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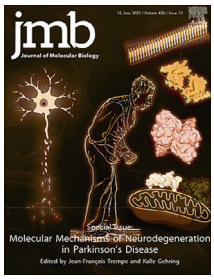

Role of Autophagy Pathway in Parkinson's Disease and Related Genetic Neurological Disorders

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Abstract

The elucidation of the function of the PINK1 protein kinase and Parkin ubiquitin E3 ligase in the elimination of damaged mitochondria by autophagy (mitophagy) has provided unprecedented understanding of the mechanistic pathways underlying Parkinson's disease (PD). We provide a comprehensive overview of the general importance of autophagy in Parkinson's disease and related disorders of the central nervous system. This reveals a critical link between autophagy and neurodegenerative and neurodevelopmental disorders and suggests that strategies to modulate mitophagy may have greater relevance in the CNS beyond PD.

Introduction

Autophagy ("self-devouring"), coined by Nobel prize winner Christian de Duve in 1963, is a conserved recycling mechanism of eukaryotic cells. Initial insights into the molecular basis of this process were achieved through identification of genes encoding core autophagic components by another Nobel prize winner, Yoshinori Ohsumi, and subsequent studies have highlighted the critical role of autophagy in removing proteins, lipids, nucleic acids, and organelles to maintain cellular homeostasis. Advances in human genetics have revealed how disruptions to autophagy is linked to many human diseases, especially neurodegenerative disorders (NDDs).

Parkinson's disease (PD) has become the fastest-growing NDD affecting more than 10 million people worldwide, with this figure expected to double within a generation's time due to ageing populations.[1] PD is characterised by selective vulnerability of dopaminergic neurons of the substantia nigra pars compacta (SNpc) and the accumulation of protein aggregates, Lewy bodies (LBs) and Lewy neurites (LNs).[2] The susceptibility of SNpc dopaminergic neurons is hypothesised to be a consequence of their elevated bioenergetic requirements and morphological characteristics such as higher basal rate of mitochondrial oxidative phosphorylation; higher density of axonal mitochondria; elevated level of basal oxidative stress; complex axonal arborization and long non-myelinated axons.[3] Understanding of the cell autonomous mechanisms of PD has resulted from the identification and analysis of a dozen genes linked to monogenic forms of PD. Mechanistic analysis of several

PD genes, including SNCA (α-synuclein),[4] leucine-rich repeat kinase 2 (LRRK2),[5] PTEN-induced kinase 1 (PINK1),[6] and PRKN (Parkin),[7] has confirmed their role in autophagy through their effects on protein aggregation, endolysosomal trafficking defects and mitochondria homeostasis respectively. Taken together, genetic and experimental evidence, identify autophagy as a severely impacted pathway in PD and other NDDs.

In this review, we provide an overview of autophagy components that are linked to monogenic forms of human disease, many of which are associated with neurodegeneration. Within this clinical landscape, we highlight the role of the PINK1 and PRKN genes in selective removal of mitochondria (mitophagy) and how this has provided exemplar understanding of fine and specific control of autophagy in neuronal homeostasis.

Overview of autophagy and core machinery

The major forms of autophagy – chaperone-mediated autophagy (CMA), microautophagy, and macroautophagy – all culminate with the delivery of cargo for degradation to the lysosome, but with distinct mechanistic frameworks.

CMA selectively targets and delivers soluble proteins into the lysosomal lumen, without the requirement for vesicle formation. This fine-tuned process is orchestrated by the cytosolic chaperone heat-shock cognate protein 70 (HSC70; HSPA8), which recognises the KFERQ or KFERQ-like pentapeptide motif of a protein to deliver it to the lysosome. Lysosomal co-chaperones (such as HSP40, HSP90, Hip, Hop and BAG-1), then mediate the translocation of the cargo protein into the lysosomal lumen through the LAMP2A multimeric receptor.[8–10] The role of CMA in mammalian cells has been implicated in stress responses, such as growth factor deprivation or oxidative stress, to remove damaged or long-lived proteins.

Microautophagy entails the direct engulfment of cytosolic proteins or organelles by lysosomes or vacuoles leading to their subsequent degradation. While proven in yeast, this process has been more elusive in mammalian cells where the invagination of the cargo can happen in endosome/multivesicular bodies as well.[11] Microautophagy, similar to macroautophagy, can exhibit exquisite levels of selectivity, either at a protein or organellar level, giving rise to terms such as micromitophagy, macropexophagy and so on. As in CMA, microautophagy can also avail of HSC70, for cargo delivery directly to the endosome. While it shares similarities to the CMA, the final destination of the proteins are endosomes instead of lysosomes and the protein internalisation step is independent of the LAMP2A receptor. It has been proposed that HSC70 might directly deform the endosomal membrane by interacting with the negatively charged phosphatidylserine via its C-terminus lid domain.[12,13]

Macroautophagy, often referred to simply as autophagy, is characterized by the formation of *de novo* double-membraned autophagosomes, that target and engulf material delivering them to the lysosome for digestion and recycling. The role of nonselective (or bulk) autophagy is best understood under conditions of nutrient starvation or other cellular stresses controlled by the mTOR and AMPK signalling pathways and has the main function to provide nutrients needed for cell survival.[14]

Selective autophagy is characterised by high specificity in the choice and delivery of cargo for degradation, mediated by distinct receptors. The targets of autophagosomes can vary from protein aggregates (aggrephagy)[15] and microorganisms (xenophagy)[16] to intracellular structures such as lipid droplets (lipophagy),[17] proteasomes (proteaphagy)[18] and ribosomes (ribophagy),[19] to organelles, such as mitochondria (mitophagy),[20] ER (ER-phagy; reticulophagy),[21] Golgi (Golgiphagy),[22] nucleus (nucleophagy),[23] lysosomes (lysophagy)[24] and peroxisomes (pexophagy).[20]

Autophagosome-mediated targeting involves five key steps: initiation, nucleation, elongation, fusion, and degradation, schematised in Figure 1.[25] Upon autophagy induction, the biogenesis and expansion of the autophagosomes are mediated through proteins encoded by the autophagy-related genes (ATG). To date, 41 core ATG proteins have been identified, 17 of which are part of the core ATG machinery, a multiphasic process essential for all autophagy-related pathways, which includes the ATG1/ULK complex, the class III phosphatidylinositol 3–kinase complex (PI3KC3), the ATG9 trafficking system, and the two parallel ubiquitin-like conjugation systems, ATG8 and ATG12.[26,27]

The ATG1/ULK complex consists of ULK1/2, FIP200, ATG13, and ATG101 in mammals (ATG1, ATG13, ATG17 and ATG29 in yeast) and is the most upstream of the core protein complexes.[14,28] It is activated by diverse signalling cascades including mTOR, insulin, PKA, and AMPK. Following activation, the complex translocates to the autophagosome formation sites on the ER for the nucleation of the phagophore (Figure 1, Initiation).[29]

The PI3KC3 complex is next recruited to the autophagosome assembly site.[30,31] In mammals the PI3KC3 has at least two forms, both containing the core machinery of class III VPS34 (PI3KC3), p150 (VPS15 ortholog) and Beclin 1 (BECN1; ATG6 ortholog). Complex I, including ATG14 and NRBF2 as well, is involved mainly in autophagosome formation, while complex II includes UVRAG and NRBF2 and participates in autophagosome and endosome maturation.[32] PI3KC3 complex

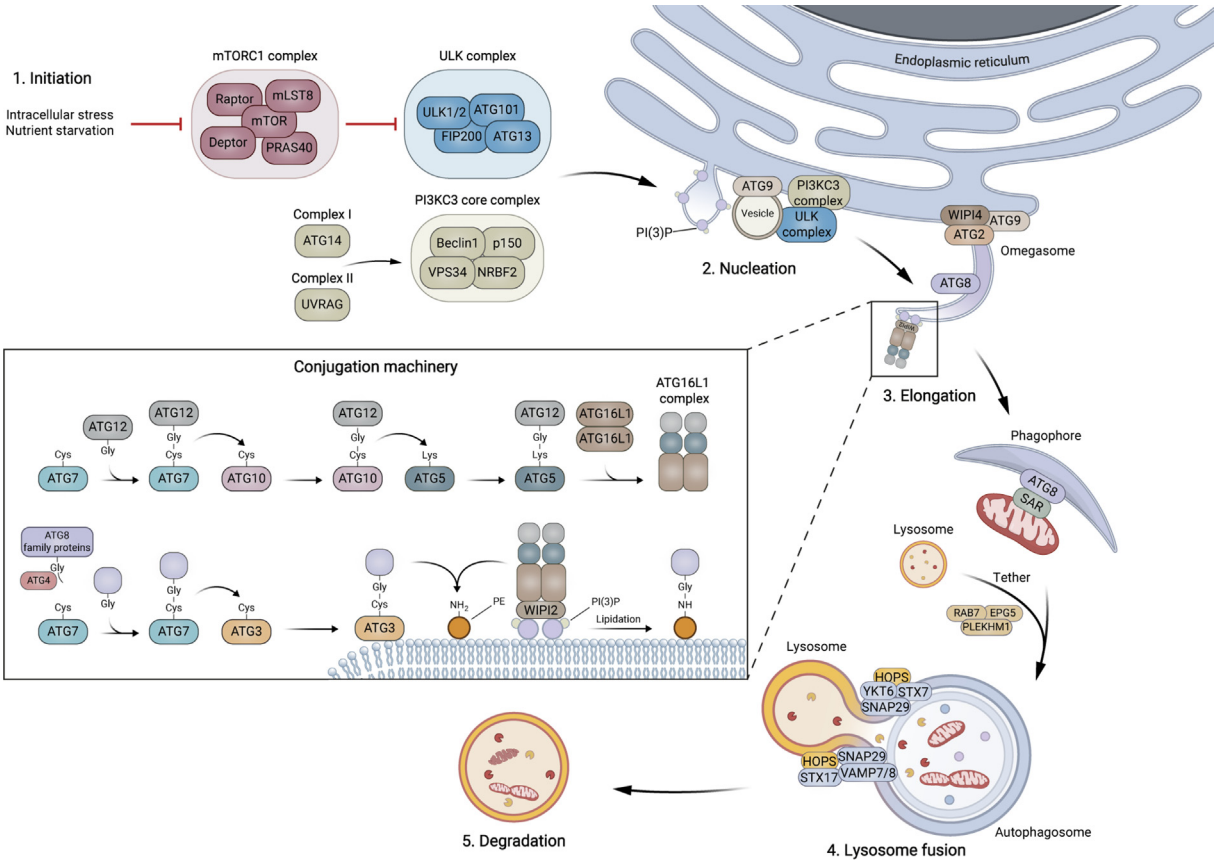

Figure 1. The five steps of macroautophagy. In the initiation phase, autophagy-inducing signalling (such as starvation, ER or oxidative stress, hypoxia, mitochondrial or DNA damage), inactivates mTOR complex 1 (mTORC1) resulting in ULK complex activation and translocation at the endoplasmic reticulum (ER) membrane. Here, during the nucleation step, it phosphorylates the PI3KC3 complex and recruits ATG9 vesicles. In turn, the PI3KC3 complex produces PI(3)P, inducing phagophore formation at the omegasome through WIPI4 and WIPI2 recruitment. The first one recruits ATG2, essential with ATG9 for the transfer of phospholipids from the ER to the expanding phagophore. During the elongation phase, the ubiquitin-like conjugation reaction of ATG12 mediates the formation of the ATG16L1 complex. This complex is targeted to the autophagosome by interaction with WIPI2. Similarly, ATG8 proteins, after cleavage by the cysteine protease ATG4, are transferred to ATG3. Finally, the ATG16L1 complex, promotes the transfer of ATG8 from ATG3 to the NH2 group of phosphatidylethanolamines (PE), resulting in lipidated ATG8. Selective autophagy receptors (SARs) mediate the binding between ATG8 and the cytoplasmic components targeted for degradation. The autophagosome is then tethered to a lysosome by PLEKHM1, EPG5, RAB7 and the HOPS complex, and the two are fused together by the SNARE complexes STX17–SNAP29–VAMP7/8 and YKT6–SNAP29–STX7. Finally, in the last phase, the acidic lysosomal environment together with hydrolases and proteases, degrade the autophagosomal cargo. In part adapted from.[43]

recruitment induces phosphatidylinositol 3-phosphate (PI(3)P) formation on the phagophore and on the phagophore-ER contact sites (omegasomes), targeting PI(3)P binding proteins, namely WIPI2 and WIPI4, to the forming membrane (Figure 1, Nucleation).[33]

ATG9 is a multi-spanning protein, localised at the Golgi under normal conditions. Following autophagy induction, ATG9 is recruited to phagophores via dynamic small vesicles and/or tubules in the vicinity of the forming phagophores that is dependent on ULK kinase activity.[34–36] Thereby, ATG9-positive vesicles serve as membrane sources for the phagophore elongation through the additional recruitment of ATG2 and WIPI4 that mediate this transaction (Figure 1, Elongation).

In mammals, expansion of the phagophores involves two ubiquitin-like conjugation systems. ATG12 is activated by its E1-like enzyme ATG7 and then is transferred to its E2-like enzyme ATG10. Subsequently, ATG12 is conjugated to the acceptor lysine residue in ATG5 via an isopeptide bond. Two ATG12-ATG5 form a complex with one ATG16L1 dimer and this complex is then recruited to the expanding phagophore by WIPI2, that anchors it to the PI(3)P on the membrane. This complex, acts as a E3-

like enzyme for the lipidation of ATG8 proteins (Figure 1, Conjugation machinery).[37]

The ATG8 family proteins comprises in mammals, microtubule-associated protein 1 light chain (LC3) and gamma-aminobutyric acid receptor-associated protein (GABARAP; ATG8 in yeast). In the ATG8 system, ATG8 (LC3-I) is first cleaved at its C-terminal region by enzymes of the ATG4 family to expose a glycine residue. Next, as with the ATG12, is activated by ATG7, transferring it to its E2-like enzyme ATG3 that conjugates it, in concert with ATG16L1 complex, to the amino group of phosphatidylethanolamines (PE) localised on autophagic membranes, ATG8-PE (LC3-II) (Figure 1, Conjugation machinery). ATG8 proteins then bind and engulf, through selective autophagy receptors (SARs), the cargo designated for degradation.

After cargo sequestration, the autophagosome fuses with the lysosome generating an autolysosome. Multiple proteins, including PLEKHM1, EPG5, RAB7 and its guanine nucleotide exchange factor (the HOPS complex) tether the lysosome to the autophagosome membrane.[38–40] The fusion is mediated by the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complexes STX17-SNAP29-VAMP7/8 and YKT6-SNAP29-STX7 (Figure 1, Lysosome fusion).[41,42] Finally, the inner autophagosomal membrane is degraded together with the autophagic cargo, releasing nutrients in the cytoplasm to be reused by the cell (Figure 1, Degradation).

Selective autophagy receptors

The main function of the autophagy adaptors, also known as selective autophagy receptors (SARs), is to mediate the cargo recognition and coupling to the phagophore, specifically to ATG8 in yeast, or to one of its six homologue proteins (LC3, GABARAP) in mammals, through either an LC3-interaction region (LIR) or GABARAP-interacting motif (GIM). In addition to LIRs and GIMs, SARs possess a cargo-binding domain which grants selectivity to the autophagy process by targeting only specific cargos, or common cargo post-translational modifications (PTMs) such as ubiquitylation or glycosylation.

Figure 2 summarises the distinct SARs identified in various selective autophagic pathways, which are contingent upon the type of cargo being targeted. The clearance of protein aggregates, particularly relevant in the context of NDDs, avails of CCT2, SQSTM1, NBR1, OPTN, TOLLIP, TAX1BP1, ALFY and UBQLN2.[44–52] The breakdown of glycogen is achieved through the Starch-binding domain-containing protein 1 (STBD1) which binds to GABARAPL1.[53] NCOA4 is involved in ferritinophagy, the breakdown of ferritin, a process vital for maintaining stable levels of intracellular iron. Perturbations can cause abnormal increase in free iron leading to oxidative stress and ferroptosis.[54–56] Bacteria are degraded through NDP52, OPTN, TAX1BP1 and SQSTM1 while viral capsids are recognized by TRIM5α and SQSTM1.[57–62] SQSTM1 is also the only identified receptor for lipophagy,[63–64] while ribosome degradation uses NUFIP1.[65] NBR1 and SQSTM1 control the clearance of peroxisomes. NIX, an already characterized receptor for mitophagy, has recently been identified to be involved in pexophagy as well.[66–68] Damaged or ruptured lysosomes are also targeted for degradation, and are recognised by the E3 ligase TRIM16, NDP52 and SQSTM1.[69–71] The identification of Golgi SARs has long been elusive until the recent discovery of GOLPH3 and CALCOCO1, and more recently, the proposal of two additional SARs, YIPF3 and YIPF4.[22,72,73] CALCOCO1 was previously identified as a regulator of ER-phagy as well, together with FAM134B (RETREG1), SEC62, RTN3, CCPG1, ATL3, TEX264, C53.[74–82] In mammals, SARs responsible for nucleophagy or proteaphagy have not yet been identified. In contrast, investigation of mitophagy has revealed a variety of receptors involved upon mitochondrial damage by different stresses. Basal mitophagy avails the use of several SARs: NIX, BNIP3, FUNDC1, and E2F3d.[83–86] The activation of PINK1 and Parkin, that leads to the ubiquitylation of several outer mitochondrial membrane (OMM) proteins, uses instead SQSTM1, OPTN, NDP52 or TAX1BP1, which are able to bind to ubiquitylated substrates (more details in Section 'Mitophagy mediated by PINK1/Parkin')[87,89] or NIPSNAP1/2 that translocates to the OMM and connects the mitochondria to the SARs or directly to ATG8.[90] While not ubiquitin-dependent, the inner mitochondrial membrane protein PHB2 has been shown to be a mitophagy receptor promoting Parkin-dependent mitophagy upon OMM clearance from the proteasome.[91] AMBRA1 is reported to interact with Parkin, but it can also induce mitophagy independently from the E3 ligase.[92,93] Other forms of ubiquitin-independent mitophagy rely on the direct interaction of LC3 with the mitochondrial lipids ceramide or cardiolipin or with the apoptotic-signalling protein BCL2L13 and FKBP8.[94–97] Lastly, NLXR1, the only NOD-like receptor with a mitochondria targeting sequence (MTS), known to be involved in bacterial-induced mitophagy, has now been shown to interact with ER protein RRBP1, to promote mitophagy upon mitochondrial protein import stress.[98,99]

Genetics of autophagy in NDDs and human diseases

Given the importance of autophagy in cellular homeostasis, disruptions in key components can lead to deleterious effects. Genetic analysis of human diseases through genome-wide association studies (GWAS) can identify genomic variants associated with a risk of disease, but

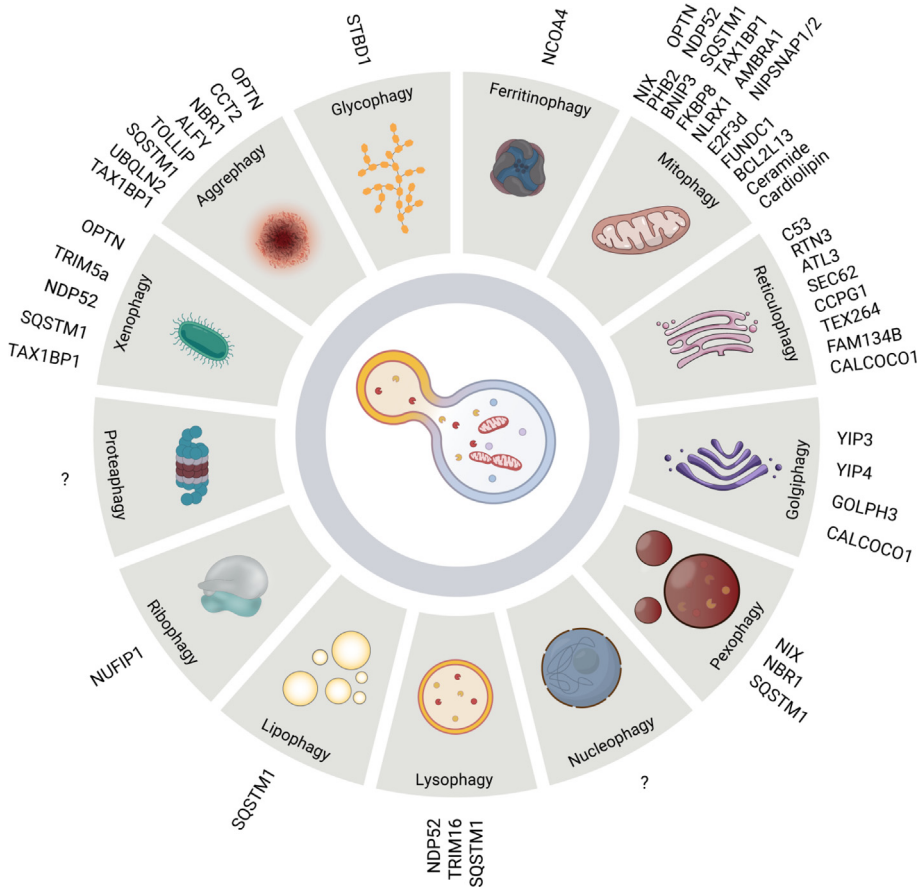

Figure 2. Selective autophagy in mammals and their respective receptors. Schematic representation of the different types of mammalian selective autophagy and the respective selective autophagy receptors (SARs) identified.

whether these are causal is uncertain in many cases. In contrast identification of gene mutations in monogenic forms of human disease provides clear-cut links of causality between gene and disease. Whilst, autophagy has been linked to many disorders such as NDDs, cancers, and autoimmune diseases, a comprehensive analysis of autophagy genes linked to the development of NDDs such as PD has not been performed. As part of this review article, we searched OMIM, UNIPROT and PUBMED databases to establish clear-cut genetic links of autophagy components to human diseases with a particular emphasis on brain disorders.

Approximately 150 autophagy-related genes were found in which autosomal or X-linked mutations were linked to human disease (Table 1 and Table S1). The broad spectrum of pathology discovered is consistent with the physiological importance assigned to autophagy. This includes human immunodeficiency disorders highlighting the key role of autophagy in immunity. Of note, the role of autophagy in development is highlighted in studies where knockout of core ATG proteins is lethal during embryonic development or soon after birth in rodent models.[100] Furthermore, genetic mutations in MAPK1 or RAF1 and SNAP29 were linked to congenital malformations and developmental disorders such as Noonan syndrome or CEDNIK (CErebral Dysgenesis, Neuropathy, Ichthyosis, and palmoplantar Keratoderma) respectively.[92–94] In terms of adult disorders, the link between autophagy and cell proliferation is exemplified by a number of hereditary cancer syndromes including Peutz-Jeghers syndrome in which mutations in LKB1 perturb AMPK signalling (Table 1).[101]

Strikingly, the nervous system was the most affected by pathologies caused by autophagy including neurodegenerative disorders, neurodevelopmental disorders and neuropathies (Table 1 and Table S1). Interestingly, studies on neuronal development have revealed substantive basal mitophagy occurring from the transition of glycolytic neural stem cells to post-mitotic, oxidative neurons during neuronal differentiation and this is dependent on BNIP3L.[102] It would be interesting to investigate dysregulation of mitophagy in these disorders. Autophagy is especially important in neuronal maintenance of the adult brain and consistent with this, mutations in autop-

Table 1 Human Genetic Diseases associated with Autophagy Genes.

Category	Disease, Genes and inheritance (where defined)
Autoimmune and immune disorders	- Autoimmune lymphoproliferative syndrome (FAS [AD], PRKCD [AR]) - Autoinflammation with infantile enterocolitis (NLRC4 [AD]) - Blau syndrome (NOD2 [AD]) - Immunodeficiency (IKBKB [AR,AD], ISG15 [AR], NFKB1 [AD], NFE2L2 [AD]) - Wolcott Rallinson syndrome (EIF2AK3 [AR]) - Yao syndrome (NOD2 [Polygenic])
Cancer	- Blastoma (ERBB2, RB1) - Breast (RB1CC1, TP53) - Burkitt lymphoma (MYC) - Carcinoma (TP53 [AD], ERBB2, FAS, TFE3) - Melanoma (STK11) - Peutz-Jeghers syndrome (STK11 [AD]) - Phaeochromocytoma (KIF1B [AD]) - Prostate (STK11) - Sarcoma (RB1)
Cardiac, vascular and skeletal disorders	- Auriculocondylar syndrome (GNAI3 [AD]) - Centronuclear myopathy (MTMR14 [AD]) - Cole-Carpenter syndrome (P4HB [AD]) - Danon disease (LAMP2 [XLD]) - Dilated cardiomyopathy (BAG3 [AD]), PSEN1 [AD], PSEN2 [AD], RAF1 [AD]) - Myopathy (VMA21 [XLR], SQSTM1 [AD], VCP [AD]) - Osteogenesis imperfecta (MBTPS2 [XLR]) - Osteopetrosis (PLEKHM1 [AD,AR]) - Paget disease (SQSTM1 [AD], VCP [AD]) - Smith-McCort dysplasia (RAB33B [AR]) - STING-associated vasculopathy (STING1 [AD])
Gastrointestinal	- Inflammatory bowel disease (ATG16L, IRGM, NOD2 [Mu]) - Microvillus atrophy/inclusion disease (STX3 [AR])
Multisystem congenital disorders	- Arthrogryposis, renal dysfunction, and cholestasis (VPS33B [AR]) - Chondrodysplasia (HDAC6 [XLD] - Cowden syndrome (PTEN [AD]) - Cystinosis (CTNS [AR]) - Glycosylation disorder (ATP6AP2 [XLR]) - IFAP/BRESHECK syndrome (MBTPS2 [XLR]) - Keratitis-ichthyosis-deafness (VPS33B [AR]) - LEOPARD syndrome (RAF1) - Lhermitte-Duclos Disease (PTEN [AD]) - Noonan syndrome (MAPK1 [AD], RAF1 [AD]) - Tuberous sclerosis (TSC1,TSC2) - Vici syndrome (EPG5 [AR]) - Yunis-Varon syndrome (FIG4 [AR]) - Wolfram syndrome (CISD2 [AR]) - Zellweger syndrome (PEX14 [AR], PEX3 [AR], PEX13 [AR])
Neurodegenerative disease	- Alzheimer's disease (APP [AD], PSEN1 [AD], PSEN2 [AD]) - Amyotrophic lateral sclerosis (ALS2 [AR], FIG4 [AD], OPTN [AD,AR], SPG11 [AR], C9ORF72 [AD], CHMP2B [AD], SQSTM1 [AD], TBK1 [AD], UBQLN2 [XLD], VCP [AD]) - Dystonia (VPS11 [AR], VPS16 [AD], EIF2AK2 [AD,AR]) - Frontotemporal dementia (PSEN1 [AD], C9ORF72 [AD], CHMP2B [AD], SQSTM1 [AD], TBK1 [AD], VCP [AD]) - Huntington disease (HTT [AD]) - Neuronal ceroid lipofuscin (CLN3 [AR], CTSD [AR]) - Parkinson's disease (LRRK2 [AD], DJ-1 [AR], PINK1 [AR], PRKN [AR]) - Parkinsonism (ATP6AP2 [XLR]) - Pick disease (PSEN1 [AD]) - Spastic paraplegia (CAPN1 [AR], SLC33A1 [AR], SPG11 [AR], SPG15 [AR])
Neurodevelopmental disorders	- Behr syndrome (OPA1 [AR]) - CEDNIK syndrome (SNAP29 [AR]) - Cowden syndrome (PTEN [AD]) - Developmental and epileptic encephalopathy (ATP6V1A [AR]) - Focal cortical dysplasia (TSC1,TSC2 [AD], mTOR) - Hypomyelinating leukodystrophy (VPS11 [AR]) - Intellectual developmental disorder (SMS [XLR], MECP2 [XLR], RAC1 [AD] TFE3 [XL], ATP6AP2 [XLR]) - Leukoencephalopathy (EIF2AK2 [AD]) - Lhermitte-Duclos Disease (PTEN [AD]) - Limb mammary syndrome (TP63 [AD]) - Lissencephaly (TP73 [AR]) - Lopes-Maciel-Rodan syndrome (HTT [AR]) - Macrocephaly/ autism syndrome (PTEN [AD]) - Microencephaly (WDFY3 [AD]) - Neonatal encephalopathy (MECP2 [XLR]) - Neurodegeneration with ataxia, dystopia and gaze palsy (SQSTM1 [AR]) - Neurodegeneration with brain iron accumulation (WIPI4 [XLD) - Neurodevelopmental disorder with spastic quadriplegia (WIPI3 [AR])

Table 1 (*continued*)

Category	Disease, Genes and inheritance (where defined)
	- Rett syndrome (MECP2 [XLD]) - Smith-Kingsmore syndrome (mTOR [AD]) - Spinocerebellar ataxia (GRID2 [AR], ITPR1 [AD], RUBCN [AR], SNX14 [AR], ATG5 [AR], ATG7 [AR], VPS41 [AR], EEF2 [AD], VPS13D [AR])
Neuropathies	- Charcot–Marie–Tooth disease (KIF1B [AD], RAB7A [AD], SPG11 [AR], HSPB8 [AD], MFN2 [AD,AR], FIG4 [AR], VCP [AD]) - Visceral neuropathy (ERBB2 [AR]) - Hereditary sensory and autonomic (TECPR2 [AR], RETREG1 [AR]) - Distal hereditary motor neuronopathy (HSPB8 [AD]) - Hereditary motor and sensory neuropathy (MFN2 [AD])
Ophthalmologic diseases	- Achromatopsia (ATF6 [AR]) - Cataract (FYCO1 [AR], CHMP4B [AD]) - Cone-rod dystrophy (DRAM2 [AR]) - Congenital cataracts (SLC33A1 [AR]) - Gillepsie syndrome (ITPR1 [AD,AR]) - Glaucoma (OPTN [AD], OPA1 [AD]) - Optic atrophy (OPA1 [AD]) - Retinopathy (STX3 [AR])
Skin, ectoderma and respiratory disorders	- Cutis laxa (ATP6V1A [AR]) - Ectodermal dysplasia (TP63 [AD]) - Emphysema (SERPINA1 [AR]) - Epidermolysis bullosa simplex (KLHL24 [AD]) - Keratosis follicularis spinulosa (MBTPS2 [XLR]) - Lymphannngioleiomyomatosis (TSC1, TSC2) - Mucocutaneous ulceration (RELA [AD]) - Olmsted syndrome (MBTPS2 [XLR]) - Primay cilia dyskinesia (TP73 [AR])
Storage and metabolic disorders	- Diabetes mellitus (MAPK8IP1 [AD]) - Gaucher disease (GBA1 [AR]) - Glycogen storage disease (GAA [AR]) - Hypohomocysteinemia (NFE2L2 [AD]) - Mucopolysaccharidosis-plus syndrome (VPS33A [AR]) - Niemann-Pick disease (NPC1 [AR])

hagy genes are linked to multiple neurodegenerative disorders including PD, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), dystonia and frontotemporal dementia. While the diseases manifestations and symptoms are diverse, common denominators include impaired mitophagy and accumulation of protein aggregates that failed to be degraded by autophagy or the 20S proteasome system. Some SARs have also been linked to neurodegenerative disorders. Mutations in the adaptor protein OPTN are linked to ALS, as is the case with SQSTM1, which is also associated with childhood-onset neurodegeneration, Paget's disease and myopathy.[103–106] The diseases and the causative genes are presented in Table 1. More information regarding the genes (including locus, interactors and biological function) can be found in Table S1.

PD and autophagy: Genetic and experimental evidence

The identification of families with monogenic forms of PD led to the designation of 23 *PARK* genes and loci (Table 2), with 13 clear-cut mutations confirmed (highlighted in Table 2).[107] Other genes have also been identified as major risk factors for late-onset PD, for example, GBA1, PARK10 (or MAPT) and PARK16, a locus containing the RAB29 gene, with the most recent GWAS analysis of sporadic PD identifying 90 gene risk variants accounting for between 16% and 36% of the heritable risk of PD.[108] The functional analysis of these genes has implicated disruptions in lysosomal biology, mitochondrial homeostasis, autophagy, vesicular trafficking, and protein aggregation. While none of the canonical autophagy genes are associated with familial PD, both genetic evidence and *post-mortem* studies have linked PD with abnormal autophagy, particularly macroautophagy, CMA and mitophagy. Initially, autophagic degeneration was detected in an histopathological analysis of SNpc dopaminergic neurons; and later LC3 signal was detected in midbrain LBs and LNs, particularly in its peripheral halo and colocalizing with α-synuclein.[109–111] The chaperone protein HSC70 and its receptor LAMP2A were depleted in the SNpc of PD patients, signifying decreased CMA.[112,113] Before the discovery of PINK1 mutations, hints of defective mitophagy came from detection of abnormal phospho-ERK found colocalized with mitochondria in autophagosomes of PD brain.[114] Abnormalities in distinct autophagy pathways; impaired vesicular and organellar trafficking; and a failure in lysosomal clearance all appear to converge in PD, as highlighted by a recent post-mortem analysis of LBs, which revealed a jammed environment, crowded with organelles and broken membranes including mitochondria, lysosome and autophagosomes.[115]

Table 2 **List of PARK genes associated with hereditary form of PD.** The 13 genes with clear-cut PD-link are highlighted in bold. Some of the PARK gene still need to be fully identified (PARK3 PARK10, PARK12) while PARK16 and PARK10 are considered a risk factors.

PARK	OMIM reference	Gene	Locus	Inheritance & frequency	Protein	Function	Clinical description and references
PARK1 PARK4	168601 605543	**SNCA**	4q22.1	AD, <1%	α-synuclein	Synaptic, mitophagy, unknown	Ranging from classical PD to early-onset cases with dementia, autonomic dysfunction, and rapid progression.[4,151,152]
PARK2	600116	**PRKN**	6q26	AR, 1%-5%	parkin RBR E3 ubiquitin protein ligase (Parkin)	Ubiquitin ligase, mitophagy	Early-onset PD, slow progression, often features of dystonia.[7]
PARK5	613643	UCHL1	4p13	AD, <1%	ubiquitin C-terminal hydrolase L1	Proteasome	Susceptibility, classical PD—only one family, findings not since replicated.[153] Causality uncertain.
PARK6	605909	**PINK1**	1p36.12	AR, 2%-5%	PTEN-induced putative kinase 1	Kinase, mitophagy	Early-onset PD, slow progression.[154]
PARK7	606324	**DJ-1**	1p36.23	AR, 1%	Parkinsonism-associated deglycase	Oxidative stress sensor	Early-onset PD, slow progression.[155]
PARK8	607060	**LRRK2**	12q12	AD, 1%-5%	Leucine-rich repeat kinase 2	Kinase, autophagy, trafficking	Classical PD with less frequent dementia and slower progression.[5]
PARK9	606693	**ATP13A2**	1p36.13	AR, <1%	Cation-transporting ATPase 13A2	Lysosomal function	Early-onset (adolescence), atypical parkinsonism with dementia, spasticity and supranuclear palsy (Kufor–Rakeb syndrome).[156]
PARK10	606852	USP24	1p32	AD, unknown	Ubiquitin specific protease 24	Autophagy regulator	Susceptibility, late-onset PD[157] Causality uncertain.
PARK11	607688	GIGYF2	2q37.1	AD, <1%	GRB10 interacting GYF protein 2	Growth factor signalling	Susceptibility, classical PD.[158] Causality uncertain.
PARK13	610297	HTRA2	2p13.1	AD	HtrA serine peptidase 2	Mitochondrial protease	Susceptibility, classical PD..[159] Causality uncertain.
PARK14	612953	**PLA2G6**	22q13.1	AR, <1%	Calcium-independent phospholipase A2 enzyme	Lipid metabolism	Early onset with atypical features (dystonia parkinsonism).[160]
PARK15	260300	**FBXO7**	22q12.3	AR, <1%	F-box protein 7	Mitophagy associated	Early onset with atypical features (pallido-pyramidal syndrome).[161]
PARK16	613164	RAB29	1q32	Risk, unknown	Ras-related protein Rab-39A	Trafficking	Susceptibility[162] Causality uncertain.
PARK17	614203	**VPS35**	16q11.2	AD, <1%	Vacuolar protein sorting-associated protein 35	Vesicular trafficking, endosome, autophagy	Classical PD.[163–164]
PARK18	614251	EIF4G1	3q27.1	AD, unknown	Eukaryotic translation initiation factor 4 gamma 1	Protein translation	Susceptibility, classical PD.[165] Causality uncertain.
PARK19	615528	**DNAJC6**	1p31.3	AR, unknown	HSP40 (Auxilin)	Endocytosis	Early-onset PD, slow progression.[166]
PARK20	615530	**SYNJ1**	21q22.11	AR, unknown	Synaptojanin 1	Endocytosis	Parkinsonism with dystonia and cognitive decline.[167]
PARK21	616361	DNAJC13	3q22	AD, unknown	Receptor-mediated endocytosis 8 (RME-8)	Endosomal function	Classical PD.[168] Causality uncertain.
PARK22	616710	CHCHD2	7p11.2	AD, unknown	Coiled-coil-helix-coiled-coil-helix domain-containing protein 2	Mitochondria-associated apoptosis	Late and early onset[169] Causality uncertain.
PARK23	616840	**VPS13C**	15q22.2	AR, unknown	Vacuolar protein sorting-associated protein 13C	Transport, trafficking	Early-onset PD, rapid progression.[170]

Below we review the contribution of PARK genes including SNCA and LRRK2 in autophagy dysfunction in PD.

SNCA

The discovery of the missense A53T mutation in the SNCA gene in Italian and Greek families affected by PD, was a landmark finding in the field.[2,4] In the same year, α-synuclein was found to be the major component of Lewy bodies.[2] Since then, this small, highly disordered protein, has been at the centre not only of PD research, but of neurodegeneration as its pathological aggregation is a common denominator of a group of brain disorders called synucleinopathies. In PD, 7 more mutations have been identified, namely the A30P, E46K, H50Q, G51D, A53E, and A53V, with the most recent one, the A30G, identified in 2021.[116]

α-synuclein can be degraded through multiple pathways, including CMA, autophagy, or the proteasome. Under physiological conditions α-synuclein, which contains the KFERQ-like peptide (^{95}VKKDQ^{99}), is recognised by HSC70, transported by LAMP2A into the lysosome and degraded. Consistently, the decreased level of CMA markers in PD brains strongly correlates with α-synuclein accumulation.[113] Additionally, mutations, PTMs or oligomeric forms of α-synuclein prevent its clearance through this pathway by binding LAMP2A and blocking protein uptake by the receptor.[117] The affinity of the binding is determined by the type of α-synuclein, with A53T and A30P mutants completely saturating the lysosomal receptor and preventing the CMA of other substrates, while PTMs of the wild-type protein only impair their own clearance.[117,118] The compensatory induction of autophagy is insufficient to restore cellular homeostasis, and α-synuclein has been shown to perturb normal autophagic function.[119] Initiation of autophagy and formation of omegasomes was impaired by overexpression of wild-type α-synuclein via RAB1A inhibition both in cells and transgenic mice.[120] An increase in autophagic flux was detected in chloroquine-stimulated iPSCs from PD patients with the SNCA triplication or in basal conditions in mice overexpressing A53T α-synuclein.[121,122] This mutant form caused, in PC12 cells, impairment of lysosomal and proteasomal degradation, as well as with accumulation of autophagic structures.[123] In primary neurons, it caused abnormal mitophagy, with an increased clearance of healthy and polarized mitochondria leading to bioenergetic deficit and mitochondrial loss[124]. Interestingly, in mice selectively expressing human A53T in midbrain dopaminergic neurons, mitochondrial defects, autophagic inclusions and a subsequent degeneration of the neurons were reported, and this was further exacerbated in PINK1 or Parkin KO mice.[125] The interaction of α-synuclein with mitochondria is reported to impair complex I and increase reactive oxygen species.[126] Recently, the interaction with mitochondrial cardiolipin, was shown to induce A53T α-synuclein aggregation, oxidative stress, mitochondrial dysfunction and toxicity.[127]

LRRK2

The link between PD and LRRK2 can be traced back to 1978, when a Japanese family was reported to exhibit autosomal dominant inherited PD.[128] However, only in 2004 did two groups succeed in identifying the mutation in the LRRK2 gene at the PARK8 locus.[5,129] LRRK2 mutations, particularly the G2019S are the most common cause of PD, accounting for at least 5% of inherited and 1–2% of sporadic PD, but can reach up to 40% in certain populations.[130] LRRK2 is a large multidomain enzyme with a catalytic kinase domain and a ROC type GTPase in addition to an armadillo, ankyrin, leucine-rich repeats and a C-terminal WD40 domain. The kinase participate in a plethora of cellular pathways, including autophagy and mitophagy, vesicular trafficking and lysosomal homeostasis through the phosphorylation of several RAB proteins, reviewed in.[131]

Today, more than 100 PD-related mutations have been identified to enhance LRRK2 kinase activity or to alter its association with microtubules.[132] Several of these mutations cause disruption of autophagy at different stages of the degradation process and in a variety of models, but while the role of LRRK2 in this pathway has been established, the precise effects of the mutations are often contradictory and thus need further elucidation. Increase in autophagic flux, measured by lipidated LC3, and in autophagic vesicles, was detected in knock-in rodent and cellular models carrying the pathogenic LRRK2 G2019S mutation.[133,134] In addition, vesicles were found to colocalize with LRRK2 in human brain tissue.[135] In neurons, retrograde autophagosome transport and maturation was also impaired by the LRRK2 G2019S mutations, an effect reversed by treatment with the LRRK2 kinase inhibitor MLi-2.[136]

Increasing number of reports indicate a critical role for LRRK2 in lysosomal function. Aged LRRK2 knock-out mice show enlarged lysosomes with accumulation of lipofuscin in the kidneys, and a recent pre-print demonstrates that depletion or inhibition of the kinase, enhanced the activity and the expression of several lysosomal hydrolases.[137,138] This recent finding is in line with previous evidence showing decreased lysosomal acidification in both G2019S and R1441C (another pathogenic mutation) models, although for the latter, the changes were independent of LRRK2 kinase activity.[139,140] Finally, the activity of the PD-risk factor GBA1 was reduced in neurons derived from PD patients through the LRRK2-dependent phosphorylation of RAB10.[139]

LRRK2 possesses eight putative domains for CMA recognition and degradation, a route that becomes compromised in the presence of the

mutant form or high concentration of wild-type protein.[141,142] The G2019S and R1441G pathogenic mutations were shown to induce LAMP2A and HSC70 accumulation, blocking the formation of the complex required for lysosomal internalization of the cargo. Interestingly, this inhibition of CMA resulted in accumulation of α-synuclein oligomers in the brain of aged mutant mice compared to controls.[142]

LRRK2 has been linked to mitochondrial biology with hyperactive mutants perturbing the organelle dynamics and clearance, calcium homeostasis, oxidative stress and mitochondrial DNA. Basal mitophagy was decreased in fibroblasts from patients and in knock-in animals carrying the G2019S mutation.[143,144] Intriguingly, in the latter, pharmacological inhibition of LRRK2 kinase activity restored the impaired organellar clearance. However, the same mutation was shown, upon LRRK2 interaction with ULK1, to stimulate mitophagy.[145] Research has linked LRRK2 biology with the PINK1/Parkin pathway, with the increased kinase activity negatively regulating mitophagy.[146–148] Interaction between Parkin and both DRP1 and the TOMM complex was decreased in the presence of G2019S LRRK2, resulting in defective mitophagy.[146] Similarly, while wild-type LRRK2 forms a complex with the OMM protein MIRO1, promoting its removal and efficient mitochondrial trafficking, the G2019S mutation prevents the formation of this complex and MIRO1 removal, ultimately slowing down mitochondrial transport and degradation.[147] It has been reported that another point of interaction between the two pathways is through RAB10, a substrate of LRRK2, that was suggested to accumulate on depolarized mitochondria and to interact with OPTN to promote mitophagy. Abnormal phosphorylation of RAB10 at Thr73, caused by the G2019S and R1441C hyperactivating mutation, resulted in decreased mitochondrial translocation, impaired RAB10-OPTN interaction and impaired mitophagy. These defects were again rescued by genetic or pharmacological manipulation of LRRK2.[148] Lastly, we have shown that two PD pathways could converge on RAB8A, which is directly phosphorylated by LRRK2 at Thr72, and at Ser111 in a PINK1-dependent manner.[149] Ser111 phosphorylation negatively affects the ability of LRRK2 to phosphorylate RAB8A, indicating a yet to be discovered crosstalk between the two kinases.[150]

PINK1 and Parkin in PD

Pathogenic mutations in Parkin and PINK1 were first identified in 1998 and 2004 respectively and the delineation of their role in mitophagy has provided the most compelling link between dysfunctional autophagy and neurodegeneration.[6,7,87,171–174] Mitophagy is an evolutionarily conserved mechanism for mitochondria quality control and homeostasis. In recent years, it has become clear that it is a complex and multi-factorial cellular response that depends on tissue, bioenergetic, stress and signalling contexts. It can occur under basal conditions or upon distinct stresses.

PINK1

PINK1, whilst evolutionary conserved across different organisms, is structurally one of the most divergent kinases in the human kinome. Human PINK1 consists of 581 amino acids comprising an N-terminal region; N-terminal extension (NTE), kinase domain containing three loop insertions, and a C-terminal extension (CTE). The N-terminal region comprises of a mitochondrial targeting sequence (MTS), responsible for the translocation of cytosolic PINK1 to the mitochondria, and a transmembrane region containing a cleavage site for the rhomboid protease PARL. Under basal conditions, PINK1 is imported into the mitochondria whereupon it undergoes cleavage by mitochondrial processing protease and PARL. The N-terminally cleaved PINK1 fragment is then degraded by the 20S proteasome.[175]

Parkin

Parkin belongs to the family of RING-IBR-RING E3 ligases, containing RING domains separated by an in-between RING (IBR) domain (Figure 3 (A)). Specifically, Parkin has an N-terminal ubiquitin-like domain (UBL), followed by four zinc-coordinating domains: RING0, RING1 (containing the pUB-binding site, His302; and the E2-binding site), IBR and RING2, (containing the catalytic residue Cys431). Under physiological conditions Parkin is autoinhibited via multiple intramolecular interfaces: the UBL domain and the repressor element of Parkin (REP) interact with the core α-helical elements of RING1, limiting access to the cognate E2 ubiquitin-conjugating enzyme. Additionally, the catalytic cysteine within RING2, is occluded by the RING0 domain (Figure 3 (A), Autoinhibited).[176–178]

PINK1/Parkin activation pathway

Under basal conditions, PINK1 is present at low levels due to the aforementioned proteolytic turnover, while Parkin is autoinhibited (Figure 3 (A), Autoinhibited). In response to mitochondrial damage, that can be artificially induced by uncoupling agents (e.g., carbonyl cyanide m-chrolophenyl hydrazone (CCCP) or Oligomycin and AntimycinA), PINK1 is stabilised at the outer mitochondrial membrane (OMM) in association with components of the translocase of the outer membrane (TOM) complex where it undergoes dimerisation, autophosphorylation and activation.[173,179–182] Recently, the mechanisms by

which PINK1 is activated has been elaborated. The structural mechanism of PINK1 activation via Ser228 has been solved using insect orthologues of PINK1 and in combination with AlphaFold modelling, an intramolecular interaction between the NTE and CTE domains of PINK1 was revealed.[183–185] Cell-based analysis of PD disease mutants located within the NTE:CTE interface demonstrated that NTE:CTE interaction is essential for PINK1 stabilisation at the TOM complex and a pre-requisite for autophosphorylation at Ser228 and subsequent activation (Figure 3 (A), PINK1 activation).[183,184] After activation, PINK1 initially phosphorylates UB attached to OMM proteins specifically at residue Ser65 (pUB) (Figure 3 (A)-(B)). The interaction between pUB and the RING1 domain of Parkin, at H302, triggers the release of the UBL domain from the core structure, promoting its accumulation at the surface of mitochondria while partially activated (Figure 3 (A), Recruited). Subsequently, the UBL domain is recognized and phosphorylated by PINK1 at Ser65. This event promotes the interaction between pUBL and RING0 and the subsequent release of RING2 from RING0-mediated repression (Figure 3 (A), Activated). Exposure of the E2-binding and catalytic sites, enables the fully activated Parkin to receive UB from E2 ligases and ubiquitylate OMM proteins, catalysing the formation of ubiquitin chains of diverse linkage types including predominantly K63 and K48-linked UB.[186–192] The signal is then propagated in a feed-forward loop, as PINK1-dependent phosphorylation of UB and Parkin at Ser65 strongly increase Parkin mitochondrial localization, ultimately resulting in amplification of the ubiquitylation of OMM, SARs recruitment and mitochondrial clearance[193] (Figure 3 (B)). Of note, recent insights have demonstrated that a second pUB molecule promotes Parkin activation and ubiquitylation activity via binding to the pUBL-binding pocket (Figure 3 (A), Alternative activation mechanism).[194,195]

Mitophagy mediated by PINK1/Parkin

The accumulation of phosphorylated and unphosphorylated ubiquitin on the OMM acts as a signal for the recruitment of autophagic receptors, able to bridge ubiquitin chains with ATG8 proteins (Figures 2 and 3 (B)). In the case of PINK1/Parkin dependent mitophagy, the SARs involved, SQSTM1, NDP52, OPTN and TAX1BP1, all possess a C-terminal ubiquitin-binding domain and an hydrophobic LIR motif to bind LC3 proteins. Interestingly, considering the bacterial origin of the mitochondrion, the fact that these SARs are also involved in xenophagy underlies a possible evolutionary conserved mechanism. Experimental evidence suggests a partial degree of redundancy and a tissue and cell-specific expression of the different receptors, with the relative abundance possibly responsible for specificity in distinct cell types.[87] However, genetic deletion of the different SARs have highlighted a preferential role for NDP52 and OPTN in Parkin-dependent mitophagy.[87,88,196,197] Phosphorylation of these two SARs by TBK1, modulates their affinity for UB and positively regulates mitophagy.[88,196,198] In the case of OPTN, TBK1-dependent phosphorylation of Ser177 in the LIR domain, also enhanced LC3 binding.[58] Intriguingly, the observation of autophagosome formation engulfing damaged mitochondria in human cells lacking all six ATG8 proteins, contrasts with the canonical model that posits the requirement of LC3/GABARAP in the creation of autophagosome membranes.[199] These findings suggest that, upon PINK1/Parkin activation, SARs are able to directly form de novo autophagosome at the mitochondria. Nevertheless the ATG8 proteins are still required for the expansion, maturation and fusion of these immature vesicle with the lysosome.[199,200]

Regulation of ubiquitin chains

The formation of ubiquitin chains at the OMM, following PINK1 and Parkin activation and leading to the clearance of the damaged mitochondria, is not solely dependent on the activity of the E3 ligase. Several deubiquitylating (DUB) enzymes, which can remove ubiquitin from a variety of substrates, have been shown to modulate Parkin stability and the ubiquitylation levels of its substrates. The most studied DUB, in the context of mitophagy, is ubiquitin specific protease 30 (USP30), one of the only two DUBs containing a transmembrane domain for OMM and peroxisomal association.[201] USP30 actively counteracts Parkin-mediated ubiquitylation of several OMM proteins including TOM20, MIRO1, and is itself a target of Parkin-mediated degradation.[202–204] Thus, USP30 degradation contributes to the feed-forward mechanism of PINK1/Parkin activation. Additionally, USP30 activity can decrease the ubiquitin present on the OMM available for PINK1 to phosphorylate, setting a trigger threshold for PINK1/Parkin dependent mitophagy.[205,206] This may also explain the increase in basal mitophagy, independent of Parkin, upon USP30 depletion.[205]

USP15, another member of the USP family, was reported to counteract Parkin ubiquitylation of OMM in patient-derived fibroblasts and, when depleted, rescued mitochondrial function in a PD fly model.[207]

The mitochondrial DUB USP35 was shown to relocate from sites of mitochondrial damage to the cytosol thereby potentially promoting Parkin-mediated mitophagy.[208] USP33 has been shown to be present on the OMM and to directly deubiquitylate Parkin.[209] USP8, a DUB involved in the endosomal pathway, can also deubiquitylate Parkin and its knockdown favours the ligase translocation to the mitochondria.[210] Inhibition of USP8 in different PD models, was found to be neuroprotective,

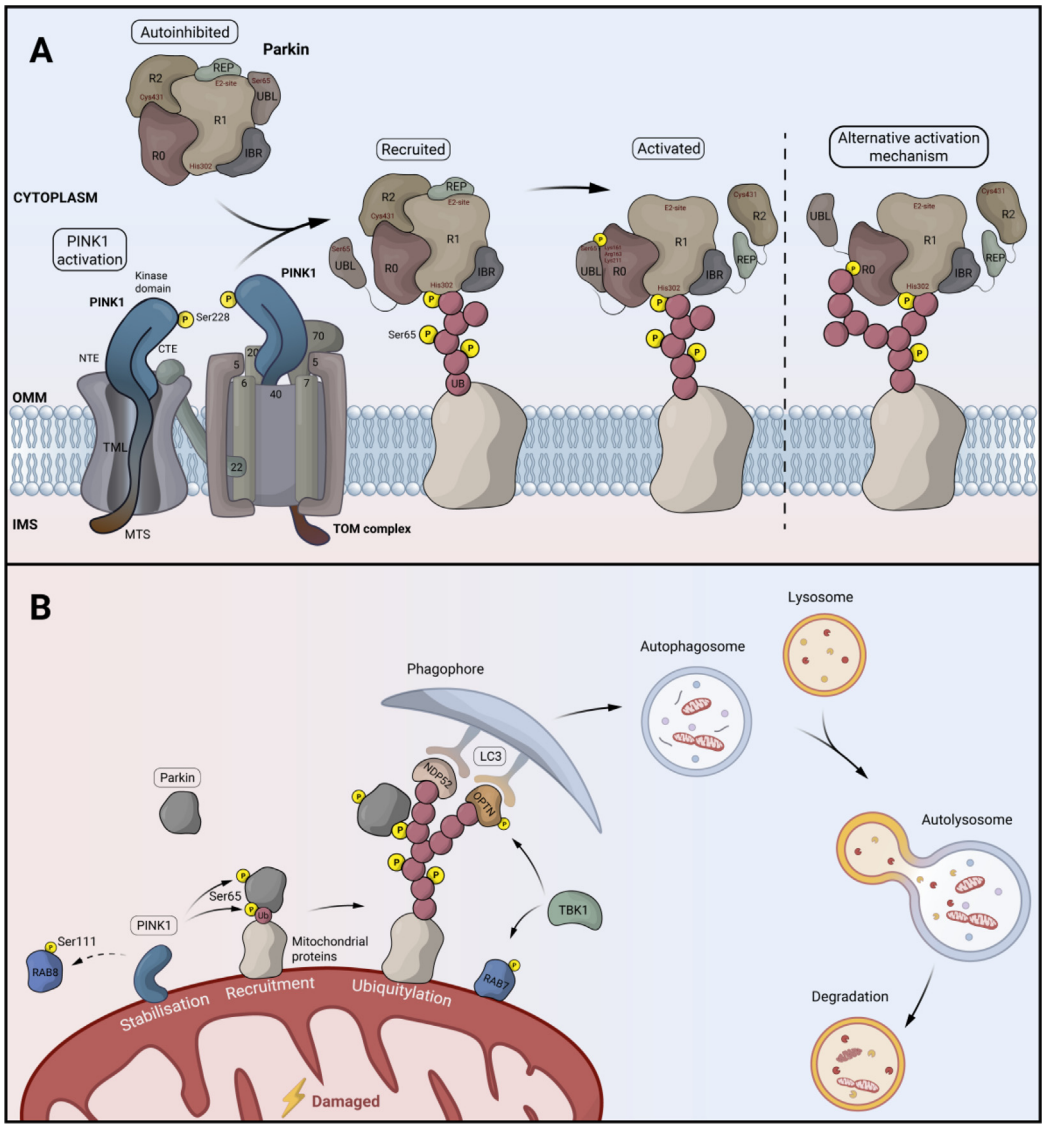

Figure 3. PINK1 and Parkin activation on the mitochondria and an overview of their mitophagy pathway. (A) PINK1 activation: Upon mitochondria damage, PINK1 stabilizes on the TOM complex through interaction between its NTE and CTE interfaces and dimerizes for trans autophosphorylation at Ser228, leading to its activation. Autoinhibited: Under normal conditions, Parkin exists in a fully auto-inhibited state where access to its E2-binding RING1 site is occluded by its UBL and REP domains and access to its RING2 active site is blocked by the RING0 domain. Recruited: Active PINK1 phosphorylates mitochondrially tethered ubiquitin at Ser65. pUB binds to Parkin RING1 releasing the UBL domain. Activated: Activation of Parkin whereby UBL phosphorylation by PINK1 at Ser65 leads to conformational changes. pUBL relocates to RING0, leading to release of the REP-RING2 segment of Parkin, exposing the active cysteine (Cys431) and freeing the E2 binding site. Alternative activation mechanism: A second pUB molecule binds RING0 (at the same pocket where pUBL binds). (B) Once PINK1 and Parkin get activated, they act in a common pathway to initiate ubiquitin-dependent mitophagy and remove the damaged mitochondria. Accumulation of UB and/or pUB on mitochondria stimulates the recruitment of selective autophagy receptors (SARs) including optineurin (OPTN) and nuclear domain 10 protein 52 (NDP52). TANK-binding kinase 1 (TBK1) phosphorylates OPTN1 to increase its affinity for UB chain binding, promotes further OPTN1 recruitment to damaged mitochondria and enhances the binding to microtubule-associated protein 1A/1B-light chain 3A (LC3 A). TBK1 phosphorylates RAB7 as well at Ser72, which has been reported to be critical for mitophagy. The SARs contain LC3-interacting region (LIR) motifs, allowing them to interact with LC3 to promote the engulfment of defective mitochondria in autophagosomes which will subsequently merge with lysosomes for degradation. PINK1 also indirectly phosphorylates RAB8A at Ser111, though its exact role in the pathway is still unknown.

underlying the pleiotropic effects of this enzyme.[211,212]

Ataxin-3, a DUB in which mutations cause the Machado-Joseph disease (or spinocerebellar ataxia type 3) directly interacts with Parkin affecting its ubiquitylation. Ataxin-3 stabilises the complex between the E2-conjugating enzyme and Parkin, impeding the discharge of ubiquitin to the E3 ligases and this interplay may explain some common features, including motor symptoms, between Machado-Joseph disease and PD.[213,214]

Finally, it is likely that other E3 ligases play a role in orchestrating the complex symphony of ubiquitylation on the mitochondrial surface following PINK1 activation. These include the mitochondrial ubiquitin ligase 1 (MUL1, or MAPL1 or GIDE).[215–217] MUL1 is thought to act in parallel with Parkin to ubiquitylate OMM proteins, however in vulnerable cell population, such as neurons, it might be an early checkpoint to prevent mitochondria degradation and bioenergetic deficit upon mild stress.[218,219] Interestingly, FBX07, a protein part of the SKP1-CUL1-RBX1 ubiquitin ligase complex and encoded by the PD-related gene PARK15, was reported to act in a common pathway with PINK1 and Parkin.[220] Recent evidence, however, points to a non-essential role of FBXO7 in this mitophagy pathway.[221]

PINK1 and Parkin beyond mitophagy

Chemical-induced mitochondria depolarization studies have been instrumental in elucidating the signalling pathway of PINK1 and Parkin. However, exploring the pathway in this manner results in overlooking the broader physiological roles that the enzymes may possess, as the focus is shifted towards a singular function that overshadows the rest. Of note, *in vivo* models, where the activation of the pathway cannot be achieved in a similar manner, are limited in their ability to reproduce the neurodegenerative phenotype observed in PD patients. Current research suggests that basal mitophagy in mice may occur independently of PINK1, although further investigation is needed to fully comprehend its contribution to this process.[222] Furthermore, studies of PINK1/Parkin-mediated mitochondrial turnover have been reported to occur independently or only partially dependent on canonical autophagy pathways.[223] Consequently, research has shifted its focus towards identifying other compensatory regulators of mitophagy, as well as exploring the alternative physiological roles of PINK1 and Parkin beyond mitophagy and mitochondrial quality control.

Experiments utilizing PINK1 and Parkin null flies have revealed the existence of motor impairments in the absence of neurodegeneration.[224] Notably, these flies exhibit a marked increase in the expression of genes involved in the innate immune response, offering valuable insight into the physiological functions of PINK1 and Parkin in the regulation of immunity.[225] Subsequent studies have further investigated this connection. Mitochondria-derived vesicles (MDVs) are involved in quality control mechanisms, which transport specific mitochondrial cargos to late endosomes. Matheoud et. al., demonstrated that PINK1 and Parkin suppress the formation of MDVs required for mitochondrial antigen presentation in immune cells in both in vitro and in vivo models. PINK1 and Parkin activity results in the degradation of mitochondrial-recruited SNX9 and RAB9, two trafficking proteins. Notably, this process is driven by MDVs, not mitophagy. These findings lend support to the emerging hypothesis that PD is connected to autoimmunity.[226]

On the same note, genetic polymorphisms in the PARK2 regulatory region are associated with increased susceptibility to intracellular bacterial pathogens as well. Studies involving Parkin-deficient mice and flies have demonstrated their increased susceptibility to intracellular bacterial infections, highlighting Parkin's significance in innate immunity. Furthermore, these findings have unveiled a hitherto unanticipated functional association between mitophagy and xenophagy.[227] Adding to this, more studies have highlighted Parkin involvement in various cellular pathways, including apoptosis, lipid metabolism regulation, and cytokine production upon infection, suggesting the potential significance of Parkin as an immune regulator.[228–230]

Recent studies have linked PD genes such as LRRK2 and PARK7 to inflammatory bowel disease.[231,232] As mentioned above, both PINK1 and LRRK2 activity is known to result in the phosphorylation of a number of RAB GTPases that are involved in the endolysosomal pathway, with RAB8A being a common substrate.[150] In conclusion, the evidence indicates a significant association between PD, immunity, and autophagy. Further investigation is needed to fully understand the complex interplay between these pathways and their contribution to the pathogenesis of PD.

Defective autophagy in other neurodegenerative disorders: ALS

It is clear how maintenance of cellular proteostasis is particularly critical for the health of post-mitotic long-lived cells such as neurons. Indeed, the pathological hallmark of nearly all NDD present misfolded protein aggregates accompanied by a dysfunctional autophagy machinery. Another example is ALS, a fatal progressive neurological disorder clinically characterized by the degeneration of motor neurons in the brain and spinal cord. Similar to PD the majority of cases are idiopathic, however genetic studies have identified disease causing mutations in several genes related to protein trafficking and autophagy, namely ALS2, FIG4,

OPTN, SPG11, C9ORF72, CHMP2B, SQSTM1, TBK1, UBQLN2 and VCP. We will briefly discuss some examples, although this has been documented more extensively in other recent reviews.[233,234]

A pathogenic hexanucleotide repeat expansion in C9ORF72 is the most common mutation associated with the disease and accounts for between a fifth and half of familial cases and up to 20% of all sporadic cases.[235] Several complexes of C9ORF72 have been implicated at different steps of autophagy, from its initiation (ULK1A-RAB1A complex), autophagosome formation (RB1CC1-ULK1-ATG13-ATG101 complex), endosome maturation (RAB7-RAB11 complex) and finally lysosome and vesicle dynamics and autophagic flux (C9ORF72-SMCR8-WDR41 complex).[236–239] The pathogenic repeat GGGGCC, located in a non-coding region of the gene and lacking the start codon AUG, causes ribosomal stalling and the initiation of the repeat-associated non-AUG translation, resulting in the formation of neurotoxic dipeptides.[240–242] The accumulation of dipeptide aggregates is further exacerbated by the decreased levels of functional C9ORF72 and the consequent impaired autophagy.[243,244]

Other mutations linked to familial cases of ALS involve the SARs OPTN, SQSTM1 and the proteasome shuttle factor, UBQLN2, hindering the ability of the receptors to bind either ubiquitylated substrates or the ATGs protein, resulting in a defective delivery of the targeted cargo to the autophagosome. In the case of OPTN, more than 20 pathogenic mutations have been identified, the majority of which are located in the ubiquitin binding in ABIN and NEMO (UBAN) domain and may impair the ubiquitin-binding property of the receptor but may also increase microglial-driven neuroinflammation.[197,245–246] UBQLN2 ALS-mutations are mainly located in the unique proline-X-X domain and are associated with a decreased ATG9-ATG16L1 binding, defective autophagy and an impaired ubiquitin–proteasome system. UBQLN2 has been also shown to colocalized with OPTN-positive vesicles containing autophagic markers, with the mutant protein associated with an age-dependent decrease in autophagic flux.[52,247,248]

Missense and nonsense mutation in SQSTM1, accounting for up to 3.5% of all ALS cases, can affect the ubiquitin-associated (UBA) domain, the LIR domain or the promoter region, decreasing respectively, cargo binding, autophagosome binding or the protein levels.[46,105,249–251] Interestingly, while SQSTM1-positive inclusions are found in the majority of ALS patients, they are also common in AD, PD and frontotemporal dementia (FTD), further underlying the close interconnection between autophagy and neurodegeneration.[252–255] Distinct clinical and pathological phenotypes are a striking characteristic of ALS and FTD genes, with mutations in C9ORF72, SQSTM1 and UBQLN2 being identified not only in ALS, but also in FTD or in patients affected by the two conditions, with these proteins often found together and colocalized with ubiquitin in the cytoplasmic inclusions characteristics of the two disorders.[256–259]

Therapeutic perspectives

Little has changed in the way PD is treated since Cotzias and colleagues administered L-DOPA to patients in 1967.[260] The aetiology of PD is still unknown despite our deepened and increased knowledge of the molecular and cellular signatures associated with disease progression. It is also now clear that PD is far from being merely a neurological disorder. It is a complex, multiorgan disease and therefore very unlikely can be treated with a single therapeutic approach. Nevertheless, the discovery of familial forms of the disease caused by loss or gain of function mutations in one specific protein, means that the altered function can potentially be reversed by a single compound and therefore attracted pharmaceutical research. Additionally, certain pathways, as highlighted in this review for autophagy, are impacted in a variety of diseases and during ageing. Therefore, restoring for example mitophagy, might benefit people affected by PD and other conditions.

LRRK2 inhibitors have been at the forefront of development, with a few compounds currently in clinical trials (see https://clinicaltrials.gov/). The compound BIIB122 (or DNL151), developed by Biogen and Denali, is currently in Phase 2, after passing a bioavailability Phase 1 study. This compound is an improvement on the DNL201, that completed Phase 1, having a better dosing schedule (once daily). Biogen is also testing an antisense oligonucleotide to reduce LRRK2 levels, BIIB094, currently in Phase 1.

Boosting mitophagy has also attracted pharmaceutical development, in particular through the inhibition of USP30 or the activation of PINK1. Small molecule inhibitors of the DUB are under development by MitoBridge LLC and Mission therapeutics, with one compound, MTX325 in preclinical study for PD.[261] Recently, a brain penetrant PINK1 activator (MTK458) developed by Mitokinin, has shown great potential in rodents models. MTK458 treatment not only rescued mitophagy and alleviated mitochondrial dysfunction, but also facilitated α-synuclein clearance.[262]

Conclusions

Autophagy mediated homeostasis plays a crucial role in the development of the central nervous system and prevention of neurodegeneration. The identification of mutations in PD patients and other neurodegenerative disorders and the subsequent demonstration of their role in autophagy illustrates the importance of autophagy in complex bioenergetic cell types such as dopaminergic neurons or motor neurons. Our systematic analysis

of human monogenic disorders reveals the broader importance of autophagy in preventing brain disorders. The proteins encoded by many of these genes and the pathways regulating autophagy in these disorders remains poorly studied suggesting completely new regulatory mechanisms of autophagy remain to be discovered. This also suggests that small molecule therapeutic strategies to modulate autophagy would have broader potential for brain disorders in general.

CRediT authorship contribution statement

Christos Themistokleous: Conceptualization, Writing - original draft, Writing - review & editing. **Enrico Bagnoli:** Conceptualization, Writing - original draft, Writing - review & editing. **Ramaa Parulekar:** Writing – original draft. **Miratul M.K. Muqit:** Conceptualization, Supervision, Writing - review & editing.

DECLARATION OF COMPETING INTEREST

M.M.K.M. is a member of the Scientific Advisory Board of Mitokinin Inc and Scientific Consultant to Stealth Biotherapeutics Inc. and Merck & Co. Inc.

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Appendix A. Supplementary data

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† Denotes Equal Contribution.

Abbreviations:
AD, Alzheimer's disease; ALS, Amyotrophic lateral sclerosis; AMPK, AMP-activated protein kinase; ATG, Autophagy-related genes; BAG-1, BAG family molecular chaperone regulator 1; CHIP, Carboxy-terminus of Hsc70-interacting protein; CMA, Chaperone-mediated autophagy; CTE, C-terminal extension; DUB, Deubiquitylating enzyme; ER, Endoplasmic reticulum; FTD, Frontotemporal dementia; GIM, GABARAP-interacting motif; Hip, Hsp70-interacting protein; Hop, Hsp70/Hsp90 organising protein; HSC70, Heat-shock cognate protein of 70 kDa; HSP40, Heat shock protein 40; HSP90, Heat shock protein 90; IBR, In-between RING; IL-1β, Interleukin-1 Beta; LAMP2A, Lysosome-associated membrane protein type 2A; LBs, Lewy bodies; LDs, Lipid droplets; LIR, LC3-interaction region; LNs, Lewy neurites; LRRK2, Leucine-rich repeat kinase 2; MDVs, Mitochondrial-derived vesicles; mTOR, Mammalian target of rapamycin; MTS, Mitochondrial targeting sequence; NDDs, Neurodegenerative disorders; NTE, N-terminal α-helix extension; OMM, Outer mitochondrial membrane; OPTN, Optineurin; p62/SQTSM1, Sequestosome 1; PD, Parkinson's disease; PI(3)P, Phosphatidylinositol 3-phosphate; PINK1, PTEN-induced kinase 1; PKA, Protein kinase A; PRKN, Parkin; PTMs, Post-translational modifications; SARs, Selective autophagy receptors; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; SNpc, Substantia nigra pars compacta; UB, Ubiquitin; UBA, Ubiquitin-associated; UBAN, Ubiquitin binding in ABIN and NEMO; UBL, Ubiquitin-like; USP, Ubiquitin specific protease; VPS, Vacuolar protein sorting-associated protein; VTA, Ventral tegmental area

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