The Different Autophagy Degradation Pathways and Neurodegeneration

Angeleen Fleming[#,1,2,3], Mathieu Bourdenx[#,4,5], Motoki Fujimaki[1,2], Cansu Karabiyik[1,2], Gregory J. Krause[6,7], Ana Lopez[1,2,3], Adrián Martín-Segura[6,7], Claudia Puri[1,2], Aurora Scrivo[6,7], John Skidmore[8], Sung Min Son[1,2], Eleanna Stamatakou[1,2], Lidia Wrobel[1,2], Ye Zhu[1,2], Ana Maria Cuervo*[,6,7] and David C. Rubinsztein*[,1,2]

[1]Department of Medical Genetics, University of Cambridge, Cambridge Institute for Medical Research, The Keith Peters Building, Cambridge Biomedical Campus, Hills Road, Cambridge, CB2 0XY. United Kingdom.

[2]UK Dementia Research Institute, University of Cambridge, Cambridge Institute for Medical Research, The Keith Peters Building, Cambridge Biomedical Campus, Hills Road, Cambridge, CB2 0XY. United Kingdom.

[3]Department of Physiology, Development and Neuroscience, University of Cambridge, Downing Street, Cambridge CB2 3DY, United Kingdom.

[4]Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France.

[5]CNRS, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France.

[6] Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, NY, USA.

[7]Institute for Aging Studies, Albert Einstein College of Medicine, Bronx, NY, USA.

[8]The ALBORADA Drug Discovery Institute, University of Cambridge, Island Research Building, Cambridge Biomedical Campus, Hills Road, Cambridge, CB2 0AH. United Kingdom.

[#]Joint first authors

*Joint corresponding authors – David C. Rubinsztein (dcr1000@cam.ac.uk); Ana Maria Cuervo (ana-maria.cuervo@einsteinmed.org)

ABSTRACT

The term autophagy encompasses different pathways that route cytoplasmic material to lysosomes for degradation and include macroautophagy, chaperone-mediated autophagy and microautophagy. Since these pathways are crucial for degradation of aggregate-prone proteins and dysfunctional organelles like mitochondria, they help to maintain cellular homeostasis. As post-mitotic neurons cannot dilute unwanted protein and organelle accumulation by cell division, the nervous system is particularly dependent on autophagic pathways. This dependence may be a vulnerability as people age and these processes become less effective in the brain. Here we will review how the different autophagic pathways may protect against neurodegeneration, giving examples of both polygenic and monogenic diseases. We have considered how autophagy may have roles in normal CNS functions and the relationships between these degradative pathways and different types of programmed cell death. Finally, we will provide an overview of recently described strategies for upregulating autophagic pathways for therapeutic purposes.

A. Overview of different autophagy pathways

The term autophagy describes a set of mechanistically distinct processes that diverse cells use to deliver cytoplasmic contents to lysosomes for degradation that includes macroautophagy, chaperone-mediated autophagy (CMA) and microautophagy. In this review, we will briefly describe these pathways, how they impact neurological functions in health and disease and the current pharmacological efforts to boost autophagic activities as therapeutic strategies in neurodegenerative diseases.

Macroautophagy core pathway

The first morphologically distinct structure in macroautophagy is the cup-shaped, double-membraned phagophore, whose edges extend and fuse to become an autophagosome (Fig. 1). Autophagosome biogenesis is complex and involves multiple proteins and lipids from various membrane sources, including the endoplasmic reticulum (ER), ER/mitochondria contact sites (MAM), ER exit sites, recycling endosomes, Golgi and plasma membrane (Axe et al., 2008; Ge and Schekman, 2014; Puri et al., 2013).

The molecular components of macroautophagy were originally described in yeast, where genetic screens identified more than 40 ATG (autophagy related) proteins, most of them with mammalian orthologues, that regulate macroautophagy at its different stages (Mizushima et al., 2011). A key event in the formation of phagophores is the conjugation of members of the ubiquitin-like ATG8 family (Fig. 1), including the LC3 and GABARAP (gamma-aminobutyric acid receptor-associated protein) subfamilies, to phosphatidylethanolamine in precursor membranes. This event occurs on RAB11A-positive recycling endosomes in a wide range of cells, including primary neurons (Puri et al., 2018). Thereafter, the autophagosomes are closed by ESCRT machinery (Takahashi et al., 2018) then released in a step mediated by DNM2 (Puri et al., 2020).

It is likely that there is lipid transfer to growing autophagosomes via the ATG2-WIPI4 complex (Maeda et al., 2019) and that some lipid remodelling occurs on nascent autophagosomes mediated by the scramblase function of ATG9 that assists membrane expansion (Matoba et al., 2020). Most of the cell biology and biochemistry of mammalian autophagy has been studied in fibroblasts and cancer cell lines. While the pathway conservation across species suggests that the core biology will be essentially similar in all cells, there may be neuron- or glial-specific adaptions.

Selective Macroautophagy (mitophagy, ER-phagy, pexophagy, aggrephagy)

Macroautophagy degrades long-lived, aggregate-prone proteins, protein complexes, and dysfunctional or damaged organelles. Substrate degradation can be facilitated by machinery that enables their preferential sequestration via adaptor proteins that bridge components of the substrate (generally surface proteins which are ubiquitinated) and elements of the nascent autophagosome, typically LC3 (Fig. 1). These forms of selective autophagy include mitophagy (mitochondria), pexophagy (peroxisomes), ribophagy (ribosomes), ER-phagy (ER) and aggrephagy (aggregate-prone proteins), among others.

Mitophagy

Mitophagy exists in several forms, depending on the mechanism of recruitment of the phagophore membrane to mitochondria. The most well-studied form relies on the phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase (PTEN)-induced putative kinase 1 (PINK1) and the ubiquitin ligase Parkin. After mitochondrial damage, PINK1 levels, normally low, increase and PINK1 auto-phosphorylates to recruit cytosolic Parkin to the mitochondrial membrane, triggering mitophagy (Matsuda, 2016). In PINK1-Parkin-dependent mitophagy, autophagy receptors such as optineurin (OPTN), NDP52 (nuclear domain 10 protein 52) and TAX1BP1 (Trans-activating transcriptional regulatory protein of HTLV-1 (TAX1) binding protein 1) recruit the autophagosome biogenesis machinery to mitochondria. (Geisler et al., 2010; Narendra et al., 2010). Neuronal PINK1 or Parkin deletions in mice cause only mild phenotypes, highlighting the existence of alternative mitophagy processes, including receptor-mediated (NIX/BNIP3L), ubiquitin-mediated (MUL1-dependent) and lipid-mediated (through exposure of the inner membrane mitochondrial lipid cardiolipin) pathways (Evans and Holzbaur, 2020).

ER-phagy (reticulophagy)

Constitutive ER turnover is required to maintain proper cellular function. Autophagy contributes to ER remodelling via ER-phagy or reticulophagy. The ER-phagy adaptor FAM134B (family with sequence similarity 134, member B), interacts directly with LC3 or GABARAP and cooperates with Reticulon 3 (RTN3- RHD-containing protein) on the ER membrane to trigger the recruitment of the specific area of the ER that need to be degraded inside the autophagosome (Grumati et al., 2017). Other ER-phagy receptors, include cell-cycle progression gene 1 (CCPG1), Sec62, Atlastin-3 (ATL3) and testis expressed 264 (TEX264) (Chino et al., 2019; Fumagalli et al., 2016). The existence of multiple receptors suggests a redundancy or selectivity for types of ER. FAM134B and RTN3L are involved in starvation-induced ER-phagy, while CCPG1 is induced during ER stress and Sec62 participates in the recovery of ER stress (recovER-phagy). Mutations in FAM134B and ATL3 have been linked to peripheral neuropathy, but the other ER-receptors have not been studied yet in the nervous system.

Pexophagy

Damaged or excess peroxisomes are degraded through autophagy via pexophagy, where ubiquitination of PEX3 or PMP34 on the cytosolic face of peroxisomes enables recognition by autophagy adaptors P62 or NBR1, which target peroxisomes for autophagic degradation (Jo et al., 2020).

Aggrephagy

Most neurodegenerative diseases manifest with the accumulation of aggregates in vulnerable cell populations in the brain. Selective degradation of protein aggregates is called aggrephagy. Misfolded, aggregate-prone proteins are ubiquitinated, recognized and linked to the autophagy machinery by adaptors like P62, NBR1, Tollip (Cue5 in yeast), OPTN (Shen et al., 2017) and TAX1BP1 (Sarraf et al., 2020).

Lysophagy

Damaged lysosomes are degraded by selective autophagy via lysophagy, which protects cells from lysosomal cell death. Lysophagy appears to be ubiquitination-dependent and involves various canonical autophagy receptors, like TAX1BP1 (Eapen et al., 2021) and TBK1 (Eapen et al., 2021), a protein mutated in various diseases, including forms of ALS.

Major regulators

Macroautophagy can be stimulated by stresses including nutrient depletion, growth factor deprivation, oxidative stress and protein aggregation (Menzies et al., 2017). Nutrient starvation inhibits mTORC1 (mechanistic target of rapamycin complex 1), a highly conserved negative regulator of autophagy (Saxton and Sabatini, 2017). In nutrient-rich conditions, mTORC1 interacts and phosphorylates ULK1, to inhibit autophagy. Upon starvation, mTORC1 sites on ULK1 are dephosphorylated and ULK1 dissociates from mTORC1, thereby activating ULK1 kinase activity (Hosokawa et al., 2009). In mammals, mTORC1 activity is stimulated by growth factors through inhibition of the tuberous sclerosis complex (TSC) 1 and 2 (Dibble and Manning, 2013). Amino acids signal to mTORC1 through Rag GTPases independently of the TSC complex (Sancak et al., 2008). Recently, leucine was shown to signal to mTORC1 in most cells, including neurons and glia, via its metabolite Acetyl-coenzyme A (Ac-CoA), which stimulates acetylation of raptor and subsequent activation of mTORC1 and inhibition of autophagy (Son et al., 2020). Autophagy can

also be induced by low cellular energy levels/low glucose (increased AMP/ATP) sensed by AMP-activated protein kinase (AMPK). In glucose-deprived cells, AMPK activates ULK1, which then phosphorylates and activates the lipid kinase PIKfyve (FYVE finger-containing phosphoinositide kinase), thereby increasing synthesis of the phosphatidylinositol 5-phosphate PI(5)P (Karabiyik et al., 2021). PI(5)P upregulates autophagosome synthesis and induces autophagic flux in the absence of PI(3)P in a VPS34-independent manner (Vicinanza et al., 2015). Another key regulator of autophagy and lysosomal biogenesis is transcription factor EB (TFEB) (Settembre et al., 2013).

Non autophagic role of the ATG protein conjugation system

Some ATGs have autophagy-independent functions. In LC3-associated phagocytosis (LAP), ATGs contribute to immune regulation and inflammatory responses, particularly in phagocytic cells. In LAP, LC3 is conjugated to phagosome single membranes (LAPosomes) that directly fuse to lysosomes (Galluzzi and Green, 2019). LAP is independent on the ULK1/FIP200/ATG13/ATG101 macroautophagy complex and is unresponsive to starvation or intracellular stress (Heckmann et al., 2017). Toll-like receptors (TLRs) and immunoglobulin (Ig) receptors participate in cargo recognition to activate LAP. The recognition of opsonized foreign particles leads to the recruitment of LAP regulatory machinery to the phagosome and the engulfed substrates are degraded following fusion with lysosomes (Heckmann et al., 2019).

LC3 can also be conjugated to RAB5-, clathrin-positive endosomes that contain amyloid-β. This new function, called LANDO (LC3-associated endocytosis), requires ATGs, such as LC3, Rubicon and ATG5, but not FIP200. LANDO was described in microglia, where it enables removal of amyloid-β and ameliorates pathology in a murine model of Alzheimer's Disease (AD) (Heckmann et al., 2019).

Non-canonical macroautophagy

Macroautophagy-like processes can also occur in the absence of some key ATG proteins, in what is called non-canonical macroautophagy. Some cell types lacking *Atg5* or *Atg7*, essential for canonical macroautophagy, still perform macroautophagy in response to specific stressors (Nishida et al., 2009). Autophagosome formation in this case is independent of the ubiquitin-like protein systems ATG5-ATG12, ATG7-ATG8, ATG16 and ATG9, but requires ULK1 and PI3K-Beclin 1-VPS34 complexes (Nishida et al., 2009). ATG5-ATG7-independent autophagosomes

originate from the trans-Golgi membrane in a RAB9-dependent manner (Honda et al., 2020). Non-canonical macroautophagy has been shown to contribute to mitochondrial clearance during erythroid maturation or iPSC cell differentiation and to the degradation of proinsulin granules in glucose-deprived β-cells (Honda et al., 2020). Neuronal non-canonical autophagy is required for the degradation of ceruloplasmin to prevent iron deposition (Yamaguchi et al., 2020).

Chaperone-mediated autophagy

In CMA, substrate proteins are translocated across the lysosomal membrane, where they are targeted following the recognition of a KFERQ-like targeting motif in their sequences by the heat shock cognate 71kDa protein (HSC70) (Fig. 2). The HSC70/substrate complex binds the cytosolic tail of the lysosome-associated membrane protein type 2A (LAMP-2A) (Cuervo and Dice, 1996), triggering its multimerization into a translocation complex. After unfolding, the substrate is internalized into the lysosomal lumen assisted by a lysosome resident HSC70, and the LAMP-2A complex is disassembled (Kaushik and Cuervo, 2018). LAMP-2A levels and its assembly/disassembly in the lysosomal membrane are rate-limiting for CMA.

HSC70 is the only chaperone required for CMA cargo recognition (Chiang et al., 1989), while HSP90, HSP40, the HSP70-HSP90 organizing protein (Hop), the HSP70-interacting protein (Hip), and the BCL2-associated athanogene-1 protein (BAG-1), facilitate substrate unfolding, enhance substrate/LAMP2A binding and stabilize LAMP2A during its multimerization (Kaushik and Cuervo, 2018). In all cell types studied to date, LAMP2A translocation complex stability is regulated by the monomeric form of the intermediate filament protein glial fibrillary (GFAP) and the elongation factor-1 α (EF1α) in a GTP-dependent manner (Bandyopadhyay et al., 2010), and by lysosomal AKT (Arias et al., 2015). Phosphorylation of lysosomal membrane AKT by mTORC2 is inhibitory for CMA, whereas its dephosphorylation by the PHLPP1 kinase-phosphatase that binds to lysosomes in a Rac-1 dependent manner, leads to maximal CMA activation (Arias et al., 2015). The CMA target of AKT is GFAP, also recently shown to be phosphorylated by class I PI3K with a similar inhibitory effect on CMA (Endicott et al., 2020). CMA is also transcriptionally upregulated by NFAT, NRF2 and TPD52, whereas signalling through retinoic acid receptor alpha (RARα) and growth hormone signalling transcriptionally repress CMA (Anguiano et al., 2013).

The KFERQ-like motif is necessary and sufficient for CMA targeting, but because binding to HSC70 is dependent on the chemical properties of the motif (i.e. charge and polarity) (Kaushik and Cuervo, 2018), multiple amino acid combinations can build a functional (canonical) KFERQ-like motif. Post-translational modifications (PTMs), such as phosphorylation or acetylation (Fig. 2), can also generate functional motifs (by adding the missing charges) or disrupt a motif (i.e. through ubiquitination of the residue's lysine). Around 46% of the proteome contains canonical motifs and an additional 30% can be generated via PTMs (Kirchner et al., 2019), but CMA degradation of those proteins only occurs when their motif becomes accessible to the chaperone (i.e. by protein conformational changes or dissociation of protein-protein interactions).

Microautophagy and endosomal microautophagy

Microautophagy involves lysosomal degradation of cellular components via membrane invaginations in compartments of the endolysosomal system (Fig. 3). Beside proteins, microautophagy can also degrade organelles in yeast such as mitochondria, lipid droplets, ER, peroxisomes and even nuclear fragments (Schuck, 2020); although thus far, only micro-ER-phagy has been identified in mammalian systems (Loi et al., 2019).

Mammalian microautophagy pathways all target their cargo to late endosomes/multivesicular bodies (LE/MVBs) (Krause and Cuervo, 2021). The term endosomal microautophagy (eMI) refers to the degradation of cytosolic proteins in LE/MVBs and can be further sub-classified based on the selectivity of the cargo and the molecular machinery involved. The first type of eMI identified requires, as in CMA, recognition of a KFERQ-like motif by HSC70 (Fig. 2) (Kirchner et al., 2019; Sahu et al., 2011). HSC70 binds to phosphatidylserine in LE/MVB membranes (Morozova et al., 2016), triggering substrate internalization into the lumen via membrane invaginations that form in an ESCRT-dependent manner. Cargo degradation protein can occur in the LE/MVB compartment itself, although the bulk of degradation occurs after LE/MVB-lysosome fusion. An additional type of mammalian eMI, independent of HSC70 but dependent on some of the ESCRT proteins involved in eMI, has been identified as part of the early response to amino acid starvation (Mejlvang et al., 2018). This pathway degrades several macroautophagy receptors, possibly regulating the switch between selective and in bulk macroautophagy.

Little is known about the regulation and functional implications of eMI in mammals. In *Drosophila*, eMI is upregulated in response to oxidative and genotoxic stress (Mesquita et al.,

2020) and to nutrient deprivation (Jacomin et al., 2021; Mukherjee et al., 2016). Basal eMI has been shown to contribute to local turnover of proteins in *Drosophila* neuromuscular junction synapses and its blockage leads to impaired neurotransmission (Uytterhoeven et al., 2015).

Autophagic crosstalk

The ubiquitin-proteasome system (UPS), mostly responsible for degradation of soluble and short-lived proteins, shares some key players with autophagy, like ubiquitin. This small protein can modulate the degradation rates of proteins or organelles through the UPS or macroautophagy (Komander and Rape, 2012). Moreover, ubiquitination of the core macroautophagic machinery serves as an important regulatory mechanism (reviewed in (Yin et al., 2020). The macroautophagy receptor, P62, has also been reported to escort ubiquitinated proteins for proteasomal degradation (Seibenhener et al., 2004), depending on its oligomerization state (Lu et al., 2017).

Accumulating evidence suggests a compensatory balance between these two degradation pathways, whereby UPS inhibition upregulates macroautophagic proteins by mechanisms still not fully understood (reviewed in (Sun-Wang et al., 2020). Proteasome inhibition enhances nuclear translocation of TFEB (Li et al., 2019a), and other transcription factors that induce autophagy, like Nrf1 and Nrf2 (nuclear factor erythroid-2-like 1 and 2) (Pajares et al., 2016; Sha et al., 2018). The proteasome itself can be a substrate of macroautophagy under stress conditions in the process called proteaphagy (Cohen-Kaplan et al., 2016; Cuervo et al., 1995). Although macroautophagy-deficient cells appear to accumulate proteasomes due to decreased proteaphagy and increased expression of the proteasome subunits (Wang et al., 2013), degradation of proteasome substrates seems to be compromised in these cells, without changes in proteasome activity (Korolchuk et al., 2009).

Different types of autophagy, although not redundant, are capable of compensating for each other. Early studies revealed that mouse fibroblasts with defective macroautophagy displayed elevated constitutive CMA activity. Compensatory activation of macroautophagy and the UPS occurs in a variety of non-neuronal tissues in CMA-deficient mouse models (mouse fibroblasts, liver, T cells) (Kaushik and Cuervo, 2018). However, this compensation is not universal as it was not observed, for example, in the retina or in hematopoietic stem cells (Dong et al., 2021; Rodriguez-Muela et al., 2013). Likewise, compensatory activation of macroautophagy was not observed in CMA-defective neurons, leading to an early phenotype of proteostasis failure (already evident at 6

months) (Bourdenx et al., 2021). In fact, a direct comparison of insoluble fractions isolated from the brains of CMA- (*Lamp2A*$^{-/-}$) and macroautophagy-deficient (*Atg7*$^{-/-}$) mice highlighted that these two pathways handle different portions of the proteome in neurons (only ~50% of the aggregated proteins were similar). Understanding the mechanisms behind reciprocal macroautophagy and CMA compensation in non-neuronal cells could identify novel therapeutic targets to upregulate these pathways in neurons in neurodegenerative conditions.

B. Roles of autophagic pathways in the healthy nervous system

Maintaining neuronal function

Neurons are post-mitotic, long-lived cells that require robust protein and organelle quality control mechanisms. Neuronal loss of ATGs results in accumulation of ubiquitin-positive protein aggregates, axonal swellings and neuronal degeneration, demonstrating that basal macroautophagy is critically important for neuronal health (Menzies et al., 2017). Similarly, loss of the CMA receptor LAMP2A disrupts neuronal proteostasis and function (Bourdenx et al., 2021). While impaired macroautophagy and CMA accelerate the accumulation of aggregate-prone proteins (a hallmark of most neurodegenerative diseases), they likely protect neuronal health via several additional mechanisms.

Neurons need to maintain a healthy pool of mitochondria, as they have high energy demands. The strong genetic connection between mitophagy and neurodegeneration emphasizes the importance of this pathway in neurons. However, the role of neuronal mitophagy in non-pathological conditions is unclear. Mice deficient for proteins involved in selective mitophagy, such as P62, PINK1 and Parkin, do not show accumulation of defective mitochondria or neuronal loss (Martinez-Vicente, 2017). In contrast, PINK1 knock-out rats or PINK1/Parkin deficient flies display mitochondrial abnormalities and neurodegeneration (Martinez-Vicente, 2017). The mitochondrial defects in the PINK1/Parkin depleted models may be independent of mitophagy. For example, PARIS (ZNF746), a substrate of PINK1-mediated phosphorylation and Parkin-mediated ubiquitination, accumulates following Parkin deletion and leads to repression of the peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), a master coregulator of mitochondrial function, biogenesis, and mitochondrial oxidative stress management (Pirooznia et al., 2020; Shin et al., 2011; Stevens et al., 2015).

Mice with neuronal loss of WIPI4, FIP200 and ATG9A, involved in early stages of autophagosome formation, or WIPI3, involved in alternative macroautophagy, show accumulation of damaged mitochondria (Liang et al., 2010; Yamaguchi et al., 2020; Yamaguchi et al., 2018; Zhao et al., 2015). Furthermore, neurons may have upregulated other mitochondria quality control pathways, such as mitochondrial-derived vesicles (MDVs) that carry oxidised proteins to lysosomes for degradation, thereby saving the entire organelle from clearance (Misgeld and Schwarz, 2017). Hence, bulk macroautophagy or MDVs may provide a quality control mechanism that is constantly active in non-pathologic conditions, whereas mitophagy is trigged upon mild or severe mitochondrial stress (Misgeld and Schwarz, 2017; Yao et al., 2020).

Synapses are dynamic structures highly dependent on controlled turnover of their components. Autophagy is emerging as a crucial player in synapse formation, pruning and plasticity (Birdsall and Waites, 2019; Stavoe and Holzbaur, 2019). Loss-of-ATG7 studies revealed that autophagy is required in motor neurons for presynaptic terminal formation, innervation of the neuromuscular junction (Rudnick et al., 2017), and in dopaminergic neurons for synaptic vesicle degradation regulated by active zone proteins, like Bassoon and Piccolo (Hernandez et al., 2012; Okerlund et al., 2017). Subsequent studies in mice lacking neuronal ATG5 revealed defective selective degradation of tubular ER in axons and increased excitatory neurotransmission through excessive calcium release from ER stores (Kuijpers et al., 2021). The relative contribution of the failure to degrade synaptic vesicles versus calcium storage dysregulation to the observed enhanced neurotransmission requires future investigation. At the postsynaptic terminal, macroautophagy is required for spine pruning, as cortical neurons lacking ATG7 have an excessive number of dendritic spines (Tang et al., 2014). Macroautophagy also drives the degradation of the scaffold proteins PSD95, PICK1 and SHANK3, and of AMPA receptors, leading to synapse destabilization (Compans et al., 2021; Nikoletopoulou et al., 2017; Shehata et al., 2012), and enables retrograde transport of brain-derived neurotrophic factor (BDNF) (Kononenko et al., 2017), a key molecule involved in neuronal differentiation, survival and synaptic plasticity.

The role of macroautophagy in synaptic plasticity has not been fully elucidated. Acute Beclin 1 knockdown revealed the need for macroautophagy induction to enhance activity-dependent plasticity changes in hippocampal neurons after chemical long-term potentiation (LTP) (Glatigny et al., 2019). Similarly, mice deficient in neuronal WIPI4 show attenuated hippocampal LTP (Zhao

et al., 2015). In contrast, suppression of macroautophagy is required for BDNF-induced LTP (Nikoletopoulou et al., 2017). During long-term depression, endocytic sorting and autophagy induction regulate the degradation of AMPA receptors (Ehlers, 2000; Shehata et al., 2012). Further studies are required to understand how macroautophagy regulates synaptic strength.

CMA plays an important role in maintenance of the neuronal proteome with higher propensity for aggregation. Acute silencing of LAMP2A in dopaminergic neurons leads to accumulation of α-Synuclein and ubiquitinated proteins, neurodegeneration, and ultimately behavioural impairments (Xilouri et al., 2016). Selective blockage of CMA in excitatory neurons leads to a shift in the solubility of the metastable proteome (proteins close to their solubility limit) (Bourdenx et al., 2021). Entrapment of CMA substrate proteins within aggregates leads to loss of their function and defects in cellular metabolism, endocytosis, and cytoskeleton organization (Bourdenx et al., 2021).

The tight communication between neurons and glia suggests that glial macroautophagy may have profound non-cell-autonomous effects on neuronal function and health. Astrocytes promote neuronal health and survival by providing nutrients, controlling the uptake of neurotransmitters and ions and protecting neurons upon injury. Astrocyte macroautophagy is emerging as an important pathway to support neuronal health by regulating the degradation of misfolded proteins (Janen et al., 2010; Tang et al., 2008) and damaged mitochondria from degenerating neurons (Davis et al., 2014; Morales et al., 2020).

Oligodendrocytes and Schwann cells are the myelin-producing cells of the central and peripheral nervous systems, respectively. Studies using mice lacking ATG5 in oligodendrocyte progenitor cells (OPC) demonstrated that macroautophagy is essential for OPC survival, maturation and proper myelination (Bankston et al., 2019). Similarly, Schwann cell-specific removal of ATG7 caused abaxonal accumulation of excess cytoplasm and organelles, as well as abnormal myelination (Jang et al., 2015), demonstrating that macroautophagy is essential for proper myelination and insulation of axons.

Microglia are the resident immune cells of the brain that constantly sense the neural environment and clear debris to maintain homeostasis (Nimmerjahn et al., 2005). Amyloid-β-induced neuroinflammation was aggravated upon microglial-specific deletion of ATG7, resulting in excessive neuronal damage (Cho et al., 2014), transition of microglia to a proinflammatory status, defects in lipid homeostasis and elevated tau spreading (Xu et al., 2021). Similarly, loss of

microglial ATG5 resulted in enhanced neuroinflammation and neurodegeneration in the striatum of conditional knock-out mice (Cheng et al., 2020), suggesting that microglial macroautophagy plays a protective role against aberrant microglial activation. Microglia have also been shown to be involved in synaptic pruning (Paolicelli et al., 2011). Neurons co-cultured with ATG7-deficient microglia showed increased synaptic markers and dendritic spine density, as well as in immature dendritic filopodia (Kim et al., 2017). However, ATG7 is also involved in LAP in peripheral macrophages (Heckmann et al., 2017), therefore further studies are required to determine whether deficiencies in macroautophagy or LAP are responsible for these disease changes. Interestingly, microglia from mice expressing human α-Synuclein in neurons engulf and sequester α-Synuclein by autophagosomes for degradation (Choi et al., 2020). Together these studies show the importance of functional macroautophagy in glia for neuronal function and viability.

Less is known about the function of CMA in glia. Neuronal CMA blockage is associated with astrocyte enlargement and microglial activation, most probably because of neuronal dysfunction (Bourdenx et al., 2021; Xilouri et al., 2016). Mice with full-body CMA blockage did not show overt astrogliosis or microglial activation (Bourdenx et al., 2021) but a functional study is lacking.

Autophagic processes and cell death pathways

Although removal of excessive neurons is important for the development of the nervous system, aberrant neuron death is one of the principal causes of neurological disorders. The cell death pathways that have been reported to interact with autophagy in the nervous system are discussed below.

Necrosis

Necrosis, characterised by plasma membrane rupture can be either regulated and genetically controlled, or unregulated (passive). Multiple types of regulated necrosis have been identified to cause neuronal cell death, including necroptosis, ferroptosis, pyroptosis and parthanatos (Fricker et al., 2018). Necroptosis is mediated by activities of receptor interacting protein kinase 1 (RIPK1), RIPK3, and mixed lineage kinase domain-like pseudokinase (MLKL) and has been reported to regulate axon degeneration induced by glutamate excitotoxicity and contribute to pathologies in conditions like ALS and AD (Degterev et al., 2019). P62 interacts with RIPK1 on early

autophagosome structures to form the necrosome and induce necroptosis in response to TNF-related apoptosis inducing ligand (TRAIL) in mouse prostate cells. Knockdown of P62 switches the cell death to TRAIL-induced apoptosis by blocking the formation of necrosome (Goodall et al., 2016).

Ferroptosis

Ferroptosis is an iron-dependent form of cell death which occurs when the phospholipid hydroperoxide (PLOOH) and lipid radicals overwhelm their scavenging systems. Agents that inhibit ferroptosis improve neuronal survival in multiple neurodegeneration models (Zheng and Conrad, 2020), and ferroptosis is involved in glial to neuron conversion after traumatic brain injury (Gascon et al., 2016). Macroautophagy promotes ferroptosis through ferritinophagy (Yang et al., 2019), since free iron is released from ferritin-bound iron via the lysosome. CMA also promotes ferroptosis by degrading glutathione peroxidase 4 (GPX4), which catalyses the reduction of lipid peroxides and prevents ferroptosis (Wu et al., 2019).

Apoptosis

BCL-family proteins stimulate or inhibit macroautophagy and apoptosis, and these activities are at the centre of the mutual regulation of these processes. Macroautophagy both positively and negatively regulates apoptosis through degradation of BCL-family proteins and their regulators (Fricker et al., 2018).

In neurons, BAX is the dominant executor of intrinsic apoptosis. P53 upregulated modulator of apoptosis (PUMA, also called BBC3) directly translocates BAX onto mitochondria in neuronal cells undergoing oxidative stress, thereby inducing apoptosis, a phenomenon that was rescued by PUMA knockout (Steckley et al., 2007). In HeLa cells, autophagy maintains low PUMA mRNA levels through an unknown mechanism (Thorburn et al., 2014). It is unclear whether similar regulation of PUMA exists in neuronal cells.

The extrinsic apoptosis pathway contributes to pathogenesis in neurological disorders. Neuronal specific deletion of caspase-8 renders neurons resistant to TNF-α ligation-induced apoptosis *in vitro* and increases neuron survival with reduced caspase-3 activation after acute brain injury (Krajewska et al., 2011). The induction of apoptosis in primary cortical neurons by the neurotoxin

6-hydroxydopamine (6-OHDA) was rescued by knockdown of ATG5 or macroautophagy inhibitor 3-methyladenine (Chung et al., 2018).

The relation between CMA and apoptosis has been mostly studied in cancer cells, where CMA prevents apoptosis through degradation of cyclin D1, PUMA or HMGB1, but facilitates immunogenic apoptosis by mediating surface exposure of calreticulin (reviewed in (Arias and Cuervo, 2020)). In untransformed cells, inhibition of CMA increases susceptibility to stressors and leads to apoptosis but the molecular mechanisms remain poorly understood.

Pyroptosis

Pyroptosis is a form of cell death seen in many common neurological diseases, like AD and PD, that manifests with inflammasome-mediated release of caspase 1 from affected cells. Macroautophagy activation protects against this form of cell death in mouse models via diverse pathways, including degradation of a key pyroptosis mediator NLRP3 (Wu et al., 2021). In this way, autophagy may also buffer neuroinflammation, a prevalent process in different neurodegenerative conditions.

Autophagic cell death and Autosis

Usually, macroautophagy promotes cell survival following stress/nutrient limitation by recycling cellular components and providing energy. However, in ischemia/hypoxia and stroke, macroautophagy has been reported to lead to cell death, termed autophagic cell death (ACD). The main morphology of ACD is accumulation of vacuoles with increased macroautophagy flux, and is rescued by knockdown or inhibition of autophagic proteins (Galluzzi and Green, 2019). However, much of the literature in this domain has caveats, including the use of imprecise chemical tools to manipulate autophagy, and difficulties measuring autophagic flux versus steady-state levels of autophagosomes *in vivo*. For example, autophagic flux can be impaired by defects downstream of autophagosome formation, which lead autophagosome accumulation. Furthermore, a reduction in cell death in such scenarios in macroautophagy knockout cells means that autophagy is required for the death process but not that autophagy is causing the cell death. To robustly support ACD, one needs to show a reduction of cell death when the flux is normalised, and not when it is ablated. Furthermore, some macroautophagy genes may have roles in cell death unconnected with their autophagic functions.

Interestingly, in all the ACD cases reported, inhibition of lysosome function fails to rescue cell death, suggesting that ACD may be an autophagy-independent pathway under the control of autophagy machinery. Moreover, no common upstream initiator-signalling pathway has been found (Galluzzi and Green, 2019).

Role of Different Autophagy Pathways in Enabling Neuronal Functions

Autophagy plays a role in the structural reorganisation of neuronal circuits via axonal growth, dendritic spine formation and pruning, synaptic assembly and vesicle turnover (Fleming and Rubinsztein, 2020; Kulkarni and Maday, 2018; Lieberman and Sulzer, 2019). These autophagy-driven structural changes have a major impact on neuronal function.

Learning and memory

In hippocampal neurons, macroautophagy is upregulated during learning and memory consolidation. Macroautophagy inhibition in the hippocampus of young mice affects their performance in different behavioural tests, indicating a deficit in the formation of novel memories (Glatigny et al., 2019). The mTORC1 complex is known to be over-activated in humans with fragile X syndrome (Hoeffer et al., 2012). In mouse models, this hyper-activation decreases macroautophagy, increases dendritic spine density with aberrant morphology and leads to exaggerated LTD in hippocampal neurons associated with impaired novel object recognition (Yan et al., 2018).

Since hippocampal macroautophagy declines with age, promoting macroautophagy has been investigated as a mechanism to improve memory in aged animals. Injection of plasma from young mice into older mice improves their memory in a macroautophagy-dependent fashion (Glatigny et al., 2019), likely via osteocalcin, a blood-brain barrier penetrant, bone-derived circulating molecule previously demonstrated to act as a hormonal regulator of hippocampal memory (Obri et al., 2018). However, upregulation of macroautophagy may not be a panacea for all memory deficits. For example, in primary neuron cultures, treatment with AICAR, a cell-permeable nucleoside used to induce AMPK hyper-activation, led to macroautophagy-dependent loss of pre- and postsynaptic markers and a decline in neuronal network function (Domise et al., 2019), suggesting that elevated macroautophagy may be as damaging as reduced autophagy and that maintaining the balance of autophagic flux is crucial.

Whole-body CMA-deficient mice have both memory and motor-coordination dysfunction, while blockage of CMA only in excitatory neurons resulted mostly in impaired short-term memory (Bourdenx et al., 2021).

Sleep and circadian rhythm

Many neurodegenerative disorders are associated with altered or poor sleep. Chronic sleep deprivation increases amyloid-β and tau in interstitial fluid and is associated with increased pathology in mouse models (Holth et al., 2019). Daily sleep–wake and feeding–fasting cycles are coupled to the central circadian clock in the suprachiasmatic nucleus. Circadian oscillations involve transcriptional circuits and non-translational controls, such as phosphorylation, which synchronize sleep/wake cycles, food intake and cellular bioenergetics (Reddy and Rey, 2014). Food intake occurs during wake cycles and autophagy is elevated during fasting (sleep). Recent work has shown that TFEB and TFE3 control the rhythmic induction of their transcriptional target genes involved in macroautophagy and lysosomal biogenesis during the light phase (sleep). Liver or muscle-specific knockouts of both TFEB and TFE3 in mice results in loss of the diurnal macroautophagy cycle. TFEB and TFE3 were shown to directly regulate the expression of Rev-erbα (Nr1d1), a transcriptional repressor component of the core clock machinery also involved in the regulation of whole-body metabolism and macroautophagy (Pastore et al., 2019).

A dual interplay between circadian rhythms and CMA has also been recently reported whereby CMA displays central and peripheral circadian activity and, at the same time, contributes to the regulation of circadian cycling through degradation of components of the clock machinery (Juste et al., 2021). Disruption of CMA *in vivo* and the subsequent impaired degradation by CMA of the positive elements Bmal1 and Clock and the regulatory element Rev-erbα, leads to temporal shifts and amplitude changes of the clock-dependent transcriptional program and fragmented circadian patterns. In contrast to the modulatory effect of TFEB on circadian cycling, the CMA-dependent regulation of the clock is nutrient-independent.

Suggested links with psychiatric diseases

Recent studies have provided some support for the hypothesis that altered neuronal macroautophagy may contribute to depression, bipolar disorder and schizophrenia. Autophagy-inducing drugs acting via independent pathways have antidepressant-like properties in mice (Kara

et al., 2018; Kara et al., 2013), and numerous clinically prescribed anti-depressants with diverse pharmacological activities enhance macroautophagy (reviewed in Gassen and Rein, 2019). Although there has been little human clinical research to support these findings, therapeutic concentrations of paroxetine and amitriptyline increase expression of macroautophagy components (Beclin1, phosphor-AKT, LC3II) in blood cells of patients and these changes predict clinical improvement (Gassen et al., 2014). Similarly, in a small study in patients with major depressive disorder, serum levels of Beclin 1 were higher in responders to selective serotonin reuptake inhibitors than non-responders (He et al., 2019).

A smaller but growing body literature provides some support for a link between autophagy and schizophrenia. When mutated, Disrupted-in-Schizophrenia 1 (DISC1) confers susceptibility to psychiatric illness. DISC1 contains an LC3-interacting region (LIR) motif and, when over-expressed, enhances mitophagy (Wang et al., 2019b). In post-mortem samples, transcriptomic analysis revealed over-representation of genes that regulate altered neuronal macroautophagy with down-regulation of expression observed in cortical and hippocampal areas in schizophrenic patients (Ryskalin et al., 2018). In addition, exome sequencing identified four rare ULK1 variants significantly associated with schizophrenia in a case-control study (Al Eissa et al., 2018).

Ageing

Ageing is a major risk factor for human neurodegenerative disease. Autophagy appears to decline with age in many organisms (Hansen et al., 2008). Age-dependent decreases have been reported for macroautophagy gene transcripts in brains from *Drosophila* (Simonsen et al., 2008) and humans (Lipinski et al., 2010), in mouse retinas (Rodriguez-Muela et al., 2013), and in autophagy proteins in mouse hypothalamus and hippocampus (Glatigny et al., 2019; Kaushik et al., 2012). Changes in lysosomal abundance with age have been extensively documented in multiple peripheral tissues in different experimental models (reviewed in (Nixon, 2020), but expansion of these compartments with age is not a universal feature, since recent studies in *C. elegans* have revealed age-dependent decreases in lysosome and autophagosome abundance in tissues, such as intestines, muscles and neurons (Chang et al., 2017). This decrease in abundance could explain the reported decreased macroautophagic activity in aged *C. elegans* (Wilhelm et al., 2017) and it is consistent with the decline in autophagy flux and autophagosome biogenesis observed in mouse brains (Park, 2021). The progressive decline in macroautophagy with age can predispose to toxic

protein and organelle accumulation in neurons and compromise neuronal health. Indeed, impairing autophagy reduces lifespan in *C. elegans*, *Drosophila* and mice, while induction of macroautophagy extends longevity in these organisms (Hansen et al., 2018).

CMA activity decreases with age in most organs and tissues, predominantly due to reduced stability of LAMP2A at the lysosomal membrane of old organisms (Kaushik et al., 2021). In peripheral tissues, reduced CMA with age contributes to loss of proteostasis, metabolic derangements, immune senescence and loss of stemness, all considered hallmarks of aging. Conversely, genetic restoration of the LAMP2A defect in old organisms has proven sufficient to prevent proteotoxicity, improve the organismal response to stress and restore organ function (Kaushik et al., 2021). Although changes in CMA activity with age in neurons are still poorly characterized, elevated levels of neuronal nitric oxide synthase, previously associated with neuronal aging, have demonstrated sufficient to reduce neuronal LAMP2A levels (Valek et al., 2019).

Most studies on autophagy in the aging brain have followed changes on steady-state markers due to the difficulties of measuring autophagy flux in live organisms. The development of mouse models constitutively expressing fluorescent probes to follow bulk macroautophagy (Lopez et al., 2018), selective macroautophagy (mitophagy, (Sun et al., 2015), or CMA (Dong et al., 2020) opens up the possibility of tracking changes in the dynamics of these processes with age. For example, studies in a mitophagy reporter mouse have demonstrated reduced mitophagy flux in aged hippocampal pyramidal neurons (Sun et al., 2015).

C. Autophagy pathways and neurodegenerative diseases

Mutations in genes encoding proteins involved at all steps in the macroautophagy pathway are implicated in different neurodegenerative diseases. Often, one mutation can affect macroautophagy at multiple stages. This section describes defects associated with selected important examples, while Table 1 summarises a more comprehensive, although not exhaustive, list of autophagy-related genes associated with neurodegenerative disorders and the autophagic disruption caused by some common neurodegenerative disease genes is summarised in Fig. 4. We have not reviewed all neurodegenerative disease genes causing autophagy defects in the text, as extensive reviews have been published previously (Menzies et al., 2017; Stamatakou et al., 2020).

Mutations in core autophagy genes

Mutations in core macroautophagy genes have been identified in relatively few human neurodegenerative diseases. This may be because core macroautophagy components are vital for cellular homeostasis and may cause early lethality if mutated. A recent study identified recessive mutations in *ATG7* in 12 patients from 5 families with a range of neurodevelopmental disorders affecting the cerebellum and corpus callosum with additional muscle, and endocrine involvement as well as facial dysmorphism. While fibroblasts from one family had no obviously detectable LC3-II, those from other families showed LC3-II conjugation, indicative of functional autophagy. Furthermore, in the family where no LC3-II was detected, autophagosomes were evident in muscle biopsies (Collier et al., 2021). Hence, further analysis is needed to determine whether the mutations result in a complete loss-of-function and whether there is compensation from non-canonical autophagy. Homozygotes with a mutation in *ATG5* (E122D) manifest with childhood ataxia and cells derived from these patients display decreased autophagic flux and reduced conjugation of ATG12 to ATG5 (Kim et al., 2016). X-linked dominant mutations in another core autophagy gene, *WDR45* (encoding protein WIPI4) cause human β-propeller protein-associated neurodegeneration (BPAN) mainly in females (Saitsu et al., 2013) and in patient-derived lymphoblastoid cells, decreased stability of WIPI4 and accumulation of aberrant early autophagic structures were observed. An autosomal recessive missense mutation in WIPI2 results in severe syndromic cognitive impairment and loss of brain volume (Jelani et al., 2019).

Mutations in genes involved in early stages of autophagosome formation

Several neurodegenerative disease-causing mutations have been identified in genes involved in membrane trafficking events required for autophagosome biogenesis. A mutation in VPS35 (D620N), a core retromer component, has been described in Parkinson's disease (PD) patients and in subsequent studies was shown to cause ATG9 mislocalization (Zavodszky et al., 2014; Zimprich et al., 2011). Similarly, an ATG9 trafficking defect was observed in cells derived from patients with early-onset progressive spastic paraplegia (SPG47 & SPG52) which are deficient for AP-4 pathway function (Davies et al., 2018).

Mutations in genes involved in substrate recognition and selective autophagy

Mutations in the autophagy receptor P62 have been identified in cases of familial and sporadic amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) (reviewed in (Deng et al., 2017), leading to disrupted degradation of SOD1 and TDP-43 (Gal et al., 2009).

Mutations in FAM134B (also called RETREG1), an ER-phagy receptor, cause hereditary sensory and autonomic neuropathy type II (HSAN II) and compromise ER-phagy, leading to ER expansion (Bhaskara et al., 2019; Khaminets et al., 2015)**.** Mutations in ATL3 that cause hereditary sensory and autonomic neuropathy type I (HSAN I) impair starvation-induced ER-phagy through direct disruption of the association of ATL3 with GABARAP (Chen et al., 2019)**.**

OPTN mutations inhibit its ability to recruit LC3 to damaged mitochondria and to induce mitophagy (Shen et al., 2015; Wong and Holzbaur, 2014a), and ALS-associated mutations in this kinase reduce binding of TBK1 to OPTN therefore decreasing mitophagy (Richter et al., 2016).

Mutations in genes involved in autophagosome trafficking, maturation and fusion with lysosomes

Autophagosomes generated in axons rely on retrograde transport to fuse with perinuclear lysosomes. Therefore, neurons are particularly vulnerable to disruption in trafficking. Dynein–dynactin is a molecular motor required for fast retrograde transport of autophagosomes, organelles, RNAs and proteins along microtubules and is the target of mutations causing axonal Charcot-Marie-Tooth hereditary neuropathy type 2 (CMT2) and ALS (Puls et al., 2003). Defects in trafficking have also been associated with disease-causing mutations in α-Synuclein (PD), *C9ORF72* (ALS) and with hyperphosphorylated tau (seen in tauopathies, see section D).

Fusion events required for autophagosome maturation involve many components of the endocytic pathway, such as the small GTPase RAB protein family. Mutations in *RAB7*, encoding the late endosomal RAB7A protein, cause Charcot–Marie–Tooth type 2B disease (Verhoeven et al., 2003). Similarly, mutations in a RAB5 regulatory protein Alsin, can result in recessive ALS (Yang et al., 2001). ALS can be also caused by mutations in *CHMP2B*, one of the subunits of the ESCRT-III complex, which impair autophagosome maturation (Filimonenko et al., 2007; Lee et al., 2007). Disruption to the ESCRT machinery may also interfere with eMI by disrupting proper LE/MVB biogenesis.

Mutations in genes involved in lysosomal function

Macroautophagy completion requires lysosomal digestion of autophagic cargo and subsequent release of recycled metabolites. The degradative capacity of lysosomes depends on low pH, which is mediated by vacuolar ATPase (vATPase). Mutations in genes associated with familial forms of neurodegeneration, such as *PSEN1* (AD) (Lee et al., 2010), α-Synuclein (Decressac et al., 2013) and *ATP13A2* (PD) (Bento et al., 2016; Dehay et al., 2012) affect lysosomal pH. Following autolysosome fusion and cargo degradation, lysosomes undergo a process called reformation. SPG11 and SPG15, encoded by genes mutated in hereditary spastic paraplegia, have been implicated in this process and loss of SPG11 or SPG15 result in the depletion of lysosomes capable of fusing with maturing autophagosomes (Vantaggiato et al., 2019).

Mutations in genes involved in CMA

Loss-of-function mutations in *LAMP2* cause Danon disease that manifests with cardiomyopathy, myopathy, variable mental retardation and with progressive retinal degeneration (Cenacchi et al., 2020). Most mutations in this disease occur in the part of the gene common to all spliced LAMP2 protein variants. Since only the LAMP2A splice variant of this gene is required for CMA, whereas the other variants LAMP2B and LAMP2C contribute to macroautophagy and lysosomal degradation of DNA and RNA, respectively, the mutations will cause defects in multiple types of autophagy. Interestingly, expression of each of the *LAMP2* proteins has been shown to be differentially affected in PD patients brains, with the earlier changes occurring in LAMP2A (Sala et al., 2016). However, further studies on the mechanism that regulate splicing of this gene are needed to determine whether these differences are linked to specific gene mutations. Further studies are also needed for the heterozygous variant in the *LAMP2* gene promoter that significantly reduces *LAMP2* transcription in a PD patient (Sala et al., 2016). Mutations in different proteins related to PD and frontotemporal dementia associated with reduced CMA activity are summarized in Table 2.

D. Polygenic diseases

Tauopathies and AD

Tauopathies are characterized by the intracellular accumulation and aggregation of tau into paired helical filaments and neurofibrillary tangles and include frontotemporal dementias (FTDs), AD, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).

Multiple studies demonstrate the roles of different types of autophagy in the degradation of tau. Tau colocalises with LC3 and P62 in post-mortem brains of familial AD, CBD, and PSP patients and the expression of P62 is reduced in AD patients (Liu et al., 2017). Tau associates with the autophagy cargo receptors NDP52 and OPTN, which also colocalize with neurofibrillary tangles and dystrophic neurites in AD patients (Osawa et al., 2011; Xu et al., 2019). Clearance of tau variants associated with different tauopathies occurs via different autophagic routes (Caballero et al., 2018). For example, phosphorylation of tau inhibits its degradation by macroautophagy and results in tau clearance via an endolysosomal pathway dependent on ESCRT complex and the small GTPase RAB35 (Vaz-Silva et al., 2018). About 50% of tau is degraded by macroautophagy and the other 50% is degraded by non-macroautophagy pathways (CMA and eMI) (Caballero et al., 2021). Interestingly, tau acetylation, a pathological post-translational modification, and pathogenic mutations, such as the FTD-related mutation A152T, favor tau degradation by macroautophagy, whereas the P301L mutation reduces overall tau degradation (Caballero et al., 2018).

Compromised removal by CMA of pathogenic forms of tau, including both mutant and post translationally modified, is further aggravated by the toxic effect that these proteins exert on this process. *In vivo*, expression of pathogenic tau protein is sufficient to induce neuronal- (but not astrocytic) specific inhibition of CMA (Bourdenx et al., 2021). Although direct evaluation of CMA activity in human brain in a cell-type specific manner is not currently possible, analysis of the transcriptional expression of the components of the CMA network in the brain of AD patients using single-nuclei RNAseq demonstrated a neuronal specific transcriptional inhibition of CMA (Bourdenx et al., 2021) that correlated with the Braak stages of tau pathology. The reduction of CMA score was higher in excitatory than in inhibitory neurons, thus corresponding well with the higher vulnerability to tau pathology of excitatory neurons.

The mechanisms behind tau's toxicity on CMA are under investigation, but at least for acetylated and P301L tau, translocation of these proteins through the LAMP2A multimeric complex is compromised due to loss of their pH-dependent interaction with luminal HSC70 (Caballero et al.,

2021). Persistent occupancy of the CMA translocation complex by pathogenic tau blocks degradation of other CMA substrates. Interestingly, this dependence on lysosomal pH for uptake through CMA, so far only described for tau, explains tau's highly efficient degradation by this pathway (Caballero et al., 2021) and highlights that the reported impaired lysosomal acidification in some forms of familial AD could also lead to reduced tau degradation by CMA (Wolfe et al., 2013).

Tau can also be a substrate of KFERQ-selective eMI, although, as is the case for CMA, pathogenic tau mutations and posttranslational modifications inhibit eMI activity at different stages (i.e. substrate binding to LE/MVB, internalization or degradation in the lumen) (Caballero et al., 2018). As different types of autophagy can clear tau, this enables re-routing of this aggregate-prone protein from one autophagy type to another when one of these routes is compromised. For example, acetylated tau can be re-routed to eMI for degradation when CMA is inhibited (Caballero et al., 2021). This re-routing of acetylated tau to eMI can lead to its extracellular release in exosomes through fusion of LE/MVBs with the plasma membrane (Caballero et al., 2021). This may provide a mechanism to remove toxic products, such as acetylated tau, from neurons when they are unable to be degraded (Perez et al., 2019) but may also contribute to disease progression through extracellular release of pathogenic tau (Caballero et al., 2021). The factors that determine whether the eMI re-routed protein is degraded in LE/MVB or released extracellularly remain unknown.

AD, the most common tauopathy and neurodegenerative disorder, is characterized by the accumulation of intracellular tau tangles, and extracellular amyloid-β deposits (Aβ plaques). Macroautophagy has been implicated in the production of amyloid-β within the autophagic vesicles and its secretion to the extracellular matrix, contributing to plaque formation *in vivo* in mice and *Drosophila* models of amyloid toxicity (Yu et al., 2004). Levels of Beclin 1 are decreased in patients with AD at early stages (Lachance et al., 2019), whereas Beclin 1 overexpression reduced amyloid aggregation in a mouse model of AD (Pickford et al., 2008). Microglial Beclin 1 modulates the inflammatory response in *Becn1*$^{+/-}$/APPPS1 mice (Houtman et al., 2019) and microglial amyloid-β removal and phagocytosis is significantly impaired in Beclin 1$^{+/-}$ mice (Lucin et al., 2013). Amyloid-β proteins also induce the accumulation of deficient mitochondria, driven by the depletion of cytosolic Parkin and PINK1 accumulation, resulting in defective mitophagy

(Cummins et al., 2019; Fang et al., 2019). TREM2, an inflammation-linked risk factor for late-onset AD (Jonsson et al., 2013), is also associated with mTOR pathway dysregulation in AD, where there is also downregulation of the Beclin 1-PI3K and ULK1/2 complexes (Lachance et al., 2019).

Brains from AD patients show a selective loss of nuclear TFEB in the hippocampus, negatively correlating with the severity of the neuropathology and reduced expression of TFEB target genes is also observed in AD patient fibroblasts and iPSC-derived human AD neurons (reviewed in (Cortes and La Spada, 2019).

Familial AD and genetic risk factors

Mutations in the genes encoding amyloid precursor protein (*APP*) and presenilin (*PSEN*) cause autosomal dominant early-onset forms of AD (reviewed in Raybould and Sims, 2021). *PSEN1* mutations increase lysosomal pH by deregulating the maturation of lysosomal v-ATPase and consequently reduce autophagic cargo degradation (Nixon, 2013). The APOE4 allele, involved lipid trafficking and metabolism, is the most common AD genetic risk factor (Bu, 2009). APOE4 carriers have more pronounced reductions in LC3, P62 and LAMP1 compared to APOE3 carriers (Parcon et al., 2018). In astrocytes from mice expressing human APOE4 variant, autophagosome formation and cargo degradation were defective (Simonovitch et al., 2016). Levels of phosphatidylinositol biphosphates, essential for autophagic function, are reduced in post-mortem human brain tissues of APOE4 carriers (Dall'Armi et al., 2013) and in primary neurons and astrocytes derived from knock-in mice expressing human APOE4 (Zhu et al., 2015). APOE4 may also affect the expression of *P62*, *LAMP2* and *MAP1LC3B* by competing with TFEB for the binding to the CLEAR domains in their promoters (Parcon et al., 2018).

The impairment of macroautophagy in AD may also be a consequence of variants in genes with a functional role in macroautophagy, such as SORL1, PICALM and PLD3 (see Table 1 for wildtype function). Reduced levels of SORL1, which regulates protein trafficking between the trans-Golgi network, are observed in iPSC-derived neurons from AD patients (Hung et al., 2021). Phosphatidylinositol Binding Clathrin Assembly Protein (PICALM) identified in a GWAS study in a locus associated with AD risk, is abnormally cleaved in AD brains and its levels inversely correlate with LC3-II and Beclin 1 levels. In addition, alternative splicing of the protein correlates

with tau aggregation and Braak stages (Raj et al., 2018). PICALM regulates endocytosis of critical SNAREs involved in both autophagosome biogenesis and degradation (Moreau et al., 2014).

The link between macroautophagy and AD is further supported by several genetic studies that associate autophagy-related genes with AD. Pathway enrichment algorithms analysing the data from three GWAS studies found an enrichment in autophagic and endolysosomal genes associated with genetic variants that increase risk of AD (Gao et al., 2018).

Gradual loss of CMA with age may also become a risk factor for AD. Thus, CMA blockage in a mouse model of AD accelerated tau phosphorylation and aggregation, tau propagation, and amyloid-β extracellular deposition (Bourdenx et al., 2021; Caballero et al., 2021). CMA deficiency increases similarity between the proteomes of brains from mouse model of disease and AD patients, thus mimicking part of the disease usually missing in conventional models (Bourdenx et al., 2021).

Although much interest has been focused on extracellular fragments (amyloid-β 40 and 42), the C-terminal fragment (CTF) of APP (C99 – originating from β-secretase cleavage) induces autophagy-lysosome impairments independently of amyloid-β accumulation (Lauritzen et al., 2016). Interestingly, APP CTFs contain a KFERQ motif (^{763}KFFEQ^{768}) that could be utilized for its degradation through CMA or eMI (Park et al., 2016a). Consistent with that notion, CMA blockage in a genetic AD mouse model caused CTF accumulation (Bourdenx et al., 2021).

Parkinson's disease (PD)

PD is characterized by the loss of dopaminergic neurons in the substantia nigra, the presence of intraneuronal inclusions (Lewy bodies, LBs) in neuronal soma and neurites enriched with filamentous forms of α-Synuclein (Spillantini et al., 1997).

α-Synuclein has been proposed to play roles in synaptic function, its levels are a major determinant of PD severity, and multiplications of the *SNCA* (α-Synuclein -encoding) locus cause autosomal dominant forms of PD. α-Synuclein can be cleared by the proteasome, macroautophagy and CMA (Cuervo et al., 2004; Webb et al., 2003). α-Synuclein accumulation compromises autophagic flux, as the presence of inclusion bodies containing α-Synuclein impairs autophagosome maturation and fusion with lysosomes (Tanik et al., 2013). Indeed, disruptions in the macroautophagy machinery

appear to be central to PD pathogenesis, with different PD-causing mutations affecting various stages of the autophagy itinerary (Karabiyik et al., 2017).

α-Synuclein overexpression in mammalian cells and transgenic mice compromises autophagosome biogenesis by inhibiting the GTPase RAB1 leading to mislocalisation of ATG9 (Winslow et al., 2010). The expression of mutant α-synuclein (A53T) leads to an accumulation of mitochondria-containing autophagosomes in PC12 cells (Stefanis et al., 2001), and to increased autophagosomal engulfment of healthy, polarized mitochondria in primary neurons, causing an abnormal clearance of functional mitochondria and therefore, a bioenergetic deficit (Choubey et al., 2011). In addition, results from *Drosophila* suggest that α-Synuclein expression impairs the autophagic flux in ageing adult neurons by disrupting the F-actin cytoskeleton (Sarkar et al., 2021).

Although CMA contributes to clearance of α-Synuclein in primary cultured cells and *in vivo* (Cuervo et al., 2004), pathogenic A53T and A30P mutant α-Synuclein proteins are still targeted by HSC70 to lysosomes, but their abnormally enhanced interaction with LAMP2A and their oligomerization at the lysosomal membrane disrupt the CMA translocation complex and block CMA of other substrate proteins (Cuervo et al., 2004). CMA malfunction is not restricted to familial PD, as post-translational modifications on α-Synuclein can also compromise its CMA degradation (Martinez-Vicente et al., 2008). While phosphorylation and covalent oligomerization mask the KFERQ-like motif in α-Synuclein (Kirchner et al., 2019) and disrupt its targeting to lysosomes, dopamine oxidation leads to formation of α-Synuclein-dopamine adducts that are still targeted to lysosomes where they disrupt CMA through similar mechanisms as the α-synuclein mutants (Martinez-Vicente et al., 2008).

Alterations in CMA-related proteins have been reported in the brains of familial and idiopathic PD patients. Reduced levels of LAMP2A and HSC70 in the substantia nigra and amygdala of PD brains occur early in the disease and correlate with α-Synuclein accumulation (Scrivo et al., 2018). Reduced mRNA levels for both proteins suggest that downregulated transcription, in addition to the physical blockage of CMA, may both contribute to compromised CMA in PD. This reduced CMA in the PD brain has a negative impact in neuronal survival, in part, by reducing degradation of the transcription factor MEF2D, normally degraded by CMA. Accumulation of the inactive form of MEF2D prevents its protective function in these cells (Yang et al., 2009). The relation between PD and eMI has not been directly analysed, but a recent study showing that a mutated

form of α-synuclein accumulates in the LE/MVB and is secreted in exosomes (Stykel et al., 2021), opens the possibility of a rerouting of α-Synuclein from CMA to eMI, similar to the one described for tau upon CMA blockage (Caballero et al., 2021).

Increasing evidence suggests that other mutations causing familial PD also affect autophagic function. In an autosomal dominant form of PD, a mutation (D620N) in the vacuolar protein sorting 35 (VPS35), a component of the retromer complex, impairs macroautophagy (see Table One). Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are responsible for most autosomal dominant PD cases, increase phosphorylation of different RAB GTPases (Alessi and Sammler, 2018) and disrupt endosome-to-lysosome trafficking. While the most common mutation (G2019S) has been associated with a reduction of macroautophagy flux (Henry et al., 2015; Wallings et al., 2019), LRRK2 deletion in neurons increases both macroautophagy (through the regulation of p62 phosphorylation) and lysosomal degradation (Park et al., 2016b; Wallings et al., 2019). Contrary to this proposed inhibitory role of LRRK2 in neurons, overexpression of LRRK2 in microglial cells increased macroautophagy flux, while LRRK2 silencing reduced degradation (Wallings et al., 2019). Furthermore, the effect of LRRK2 may also differ depending on the type of autophagy. Thus, the LRRK2 G2019S mutant was also suggested to induce mitophagy in multiple studies by causing calcium imbalance, resulting in mitochondrial depolarization (Cherra et al., 2013).

Heterozygous mutations in the gene encoding the lysosomal enzyme *glucocerebrosidase 1 (GBA1)* are amongst the most common genetic risk factors for PD. iPSC-derived neurons from PD patients with *GBA1* mutations showed increased α-Synuclein levels, macroautophagy and lysosomal defects, including impaired fusion between autophagosomes and lysosomes (Schöndorf et al., 2014), further corroborated in neuroblastoma cells with nonsense mutations in *GBA1* (Bae et al., 2015) and in GBA1-deficient cells (Magalhaes et al., 2016).

Mutations in *ATP13A2/PARK9*, which encodes a transmembrane lysosomal P-type ATPase polyamine transporter, cause familial Kufor-Rakeb syndrome with early-onset Parkinsonism and impairs lysosomal function (Dehay et al., 2012). Loss of ATP13A2 causes α-Synuclein accumulation in mammalian cells and in *C. elegans* (Karabiyik et al., 2017) and *in vitro,* depletion leads to a decrease in the levels of synaptotagmin 11 (SYT11), another PD-associated gene (Bento et al., 2016). Overexpression of SYT11 rescues the macroautophagy defects observed in

ATP13A2-depleted cells, implying that the two proteins lie within the same pathway (Wang et al., 2019a). ATP13A2 also recruits the histone deacetylase 6 (HDAC6) to lysosomes to deacetylate a protein implicated in autophagosome-lysosome fusion, cortactin, resulting in increased fusion and autophagy flux (Borsche et al., 2020).

Autosomal recessive mutations in *PTEN-induced kinase 1* (*PINK1 or PARK6*) and *Parkin* (*PARK2*), key regulators of a form of mitophagy, have been discussed above. Low CMA activity in PD has also been linked to alteration of mitochondria dynamics. Failure to degrade PARK7/DJ1 through CMA leads to its accumulation, disruption of mitochondrial homeostasis and cell death (Wang et al., 2016). Similarly, MARCHF5, an E3 ubiquitin ligase required for mitochondrial fission, is a CMA substrate that upon CMA blockage gets stabilized, increasing mitochondrial fission and altering mitochondrial homeostasis. Overexpression of LAMP2A in a 6-OHDA PD mouse model was sufficient to rescue its phenotype (Nie et al., 2020).

The reported interaction between UCH-L1 with LAMP2A, HSC70 and HSP90 is abnormally enhanced in the case of the PD-related UCH-L1 I93M mutant and results in reduced degradation of proteins, including α-Synuclein via CMA (Scrivo et al., 2018). Similarly, although a fraction of cellular LRRK2 undergoes degradation via CMA, mutant forms of LRRK2 block the formation of the LAMP2A translocation complex and degradation of other proteins through CMA (Orenstein et al., 2013). In other instances, reduced CMA by PD-related pathogenic proteins is a consequence of a more general effect in the lysosomal compartment. This occurs with VPS35, whose deficiency or mutant form D620N reduces lysosomal levels of LAMP2A through its inefficient retrieval from the Golgi (Scrivo et al., 2018). Reduced enzymatic activity of GBA1 reduces lysosomal levels of LAMP2A (Murphy et al., 2014), likely by inducing changes in the lipid composition of the lysosomal membrane associated with increased levels of cathepsin A, the enzyme that triggers LAMP2A degradation in lysosomes (Kaushik and Cuervo, 2018). A similar destabilizing effect on lysosomal LAMP2A has been described for the loss of function mutants of PARKK7/DJ1, although the mechanism behind this effect remains unknown (Xu et al., 2017).

ALS

Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease characterised by upper and lower motor neurons (MNs) degeneration. While 90% of all ALS cases

are sporadic (sALS), around 10% are due to a genetic mutation. To date, more than 20 genes have been associated with ALS (Mathis et al., 2019), including *C9ORF72*, TAR DNA binding protein (*TARDBP/TDP-43*), P62 (*SQSTM1*), TANK binding kinase 1 (*TBK1*), and optineurin (*OPTN*), whose mutations can result in autophagy and mitophagy defects, and the accumulation of protein inclusions in familial ALS (fALS) patients.

Hexanucleotide repeat expansions (HREs) in the 5' non-coding sequence of the *C9ORF72* gene have been identified as the most common cause of fALS and frontotemporal dementia due to loss-of-function or gain-of-function through three possible mechanisms: (1) haploinsufficiency, (2) repeat associated non-AUG (RAN) translations creating toxic dipeptide repeat (DPR) proteins and (3) sequestration of RNA-binding proteins (RNPs) through generation of RNA foci involving the *C9ORF72* HRE RNA (Wen et al., 2017). While the first mechanism results from loss-of-function, the latter two mechanisms are considered toxic gain-of-function.

Although protein levels of C9ORF72 are reduced by 10-75% in post-mortem tissues, a significant reduction of *C9ORF72* expression is not observed in patient-iPSC-derived MNs (Renton et al., 2011). LC3-II levels are decreased in C9ALS- patient-iPSC-derived neurons but silencing of *C9ORF72* enhances autophagy via inhibition of mTOR activity and elevation of TFEB levels (Ugolino et al., 2016). C9ORF72 forms a stable complex with two proteins, the Smith-Magenis syndrome chromosome region, candidate 8 (SMCR8) and the WD repeat-containing protein 41 (WDR41). C9ORF72-SMCR8 recruits ULK1 complexes on phagophores in a RAB1A-dependent manner and deficiency of C9ORF72 causes a decrease in ULK1 protein, compromising the initiation of autophagy (Pang and Hu, 2021). The sense repeat RNA of *C9ORF72* results in the accumulation of nuclear and cytoplasmic RNA foci, the latter resulting in the formation of stress granules (SG) (Mizielinska et al., 2013). Wild-type C9ORF72 lowers SGs via autophagic degradation by cooperating with P62 (Chitiprolu et al., 2018). Overall, a reduction of autophagic activity caused by *C9ORF72* loss-of-function results in the accumulation of TDP-43, DPR, and SGs which would otherwise be eliminated by autophagy.

The accumulation of TDP-43 is frequently seen in ALS and is also mutated in some cases. Knockdown of *TDP-43* impacts autophagy at multiple steps, such as downregulation of ATG7 and reduction of dynactin subunit 1 expression resulting in an overall inhibition of autolysosome formation and impaired autophagic flux (Xia et al., 2016). Mutations of OPTN and TBK1 observed

in ALS patients prevent ubiquitin binding to OPTN and OPTN binding to TBK1, respectively, compromising mitophagy (Evans and Holzbaur, 2019).

Although few studies have investigated the status of other autophagic pathways in ALS, growing evidence supports possible involvement of CMA failure on ALS disease progression. Inhibition of CMA results in the accumulation of the truncated form of TDP-43 leading to TDP-43 aggregation (Scrivo et al., 2018). Furthermore, TDP-43 aggregates (but not overexpressed soluble TDP-43) promote transcriptional upregulation of LAMP2A and HSC70, which has been interpreted as a possible early protective mechanism against TPD-43 mediated proteotoxicity. However, as TPD-43 aggregation persists, the associated lysosomal damage may likely lead to CMA failure (Scrivo et al., 2018). Interestingly, intrabody-mediated targeting of misfolded TDP-43 protein to CMA has proven effective in reducing TDP-43 aggregates and decreasing neurotoxicity (Tamaki et al., 2018).

CMA has also shown to contribute to degradation of the ubiquitin-like protein, ubiquilin-2, which is mutated in forms of ALS and ALS-like dementia. Physiological clearance by CMA of ubiquilin-2, a known regulator of macroautophagy, has been proposed to contribute to the crosstalk between the two autophagic pathways (Rothenberg et al., 2010). However, expression of mutant *UBQLN2*^{P497H} in neuronal cells is associated with reduced expression of LAMP2A in the ventral horn of the spinal cord and its accumulation in ubiquilin-2-positive inclusions (Chen et al., 2018).

A still poorly explored change in ALS, but with the potential of linking this condition with CMA and KFERQ-selective eMI, is the sequestration of HSC70 mRNA into inclusions resulting from overexpression of either TDP-43 or C9orf72 (Coyne et al., 2017). Lower levels of HSC70 protein have also been noted in peripheral blood mononuclear cells from sporadic ALS patients. and silencing of *HSC70* in neuroblastoma cell line is sufficient to precipitate formation of TDP-43 aggregates (Arosio et al., 2020). Although the multiplicity of intracellular functions of HSC70 precludes the ability to exclusively attribute these changes in proteostasis to defective CMA or eMI, these findings should generate future interest in exploring the status of both pathways in ALS.

E. Therapeutic Strategies

A number of drug-like small molecules and genetic tools upregulate macroautophagy and ameliorate pathologies in cellular and animal models of different neurodegenerative diseases (reviewed in (Lee et al., 2018; Li et al., 2014; Menzies et al., 2017). Here, we will focus on more recent developments and also consider other types of autophagy.

Macroautophagy targeting

L-type Ca^{2+} channel blockers, such as felodipine, enhance macroautophagy in mouse neurons (Siddiqi et al., 2019). Felodipine has good brain penetration, enhances macroautophagy flux in the brain and was found to reduce mutant huntingtin aggregates a Huntington's disease (HD) mouse model and to ameliorate motor phenotypes. Felodipine administered to mimic the plasma concentration of humans taking the drug for hypertension, reduced levels of insoluble A53T α-Synuclein, and ameliorated neurodegeneration and motor phenotypes in a PD mouse model (Siddiqi et al., 2019).

Lonafarnib, a brain-penetrant farnesyltransferase-inhibitor reduced levels of pathogenic tau and ameliorated brain shrinkage and behavioural abnormalities in a tauopathy mouse model, likely through inhibition of the GTP-binding protein Rhes (Hernandez et al., 2019).

Genetic deletion of the mGluR5 receptor reverses disease pathology in Q111 mHtt knockin mice (HD model) (Ribeiro et al., 2014). CTEP, a well-characterised, potent, CNS penetrant mGluR5 negative allosteric modulator, facilitated autophagy-dependent clearance of the huntingtin aggregates and improved motor deficits and cognitive impairment in an HD mouse model (Abd-Elrahman and Ferguson, 2019).

The D_2/D_3 dopamine receptor (DR) agonist pramipexole promotes macroautophagy in cell culture by enhancing *Beclin 1* transcription (Wang et al., 2015), and ameliorates disease in the R6/1 HD mouse model where it increased LC3-II and decreased p62 in the striatum (Luis-Ravelo et al., 2018).

PPARα agonists, gemfibrozil and Wy14643, which induce macroautophagy in cellular models via PPARα, reduce soluble amyloid-β levels in the cortex and hippocampus of an AD mouse model, induce macroautophagy and improve behavioural deficits (Luo et al., 2020).

Rapid progress has been made developing small molecules such as molecular glues, that stabilise protein-protein interactions (Schreiber, 2021) and bifunctional molecules, like PRoteolysis TArgeting Chimeras (PROTACs) that degrade proteins by forcing their interaction with a ubiquitin E3 ligase that ubiquitinates the target enabling its subsequent proteasomal clearance (Paiva and Crews, 2019). Similar approaches have been developed for macroautophagy. Molecules dubbed AuTophagosome-TEthering Compounds (ATTECs) bind both LC3 and mHTT to target the mutant protein to phagophores for macroautophagic degradation (Li et al., 2019c) (Fig. 5). Such ATTECs can lower levels of mutant but not wild-type huntingtin, and ameliorate disease in an HD mouse model (Li et al., 2019c).

Chimeric molecules called AUTACs (AUtophagy TArgeting Chimera) (Takahashi et al., 2019) utilize endogenous tagging by S-guanylation of cysteine residues by 8-nitro-cGMP tag to trigger ubiquitination and then macroautophagic clearance. AUTAC molecules consist of Cys-S-*p*-fluorobenzylguanine (dubbed FBnG), a mimetic of Cys-S-cGMP with improved physicochemical properties, attached to a target-specific ligand via a polyethylene glycol (PEG) linker (Fig. 5). The approach was extended to mitophagy of fragmented mitochondria through the generation of AUTAC4 in which the FBnG is attached to a warhead binding to the mitochondrial translocator protein (TSPO). AUTAC4 promoted mitophagy, reduced apoptosis and maintained levels of intracellular ATP when mitochondrial fragmentation was induced.

Clinical trials of autophagy-enhancing drugs for neurodegeneration are relatively rare. Much of the effort to-date has focused on repurposing and the next phase will likely see the development of specific autophagy-enhancing drugs through focussed medicinal chemistry on well-validated targets. Such effort within the pharmaceutical and biotech sectors should increase the chance of projects progressing from preclinical to clinical studies.

Therapeutic targeting through CMA

The recently described broad role of CMA in neuronal proteostasis and degradation of pathogenic proteins, and the growing evidence of reduced CMA activity in PD, FTD and AD, has made CMA an attractive target to prevent neuronal proteotoxicity and neurodegeneration.

Genetic modulation of CMA in neurodegeneration models has primarily focused on LAMP2A. Lentiviral-based LAMP2A overexpression in rats substantia nigra reduced human α-Synuclein aggregation and protected dopaminergic neurons from degeneration (Xilouri et al., 2013).

Since retinoic acid receptor α (RARα) negatively regulates CMA, activation of this pathway can be attained with retinoic acid derivatives (Anguiano et al., 2013). Extensive medicinal chemistry optimized one of these derivatives (CA77.1), which improved behaviour and tau and Aβ-related pathology in FTD mouse models (Bourdenx et al., 2021). Although interventions that improve lysosomal function should also indirectly enhance CMA, this possibility has been rarely investigated. For example, lactulose has been proposed to improve Aβ pathology through macroautophagy and CMA, but CMA activity was not measured (Lee et al., 2021). Similarly, inhibition of HDAC6 with tubastatin A was reported to reduce PD-related pathology through CMA activation (Francelle et al., 2020). Although CMA activity was not directly measured, the fact that the intervention increased LAMP2A levels justifies future studies.

PROTAC-like approaches have also been attempted for CMA. A fusion molecule containing the KFERQ-like motif and the polyglutamine binding peptide 1, which interacts with polyglutamine chains, was effective in targeting mutant huntingtin for degradation via CMA (Bauer et al., 2010). Intra-striatal delivery of this fusion molecule reduced pathology in HD models and improved the disease phenotype (Bauer et al., 2010). KFERQ-containing peptides designed to bind Aβ oligomers and promote degradation through CMA have been effective (Dou et al., 2020), although this strategy may not involve CMA, as Aβ oligomers are usually extracellular and CMA requires protein unfolding before internalization. It is still possible that KFERQ-tagging targets instead these proteins to LE/MVB via eMI.

F. Conclusions and important future questions

To maximise our understanding of these areas of biology and increase the probabilities of contributing to therapeutic strategies, there are several domains that deserve further exploration. From a basic science perspective, it will be important to appreciate how different autophagic pathways, the UPS and unconventional secretion communicate and influence each other. One challenge is to devise approaches different from knockout systems (e.g. ATG-null cells) or

pharmacological inhibitors, as these can affect other systems or induce compensatory effects. One approach that may contribute to such analyses is autophagosome and lysosomal content proteomic profiling (Le Guerroue et al., 2017; Schneider et al., 2015).

We need a better understanding of the roles of autophagic pathways in different glia. This will expand understanding of glial physiology and disease relevance, for example, for neuroinflammatory-like. Furthermore, growing evidence of non-cell autonomous control of neuronal autophagy by glia that could be utilized as a therapeutic target. For example, chemical enhancement of CMA in PD astrocytes has proven protective *in vitro* against a-Synuclein-mediated toxicity in neurons (di Domenico et al., 2019).

Further studies testing links between autophagy and psychiatric disease and conditions like autism will be important for understanding their etiologies, therapeutic potential and, by extension, may also shed light on processes underpinning the very challenging behavioural features in common neurodegenerative diseases.

Harnessing autophagy-stimulating strategies has real potential for many neurodegenerative diseases, but translational success may depend on the identification of human biomarkers that reflect brain autophagic activities. Dynamic metabolite tracing (metabolic fluxomics) and multiplex quantitative proteomics including PTMs (Wesseling et al., 2020) and more sensitive and specific tools for *in vivo* imaging of human brains of disease-causing autophagic substrates, like tau, α-Synuclein and huntingtin (van Waarde et al., 2021) may help reveal the molecular signatures of defects in autophagy. Early treatment, ideally in presymptomatic individuals, may be necessary, as disease-protein lowering later in the disease course is not nearly as effective as early removal (Rubinsztein and Orr, 2016). In this respect, trial strategies and approval processes should evolve to enable development of preventive agents administered to healthy/presymptomatic people, analogous to the use of statins in heart disease.

Enhancing autophagosome formation, although effective in disease animal models, may have risk in conditions when autophagosome clearance is defective. This may be resolved by careful *in vivo* studies aiming to mimic the physiological/disease scenario in a model organism. In advanced states of disease, when multiple autophagy steps and pathways may be compromised, it would be worth considering combinatorial interventions aiming at restoring flux through multiple autophagic pathways, since even partial restoration of each of them may have an additive beneficial effect.

The coordinate functioning of autophagy with the UPS and chaperones also makes an attractive combination of chemical regulators of these components with autophagy enhancing interventions.

Consideration should also be given to the changes on autophagy in aging and the higher probabilities of comorbidities at advanced ages that may contribute to disease (i.e. diabetes and AD). Consequently, it will be important to consider the effects of therapeutic agents not only on the neurodegenerative disease itself, but also on comorbidities and on healthy older people.

Enhancing autophagic pathways to treat diseases or delay symptom onset has the added benefit that constitutive upregulation in animals is generally associated with longevity and other health benefits (e.g. (Fernandez et al., 2018; Pyo et al., 2013). Furthermore, the autophagy-inducing agent may not need to engage its target all of the time like an antihypertensive drug but may have efficacy if administered in a pulsatile fashion e.g. every few days, which would reduce liabilities of the agent, increasing the feasibility of this approach.

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CONFLICTS OF INTEREST

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Table 1: Mutations in neurodegeneration-related genes that affect macroautophagy

Gene/ Protein	**Neurodegenerative disease**	**Stage of the autophagy pathway were a protein acts**	**Cellular phenotype upon mutation or loss of function of a protein**
Core macroautophagy			
ATG5/ Autophagy-related 5	Hereditary childhood ataxia	Early phagophore formation and elongation	Decreased autophagosome formation caused by weak binding of ATG5 to ATG12 (Kim et al., 2016)
WIPI2/ WD repeat domain phosphoinositide-interacting protein 2	Severe cognitive impairment	Early phagophore formation and elongation	Decreased autophagosome formation caused by reduced binding of WIPI2b to ATG16L1, as well as ATG5-12 (Jelani et al., 2019)
WDR45/ WD repeat domain phosphoinositide interacting protein 4 (WIPI4)	Beta-propeller protein-associated neurodegeneration (BPAN, NBIA, SENDA)	Early phagophore formation and elongation/ Autophagosome-lysosome fusion	Impairment in autophagy flux and an accumulation of LC3-positive autophagosome membranes (Saitsu et al., 2013) and ubiquitin-positive aggregates (Zhao et al., 2015); impaired formation of fusion machinery (Ji et al., 2021)
Other genes that impact autophagy			
ATXN3/ Ataxin-3	Spinocerebellar ataxia type 3 (SCA3)	Early phagophore formation	Impaired initiation in starvation-induced autophagy (Ashkenazi et al., 2017)
GJB1/ gap junction protein connexin 32	Charcot-Marie-Tooth type 1 (CMT1)	Autophagosome formation	Reduced autophagosome formation (Bejarano et al., 2014)

VPS35 / Vacuolar protein sorting-associated protein 35	Parkinson's disease (PD)	Autophagosome formation and elongation	Abnormal trafficking of mATG9 and autophagy impairment (Zavodszky et al., 2014)
EPM2A, *EPM2B*/ Laforin, Malin	Lafora disease	Autophagosome formation and elongation	Decreased LC3 lipidation and increase in p62 (Aguado et al., 2010); defective regulation of PI3KC3 complex; decreased PI(3)P levels (Sanchez-Martin et al., 2020)
TECPR2 / Tectonin beta-propeller repeat containing 2 TECPR2	Spastic paraplegia type 49 (SPG49)	Phagophore membrane elongation	Decrease in LC3 lipidation and levels of LC3 and WIPI2 (Oz-Levi et al., 2012; Stadel et al., 2015)
AP4S1/ AP-4 complex subunit sigma-1	Hereditary spastic paraplegia (SPG47, SPG52)	Phagophore membrane elongation	Deficiency causes mis-sorting of mATG9 (Davies et al., 2018)
PICALM/ Phosphatidylinositol-Binding Clathrin Assembly Protein	Alzheimer's disease (AD)	Autophagosome formation/ maturation	Autophagosome formation and maturation dysfunction; impaired APP cargo recognition (Moreau et al., 2014 ; Tian et al., 2013)
C9ORF72 / Hexanucleotide-repeat expansions in a non-coding region of chromosome 9 open reading frame 72	Amyotrophic lateral sclerosis (ALS); frontotemporal dementia (FTD)	Autophagosome formation/ maturation	Impaired autophagy flux (Farg et al., 2014); impaired trafficking of the ULK1 initiation complex to the phagophore (Webster et al., 2016)
SNCA/ α-synuclein	Parkinson's disease (PD)	Autophagosome formation/ maturation	Impaired autophagosome transport (Tanik et al., 2013; Volpicelli-Daley et al., 2014); abnormal mATG9 trafficking (Winslow et al., 2010); disturbed TFEB-mediated lysosomal biogenesis (Decressac et al., 2013)

VCP/ Valosin-containing protein VCP	Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia (IBMPFD), Amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth type 2 (CMT2), tauopathies	Autophagosome formation / maturation	Loss of ATPase activity causes impaired autophagosome formation (Hill et al., 2021); impaired autophagosome maturation (Ju et al., 2009; Tresse et al., 2010); recruited to damaged lysosomes to facilitate lysophagy (Papadopoulos et al., 2020)
SPG11/ spatacsin	Hereditary spastic paraplegia (SPG11)	Autophagosome maturation	Impaired autophagic lysosome reformation (Chang et al., 2014; Vantaggiato et al., 2019)
ZFYVE26 / spastizin (SPG15)	Hereditary spastic paraplegia (SPG15)	Autophagosome maturation	Disrupts interaction with Beclin 1 which impairs autophagosome maturation (Vantaggiato et al., 2013) and lysosomal biogenesis (Chang et al., 2014; Vantaggiato et al., 2019)
RAB7A / Ras-associated protein Rab-7a	Charcot-Marie-Tooth type 2 (CMT2)	Autophagosome maturation	Impaired autophagosome-lysosome fusion (Ganley et al., 2011)
ALS2/ ALSIN	Amyotrophic lateral sclerosis (ALS)	Autophagosome maturation	Impaired autophagosome fusion with endosomes through its regulation of RAB5 (Ravikumar et al., 2008)
UBQLN2 / Ubiquilin 2	Amyotrophic lateral sclerosis (ALS)	Autophagosome formation/ maturation/ Lysosomal function	Impaired autophagosome maturation (N'Diaye et al., 2009); impaired LC3 lipidation (Rothenberg et al., 2010); impaired autophagic flux caused by lysosomal defect (Şentürk et al., 2019; Wu et al., 2020); decrease in the levels of autophagic proteins (Chen et al., 2018)
HTT / Huntingtin	Huntington's disease	Autophagosome formation/ Autophagosome-lysosome fusion/ Cargo recognition	Impaired cargo recognition (Martinez-Vicente et al., 2010; Ochaba et al., 2014; Rui et al., 2015); decreased autophagosome transport (Wong and Holzbaur, 2014b); impaired starvation-induced autophagy initiation (Ashkenazi et al., 2017)

CHMP2B/ Charged multivesicular body protein 2b	Amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD)	Autophagosome-lysosome fusion Required for eMI	Impaired autolysosome formation (Filimonenko et al., 2007; Lee et al., 2007)
MAPT/ microtubule-associated protein tau	Alzheimer's disease (AD), tauopathies	Autophagosome-lysosome fusion	Dysfunction of the retrograde axonal transport of autophagosomes (Butzlaff et al., 2015; Majid et al., 2014)
SNX14/ Sorting nexin-14	Spinocerebellar Ataxia Type 20 (SCAR20)	Autophagosome-lysosome fusion	Impaired autophagosome clearance (Akizu et al., 2015); impaired lysosomes (Bryant et al., 2018)
DCTN1/ Dynactin	Amyotrophic lateral sclerosis (ALS)	Autophagosome-lysosome fusion	Impaired autophagosome-lysosome fusion (Ravikumar et al., 2005)
PSEN1/ Presenilin 1	Alzheimer's disease (AD)	Lysosomal function	Impaired autophagosome-lysosome fusion and defective lysosomal acidification (Chong et al., 2018; Lee et al., 2010; Zhang et al., 2012)
GBA / Lysosomal acid glucosylceramidase	Parkinson's disease (PD)	Lysosomal function	Impaired autophagy caused by lysosomal dysfunction (Murphy et al., 2014); impaired removal of dysfunctional mitochondria by mitophagy (Li et al., 2019b)
ATP13A2/ Polyamine-transporting ATPase 13A2	Parkinson's disease (PD)	Lysosomal function	Impaired lysosome acidification (Bento et al., 2016; Dehay et al., 2012)
SYT11/ synaptotagmin 11	Parkinson's disease (PD)	Lysosomal function	Lysosomal dysfunction ((Bento et al., 2016)
GRN/ Progranulin	Frontotemporal lobar degeneration (FTLD)	Lysosomal function	Impaired lysosomal function (Logan et al., 2021); deficiency in neurons increases autophagy flux and causes abnormally enlarged lysosomes (Elia et al., 2019)

FIG4/ Polyphosphoinositide phosphatase FIG4	Charcot-Marie-Tooth disease 4J (CMT4J), Amyotrophic lateral sclerosis 11 (ALS11), Yunis-Varon syndrome (YVS)	Lysosomal function	Impaired production of PI(3,5)P(2), impaired endo-lysosomes, accumulation of p62 (Ferguson et al., 2009)
VPS13D/ Vacuolar protein sorting 13D	ataxia and/or spastic paraplegia	?	Accumulation of damaged mitochondria (Anding et al., 2018)
PEX13/ Peroxisomal membrane protein PEX13	Human peroxisome biogenesis disorders (PBDs)	?	Impaired mitophagy without disruption of general autophagy (Lee et al., 2017)
Macroautophagy adaptors			
SQSTM1/ Sequestosome-1 (p62)	Amyotrophic lateral sclerosis (ALS), Frontotemporal lobar degeneration (FTLD)	Cargo recognition	Impaired recruitment into autophagosomes (Goode et al., 2016); impaired cargo recognition and protein clearance (Gal et al., 2009)
OPTN / Optineurin	Amyotrophic lateral sclerosis (ALS)	Cargo recognition/ Autophagosome formation and maturation	Impaired cargo recognition and protein clearance (Shen et al., 2015); impaired ATG5-ATG12-ATG16L recruitment to phagophore and decreased formation (Bansal et al., 2018; Song et al., 2018); impaired autophagosome trafficking to lysosomes (Sundaramoorthy et al., 2015; Tumbarello et al., 2012)
TBK1/ TANK-binding kinase 1	Amyotrophic lateral sclerosis (ALS)	Promotes efficient cargo recognition by OPTN and regulates other autophagic proteins	Impaired mitophagy (Moore and Holzbaur, 2016; Pilli et al., 2012; Richter et al., 2016)
RETREG1/ Reticulophagy regulator 1 (FAM134B)	Hereditary sensory and autonomic neuropathy type II (HSAN II)	ER-phagy receptor	Impaired ER-phagy though decrease binding to autophagy modifiers LC3 and GABARAP (Bhaskara et al., 2019; Khaminets et al., 2015)

ATL1 and *ATL3*/ Atlastin 1 and 3	hereditary spastic paraplegia (HSP), hereditary sensory and autonomic neuropathies (HSAN)	ER-phagy receptor / autophagy initiation at ER	Depletion inhibits ER-phagy, acts downstream of FAM134B during ER-phagy (Liang et al., 2018); impaired association with GABARAP and impaired ER-phagy *(*Chen et al., 2019); impaired recruitment of ULK1 complex to ER-specific site of autophagosome formation (Liu et al., 2021)
PINK1/ Serine/threonine-protein kinase PINK1	Parkinson's disease (PD)	Sensor of mitochondrial stress/ Promotes efficient mitophagy	Impaired mitophagy (reviewed in (Ge et al., 2020)
PRKN/ E3 ubiquitin-protein ligase PARKIN	Parkinson's disease (PD)	Amplifies damage mitochondria detection signal/ Promotes efficient mitophagy	Impaired mitophagy (reviewed in (Ge et al., 2020)

Table 2. Mutations in neurodegeneration-related genes with impact on CMA				
Gene	**Mutation/s**	**Associated disease**	**Effect on CMA**	**References**
SNCA	A53T A30P	PD	Blocks CMA uptake	(Cuervo et al., 2004)
LRRK2	G2019S R1441C D1994A	PD	Reduces LAMP2A stability and blocks CMA uptake	(Orenstein et al., 2013)
VPS35	D620N	PD	Reduces LAMP2A stability	(Tang et al., 2015)
UCH-L1	I93M	PD	Blocks CMA substrates degradation	(Kabuta et al., 2008)
LAMP2	$LAMP2^{4127A>C}$	PD	Reduces LAMP2A transcription	(Pang et al., 2012)
MAPT	P301L	FTD	Blocks CMA degradation	(Caballero et al., 2018)

FIGURE LEGENDS

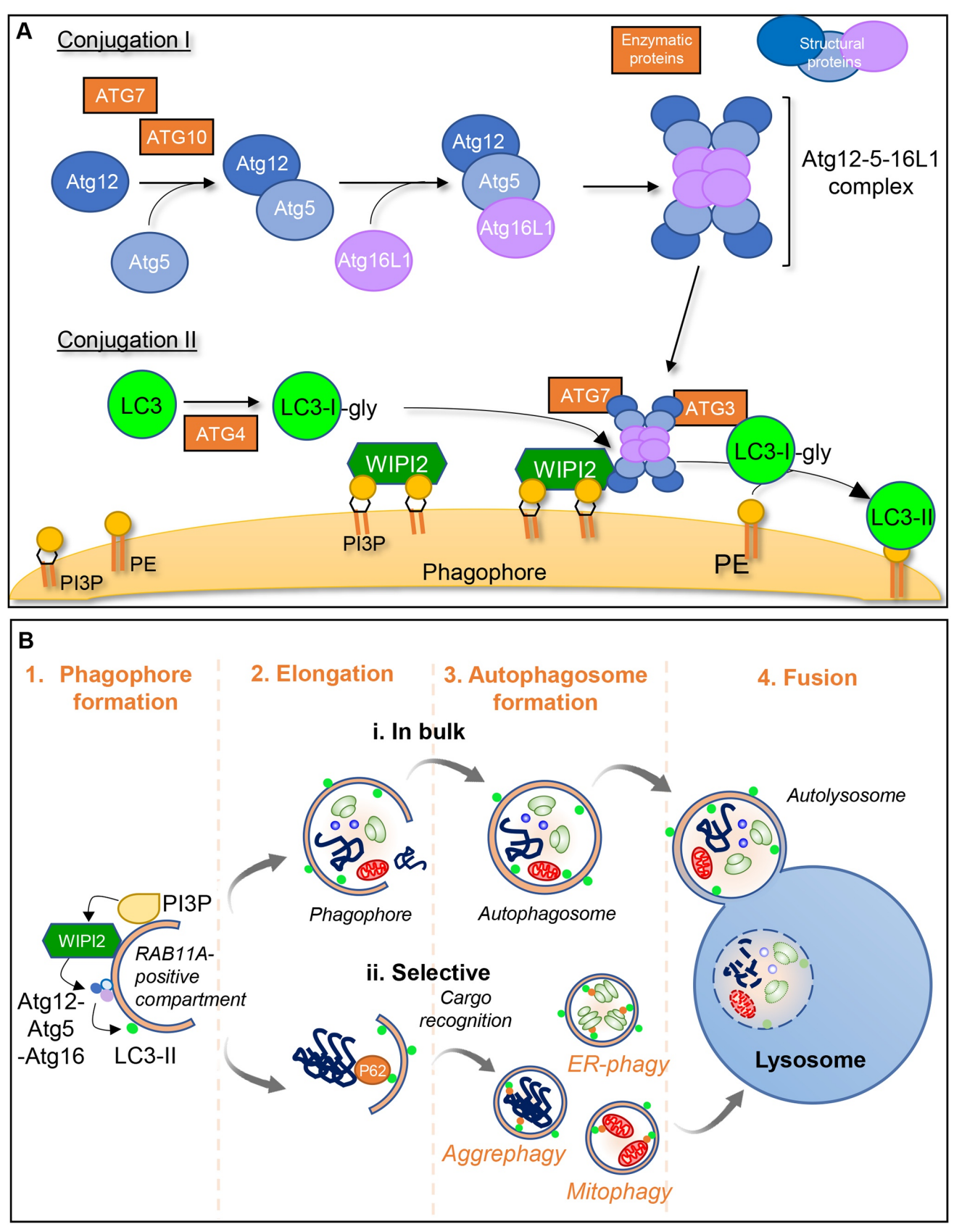
Figure 1. Schematic representation of macroautophagy: Cell components to be degraded are engulfed in a double membraned structure called the phagophore, the edges of which elongate and close to form autophagosomes. These ultimately fuse with the lysosomal membrane for cargo degradation. **A**. Early steps in macroautophagy involve 2 ubiquitin-like conjugation cascades. Conjugation I leads to the formation of the Atg5-Atg12 conjugate mediated by ATG7 (E1-like) and ATG10 (E2-like). This then forms a complex with ATG16L1. During Conjugation II, ATG4 cleaves the C-terminus of LC3 generating LC3-I whose C-terminal glycine can be conjugated to phosphatidylethanolamine (PE) by ATG7 (E1-like), ATG3 (E2-like) and ATG5-ATG12/ATG16L1 (E3-like) (generating lipidated LC3 (LC3-II)). The other ATG8 family members (GABARAPs) use the same machinery to enable their conjugation to PE as LC3 proteins. The sites of LC3 conjugation to membranes are determined by the ATG5-ATG12-ATG16L1 complex, which localizes to the surface of the forming phagophore by interacting with WIPI2. WIPI2 is recruited to these membranes by binding both to phosphatidylinositol 3-phosphate (PI3P) and RAB11A. **B**. During autophagosome formation, the phagophore double membrane elongates and fuses to form a double-membraned vesicle termed the autophagosome. Cargo within autophagosomes can be trapped in a (i) bulk or (ii) selective manner by autophagy cargo receptors, such as P62, leading to the selective autophagy of specific substrates. Completion of vesicle closure to engulf regions of cytoplasm and organelles or to engulf specific cargoes such as aggregates (aggrephagy), mitochondria (mitophagy) or ribosomes (ribophagy) is followed by release from the recycling endosome-RAB11A platform to which the LC3 conjugates. Finally, the autophagosome outer membrane fuses with the lysosomal membrane and cargo is released for complete degradation in the lysosomal lumen.

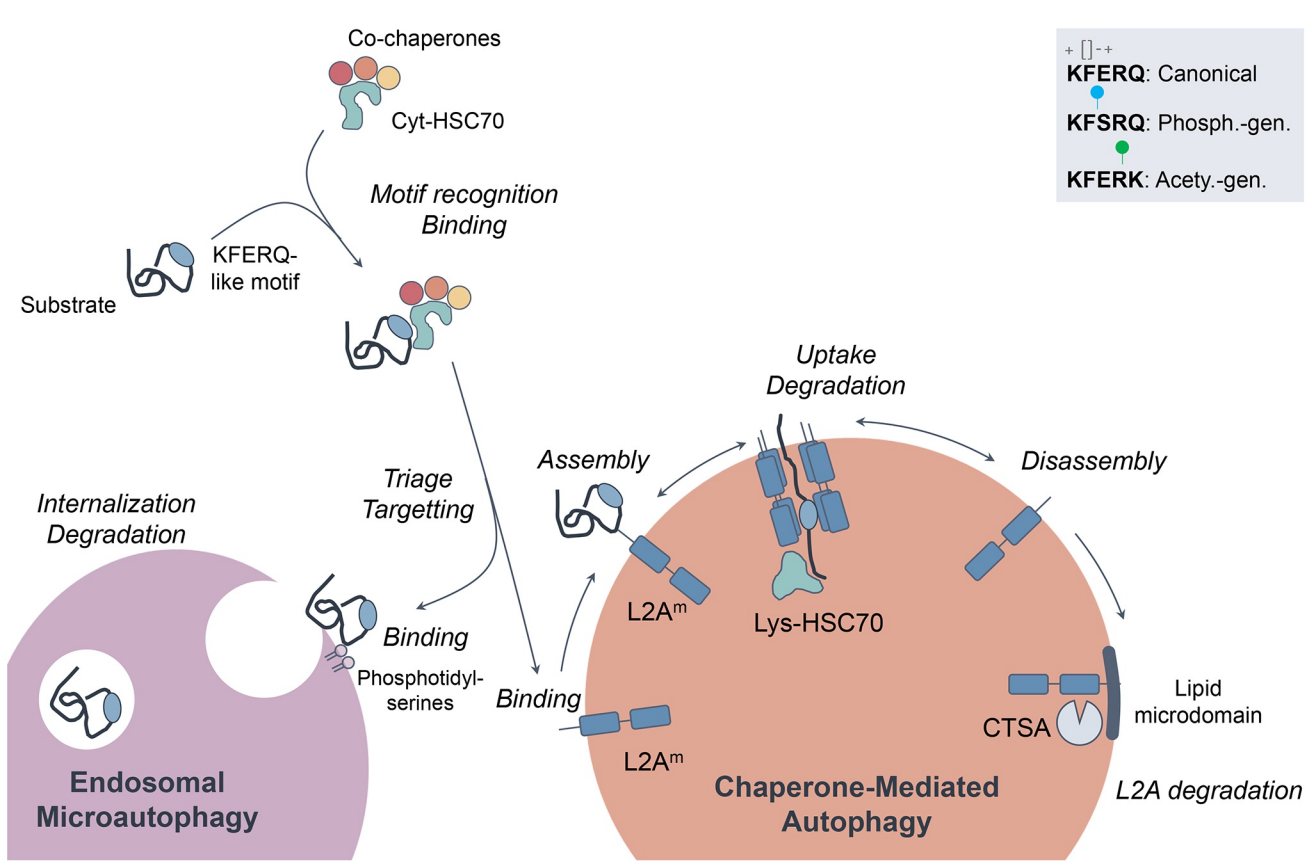
Figure 2. Schematic representation of chaperone-mediated autophagy (CMA) and endosomal microautophagy (eMI). The first steps for cargo recognition are shared by CMA and eMI and are mediated by the binding of HSC70 to a targeting motif in the protein sequence biochemically related to the pentapeptide KFERQ. The inset (top right) highlights the chemical requirements for KFERQ motifs and the post-translational modifications such as phosphorylation or acetylation that can generate motifs by providing the missing charges. This motif is necessary and sufficient for CMA, whereas it is necessary but insufficient for eMI. Additional, as yet unknown, mediators are required for eMI targeting. HSC70 binds to the surface of late endosomes via phosphoserine and triggers assembly of the ESCRT machinery for internalization of substrate into intraluminal vesicles. In CMA, binding of the HSC70/substrate complex to LAMP2A at the lysosomal membrane triggers its multimerization to form a translocation complex that mediates the internalization of the substrate protein into the lumen for degradation. LAMP2A is actively disassembled from the complex to initiate a new cycle of binding/internalization. LAMP2A also mobilizes laterally to incorporate into lipid microdomains for its own degradation triggered by cathepsin A (CTSA). Phosph. gen.: phosphorylation generated. Acetyl. gen: Acetylation generated.

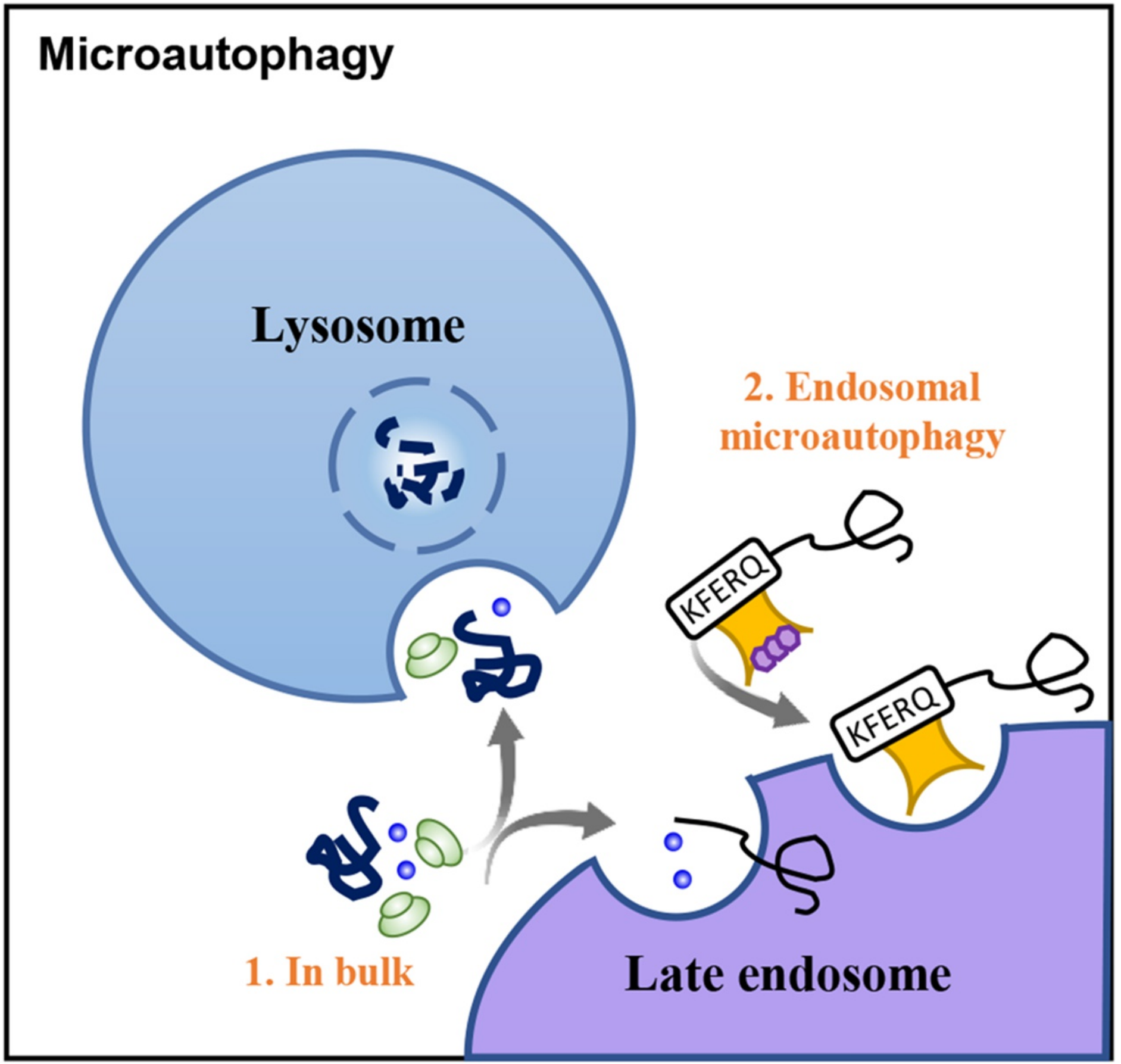
Figure 3. Schematic representation of microautophagy: Bulk of proteins and cells components such as organelles (*1. In bulk*) can be integrated into lysosomes and late endosomes directly through invaginations at the lysosomal membrane. Cytosolic proteins targeted by Hsc70 can be also selectively degraded by its internalization into late endosome invaginations in a process known as *Endosomal microautophagy* (*2).*

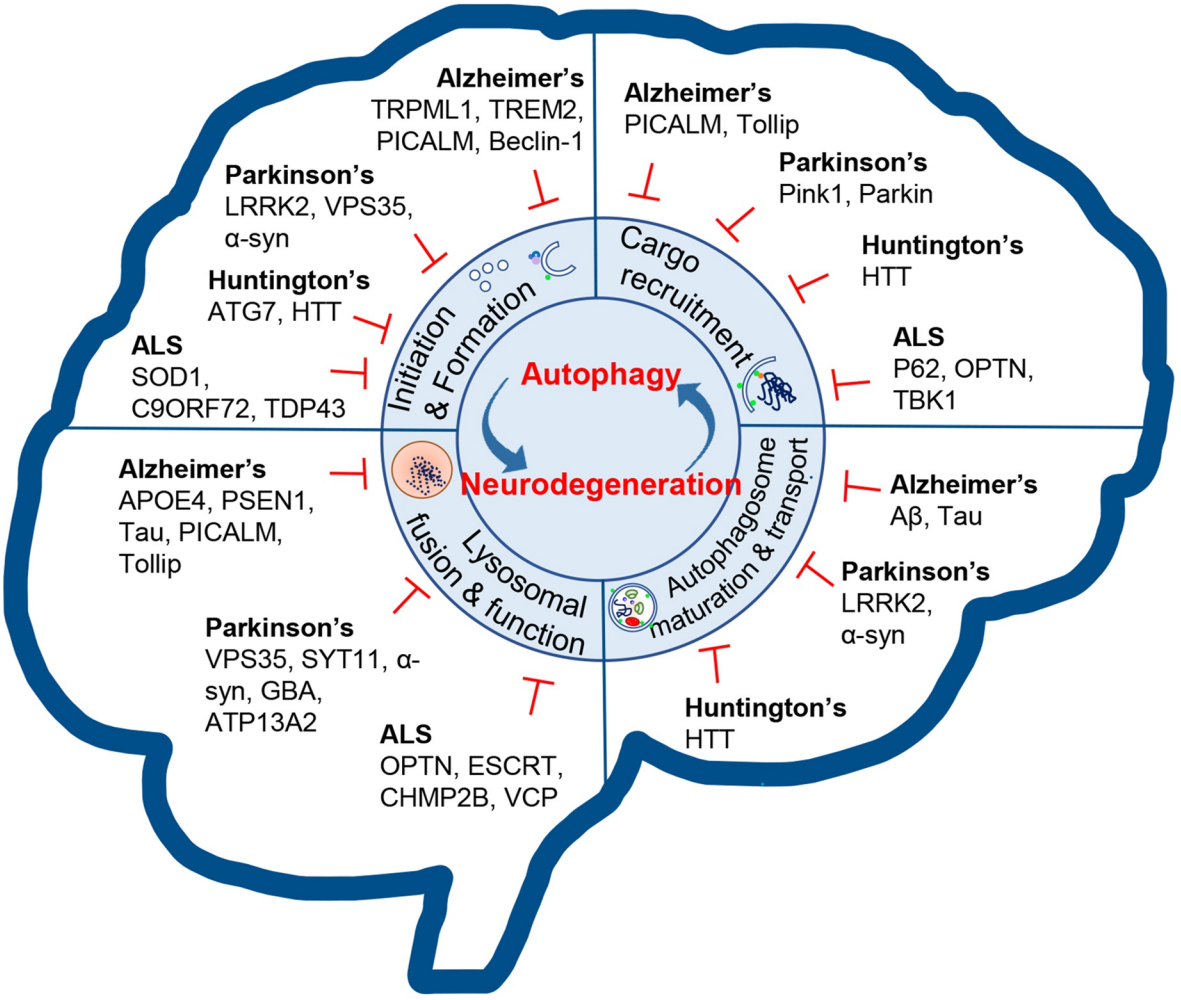
Figure 4. Overview of the role of macroautophagy in the nervous system in health and neurodegeneration. Autophagy is fundamental to sustain the homoeostasis and function of the CNS. Perturbations in the macroautophagy pathway at different stages have been observed during neurodegeneration and distinct disease-associated genes are also key contributors to macroautophagy dysfunction. Defective autophagy compromises protein clearance and organelle turnover, leading to the accumulation of toxic proteins and damaged cellular components that finally alter neuronal function and induce neuronal loss.

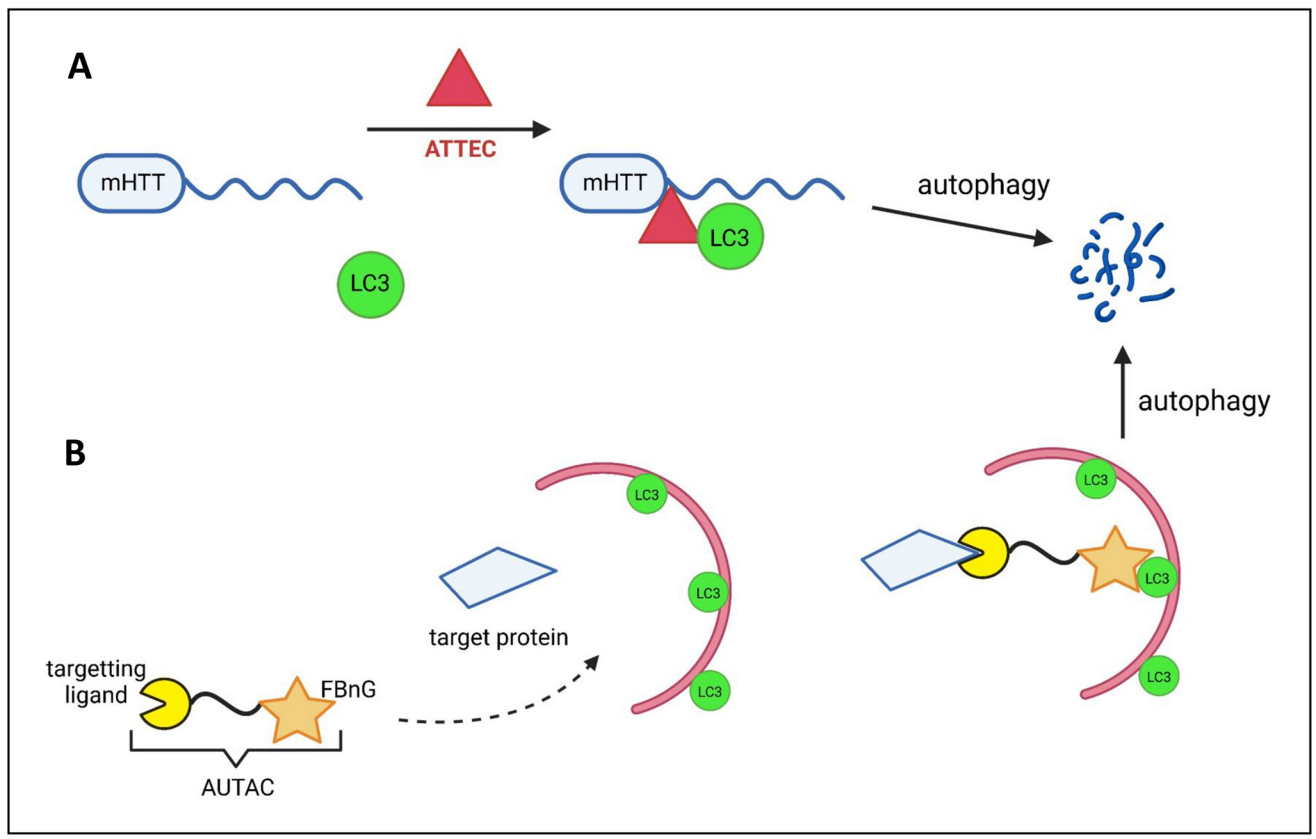
Figure 5. Autophagy tethering compounds (ATTEC) and the autophagy-targeting chimera (AUTAC) system. A) ATTEC molecules tether the protein of interest to the autophagosomes by direct binding to the protein of interest and to LC3. A proof-of-concept study using the mutant HTT protein (mHTT) demonstrated that these compounds can degrade mHTT both in cells and *in vivo* in animal models and demonstrated targeting of mHTT to autophagosomes for subsequent degradation without influencing autophagy activity *per se*. B) AUTAC technology has a similar design to the PROTAC technology and both use ubiquitination to target proteins for degradation. The AUTAC molecule contains a degradation tag (a guanine derivative called FBnG) which induces K63 polyubiquitination and a ligand which binds to the target protein to provide target specificity. The resulting K63 ubiquitination targets the labelled protein for degradation via macroautophagy.


A
Conjugation I
Enzymatic proteins
Structural proteins
ATG7
ATG10
Atg12
Atg5
Atg16L1
Atg12-5-16L1 complex
Conjugation II
LC3
ATG4
LC3-I-gly
ATG3
WIPI2
PI3P
PE
Phagophore
LC3-II
B
1. Phagophore formation
2. Elongation
3. Autophagosome formation
4. Fusion
i. In bulk
Phagophore
Autophagosome
Autolysosome
Lysosome
RAB11A-positive compartment
Atg12-Atg5-Atg16
ii. Selective
Cargo recognition
P62
ER-phagy
Aggrephagy
Mitophagy


Co-chaperones
Cyt-HSC70
Motif recognition
Binding
Substrate
KFERQ-
like motif
+ [] - +
KFERQ: Canonical
KFSRQ: Phosph.-gen.
KFERK: Acety.-gen.
Uptake
Degradation
Assembly
Disassembly
Triage
Targetting
Internalization
Degradation
L2A^m
Lys-HSC70
Binding
Phosphotidyl-
serines
Binding
CTSA
Lipid
microdomain
L2A^m
Endosomal
Microautophagy
Chaperone-Mediated
Autophagy
L2A degradation


Microautophagy
Lysosome
2. Endosomal microautophagy
KFERQ
KFERQ
1. In bulk
Late endosome


Alzheimer's
TRPML1, TREM2, PICALM, Beclin-1
Alzheimer's
PICALM, Tollip
Parkinson's
Pink1, Parkin
Huntington's
HTT
ALS
P62, OPTN, TBK1
Parkinson's
LRRK2, VPS35, α-syn
Huntington's
ATG7, HTT
ALS
SOD1, C9ORF72, TDP43
Initiation & Formation
Cargo recruitment
Autophagy
Neurodegeneration
Autophagosome maturation & transport
Lysosomal fusion & function
Alzheimer's
APOE4, PSEN1, Tau, PICALM, Tollip
Alzheimer's
Aβ, Tau
Parkinson's
LRRK2, α-syn
Parkinson's
VPS35, SYT11, α-syn, GBA, ATP13A2
Huntington's
HTT
ALS
OPTN, ESCRT, CHMP2B, VCP


A
ATTEC
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mHTT
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autophagy
autophagy
B
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LC3
LC3
target protein
targetting ligand
FBnG
AUTAC
LC3
LC3
LC3