and the lack of adequate biomarkers to monitor drug efficacy (Lang and Espay, 2018). Even if a clinical trial purports to show a benefit, there are difficulties in distinguishing the disease-modifying effect from a symptomatic improvement (Mehta et al., 2010). Therapies could be developed to specifically target the pathways known to be involved, such as mitophagy, mitochondrial biogenesis, fusion/fission and trafficking. Larger clinical trials with more uniform sample populations will be useful. Highly specific and sensitive disease biomarkers would allow detecting even subtle improvements due to novel drug therapies. There are reasons for optimism with a recent study of exenatide showing benefit (Ammal Kaidery and Thomas, 2018; Athauda et al., 2017) and several large clinical trials underway. Given that loss of function mutations in Parkin and PINK1 can cause PD, this may be rescued by the overexpression of functional mitophagic proteins, opening up gene therapy as another potential avenue for treatment (Koentjoro et al., 2017; Valdes and Schneider, 2016).

New research is emerging at a rapid pace, providing further insights into mitochondrial dysfunction in PD. Despite this progress, there is still much to learn about the precise disease mechanisms involved. Mitochondrial dysfunction clearly plays a fundamental role in PD and should be a key theme for future research.

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