The mechanisms and roles of selective autophagy

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Abstract:

Autophagy is a process that targets intracellular elements for degradation by sequestering them in double-membrane autophagosomes which then fuse with late endosomes/lysosomes forming degradative autolysomes. Autophagy can be associated with the engulfment of bulk cytosolic components, thereby being non-selective, which occurs for instance in response to starvation and is commonly referred to as bulk or non-selective autophagy. By contrast, selective autophagy has specific targets, such as damaged organelles (mitophagy, lysophagy, ER-phagy, ribophagy), aggregate proteins (aggrephagy) or invading bacteria (xenophagy), thereby being importantly involved in cellular quality control. Hence, not surprisingly, insufficiency of selective autophagy pathways has been associated with various human pathologies, prominently including neurodegeneration and infection. Determination of cargo specificity has been attributed to selective autophagy receptors such as p62, NBR1, OPTN, NDP52, which can both bind the cargo and ubiquitin simultaneously to initiate pathways leading to autophagosome membrane recruitment. In recent years a considerable progress has been made in understanding mechanisms governing selective cargo engulfment, which opens up the possibilities of enhancing selective autophagy pathways to boost cellular quality control capabilities and alleviate pathology.

Introduction:

Autophagy is one of the important bulk degradation systems in cells; it is a process to break down cellular components when required. The word “autophagy” is a combination of Greek prefix “self” as Auto and “to eat” as phagy, and was defined by Christian de Duve in 1963[1]. Autophagy is a mechanism conserved in eukaryotes, from yeast to humans, and is involved in maintaining homeostasis by preventing the accumulation of abnormal proteins in cells, recycling proteins when cells face nutritional deficits, eliminating pathogenic microorganisms that have invaded the cytoplasm, eliminating damaged organelles and abnormal proteins and so on. Many diseases are caused by the inability of cells to maintain such homeostasis, thus autophagy is now reported to be involved in diverse diseases including neurodegenerative diseases, infections, inflammation, metabolic dysfunction, cancer, and aging[2]. There are mainly two types of autophagy defined by its degradation target. One is called “bulk” or “non-selective” autophagy, the target is rather random, and encloses and degrades parts of cytoplasm and organelles at random. The other is called “selective” autophagy, which is more selective in its targets for degradation.

Non-selective autophagy allows cells to survive through nutrient starvation until the next nutrient source is available[3]. Once cells sense lack of nutrient, an isolation membranes is mostly formed at ER-mitochondria contact sites[4], LC3-II (homologue of Atg8, used for an autophagosome membrane

marker) labelled membranes elongate as they engulf materials and eventually closes to form spherical organelles, called autophagosomes (**Fig. 1**). Thus, autophagosomes are organelles that are formed *de novo*, and are therefore unique to most other pre-existing organelles. Autophagosomes then fuse with lysosomes to degrade their contents. Size is up to 1 um in diameter and are enclosed by double lipid bilayer membrane[5] (**Fig. 1**). Core autophagy-related (Atg) proteins involved in formation of autophagosomes are conserved from yeast to mammalian cells. Yoshinori Ohsumi identified Atgs and the two ubiquitin-like conjugation systems involved in autophagosome biogenesis and maturation. For these discoveries, Ohsumi won the Nobel Prize in Physiology or Medicine in 2016. Nowadays, there are over 40 Atg genes identified; among them, core Atgs from 1 to 18 excluding 11 are involved in non-selective autophagy and Selective autophagy requires most of core Atgs plus receptors. Most of the rest are involved in selective autophagy. Please see the review for detailed functions of each Atg proteins[6].

Selective autophagy plays a role in maintaining cellular homeostasis by clearing specific cargos such as invading pathogens, damaged organelles, and misfolded proteins, which are harmful to cells[7] (**Fig.1**). In selective autophagy, many cargos are ubiquitinated, which does not happen in non-selective autophagy. Cargos can then be specifically targeted by receptor proteins, which have LIR (LC3-interacting region) domains and ubiquitin binding domains to bridge cargo and LC3-II: p62, TAX1BP1, NDP52, NBR1, OPTN and more[8] (**Fig 1, Table 1**). Selective autophagosomes vary in size from 1-10um depending on

the target[9]. Nowadays, selective autophagy is classified according to their targets and is named; xenophagy (intracellular pathogens), lysophagy (lysosomes), mitophagy (mitochondria), aggrephagy (aggregates), ER-phagy (ER), pexophagy (peroxisomes), ribophagy (ribosomes), ferritinophagy (ferritin), lipophagy (lipid droplets), glycophagy (glycogen), fluidophagy (droplets) and so on (Table 1). The many target cargos of selective autophagy are linked to diverse physiological roles, and failure to degrade these cargos lead to many types of diseases[10].

In this review, we will focus on different types of selective autophagy in mammalian cells, how cargos are tagged, recognized, selectively sequestered, and degraded with a primary emphasis on mitophagy, aggrephagy, lysophagy, and xenophagy.

[H1] Mitophagy

[H2] PINK1 and Parkin as a main a surveillance mechanism for damaged mitochondria

The maintenance of the mitochondrial network is critical for the fitness of many eukaryotic cells. Defects in the respiratory chain complex proteins can result in energy insufficiency and the accumulation of reactive oxygen species, which are detrimental to the cell. Therefore, in order to prevent the

accumulation of impaired mitochondria, damaged mitochondria are selectively degraded via autophagy in a process termed mitophagy.[11]

A main mechanism that provides specificity for damage-induced mitophagy is the ubiquitination of outer mitochondrial membrane proteins, which fosters the recruitment of autophagy receptors only to the organelles that need to be degraded[12]. Indeed, PTEN-induced putative kinase 1 (PINK1) and Parkin are the key regulators of this ubiquitin-tagging process. PINK1 provides a surveillance mechanism for mitochondrial fitness by accumulating solely on damaged mitochondria[13]. In healthy mitochondria, PINK1 is imported by the TOM and TIM complex, then subsequently cleaved by the proteases PARL, and to a minor extent Oma1, both localized on the inner mitochondrial membrane[13,14] resulting in the 52 kD N-terminal-deleted PINK1 to be degraded through N-degron pathway[15,16]. However, when mitochondrial membrane potential is lost, TIM complex import is impaired and PINK1 does not reach the inner membrane, preventing access to PARL[13]. This leads to the outer mitochondrial membrane accumulation of PINK1, where it can then phosphorylate ubiquitin chains specifically on serine 65 attached to a variety of outer mitochondrial membrane proteins[17–20]. In this manner PINK1 activity is restricted to damaged mitochondria. Mitochondrially stabilized PINK1 also phosphorylates Parkin within its ubiquitin-like domain, also in position serine 65[21] releasing Parkin from its autoinhibited state[22,23]. Parkin, once active on the mitochondria, ubiquitinates myriad outer membrane mitochondrial proteins[24–26]. These nascent ubiquitin chains can then be further phosphorylated by PINK1,

leading to even more Parkin recruitment and activation on the mitochondria[25]. This feedback amplification of OMM protein ubiquitination leads to the ubiquitin-dependent recruitment of many other proteins critical for efficient mitophagy, such as the VCP/p97 complex[27], Rab GTPases[28–30], and importantly, autophagy receptors[31–33]. Interestingly, recent work revealed that PINK1/Parkin conjugate mono and short phosphoubiquitin chains on damaged mitochondria to initiate mitophagy[34]. This work may have important implications for the understanding of mitophagy receptors, which rely on the PINK1/Parkin-generated phosphoubiquitin chains to localize to damaged mitochondria.

[H2] NDP52 and OPTN are ubiquitin-dependent mitophagy receptors

A systematic analysis of receptor proteins using combinatorial CRISPR/Cas9 KO lines revealed that OPTN and NDP52 are the two ubiquitin-dependent receptors most critical for Parkin-dependent mitophagy[31]. OPTN and NDP52 recruit to mitochondria via their respective ubiquitin-binding domains[31–33,35]. Importantly, more subtle damage to mitochondria induced by accumulation of matrix-localized protein aggregates also results in the focal recruitment of receptor proteins to these aggregates and their clearance, which depends on Parkin[36]. As discussed in the xenophagy section, NDP52 and OPTN are also involved the in the clearance of invading bacteria[37–39]. Bearing in mind the bacterial origin of the mitochondria, the overlap between xenophagic and mitophagic ubiquitin-binding receptors is quite interesting. Indeed, TBK1 kinase, which also plays a key role in innate immune response, is also important for the

timely progression of mitophagy[33,40,41]. Both NDP52 and OPTN interact with and are themselves substrates of TBK1[37,39,40]. The phosphorylation of NDP52 and OPTN by TBK1 aids in the retention of these receptors on the mitochondria by affecting their capacity to bind ubiquitin chains, and thus, positively regulates the rate of mitophagy[32,33,40]. Furthermore, phosphorylation of OPTN within its LIR domain by TBK1 increases the affinity of OPTN to lipidated LC3[39].

Lastly, there are other mitophagy receptors that function in a ubiquitin-independent manner (**Table 1;** [42]). Many of these receptors, for instance NIX (19 kDa interacting protein-3 (NIP3)-like protein X) and BNIP3 (BCL2/adenovirus E1B 19 kDa protein-interacting protein 3)[43], are mitochondrially localized. NIX was initially discovered to be an important mitophagy receptor during reticulocyte maturation [44,45]. BNIP3, a homologue of NIX, was demonstrated to regulate mitophagy, as well as ER-phagy [46]. Although NIX and BNIP3 possess LIR domains, these mitochondrially-localized receptors do not have ubiquitin-binding domains which characterizes OPTN and NDP52. It was recently demonstrated that the mitochondrial matrix resident proteins NIPSNAP1/2 accumulate on the OMM after mitochondrial depolarization and can recruit LC3. Intriguingly, NIPSNAP1/2 also associate directly with NDP52 via its zinc finger domain, the same domain that interacts with ubiquitin chains generated by Parkin[47]. Thus, mitochondrial-resident receptors may have crosstalk and recruit ubiquitin-binding receptors, which can then initiate the autophagic cascade via recruitment of autophagy components.

[H2] OPTN and NDP52 mediate de novo autophagosome biogenesis during mitophagy

A recent study showed that even in the absence of LC3/GABARAP family proteins a mitophagosome can still selectively engulf mitochondria after Parkin activation[48]. The authors demonstrate that in the absence of LC3/GABARAP proteins, the rate of expansion of the mitophagosome is impaired and the fusion of the mitophagosome to lysosome is blocked. Indeed, both ATG9A and the ULK1 complex recruit normally to the mitochondria during PINK1/Parkin mitophagy in cells lacking ATG3, a protein that plays an essential role in LC3 lipidation[49]. These findings strongly suggest that LC3/GABARAP proteins are not required for the initiation of Parkin-mediated mitophagy but are instead essential for the expansion of the nascent autophagosome and its subsequent fusion to the lysosome.

The aforementioned studies raise a possible alternative model wherein mitophagosomes are generated *de novo* on the surface of mitochondria destined to be degraded. In line with this model, it was previously reported that in the absence of NDP52 and OPTN, the recruitment of ULK1 to mitochondria is impaired suggesting that receptor proteins have the capacity to recruit the upstream autophagy machinery to the mitochondria[31]. Recent work revealed that NDP52 interacts with FIP200, a core scaffolding component of the ULK1 complex, and that this interaction is critical for the de novo formation of phagophore by activating ULK1 directly on damaged mitochondria and also on

invading bacteria[38,41,50]. Furthermore, the interaction of NDP52/FIP200 is facilitated by TBK1 activity[41]. Consistently, a recent study highlighted the effect of NDP52-FIP200 interaction, demonstrating that NDP52 allosterically stimulates the membrane affinity of FIP200 and ULK1[51]. Strikingly, the capacity of NDP52 to recruit ULK1/FIP200 is markedly enhanced by the addition of ubiquitin chains[52], further demonstrating the importance of ubiquitin chains in serving as platforms for receptors. Experimental tethering of NDP52 to mitochondria by a chemical dimerization assay is sufficient to drive autophagic degradation of the organelle[41].

OPTN was also recently shown to associate with ATG9A vesicles[53,54], as well as FIP200[55]. The interaction of OPTN, via its leucine zipper domain, with ATG9A was shown to be important for mitophagy induction[53]. A recent compound screen for novel mitophagy activators found that the anti-parasitic compound ivermectin stimulates mitophagy[56]. The authors found that ubiquitin ligases cIAP1, cIAP2, and TRAF2 are involved in the mitophagy induced by ivermectin. In addition, ivermectin also activates TBK1, which aids in the recruitment of OPTN to mitochondria[56]. Another recent study using proximity-based proteomics determined that various ATG components are associated with OPTN and TAX1BP1 during mitophagy[57]. Additionally, OPTN has been shown to interact with the ATG16L1/ATG5/ATG12 complex[58] as well as ATG9A[53,59]. Furthermore, ubiquitin chains enhance LC3-lipidation by OPTN, NDP52 and TAX1BP1, consistent with the model whereby receptor protein oligomerization on cargo is essential for their function[51,60–63]. Interestingly,

OPTN is able to bypass ULK1 to promote LC3 lipidation and only requires active PI3KC3-C1 complex and WIPI2D in these reconstitution experiments[62].

LC3/GABARAP proteins and the LIR domains of NDP52 and OPTN are nonetheless critical for mitophagy. For instance, a study demonstrated that once nascent autophagosomes are formed on mitochondria, lipidated LC3 can further recruit NDP52 and OPTN via the LIR domain, in a ubiquitin-independent manner[64]. This ubiquitin-independent, but LC3-dependent recruitment of NDP52 and OPTN is thought to recruit more upstream autophagy machinery to the maturing autophagosome to further facilitate its expansion rate[64].

All together these recent findings lead to the model that receptor proteins NDP52 and OPTN act in tandem to initiate mitophagy by stimulating the biogenesis of the autophagosome directly on damaged mitochondria through their interaction with core upstream autophagy components. (**Fig. 2**).

[H2] Importance of mitophagy in health and disease

In addition to playing a critical role in energy production, mitochondria are also recognized as a signaling hub for various cellular processes, such as apoptosis and innate immunity. For instance, RNA viruses activate the mitochondrial antiviral signaling protein (MAVS), which is localized on the OMM[65]. Mitochondria also regulate apoptosis through the release of various cytotoxic proteins mediated by Bcl-2 family proteins[66] and the ubiquitination of

Bak and Bax by Parkin is able to fine tune apoptosis[67,68]. Furthermore, a recent study reported that VDAC1, a known Parkin substrate, is involved in the triaging between mitophagy and apoptosis[69]. The authors find that the polyubiquitination and monoubiquitination of VDAC1 by Parkin, which occurs at distinct lysine residues, control mitophagy and apoptosis independently. Specifically, K274 is monoubiquitinated and is involved in modulating apoptosis[69]. Parkin also ubiquitinates Bak in a conserved lysine crucial for its homo-dimerization. Ubiquitination of Bak impaired its capacity to form lethal Bak oligomers during apoptosis[68]. Thus, mitophagy also regulates physiological signaling pathways that depend on the mitochondria as a signaling platform by altering the total mitochondrial content within cells or via ubiquitination of OMM proteins involved in various pathways.

Innate immune pathways in eukaryotes are able to respond to myriad invading pathogens, such as bacteria, virus, and fungi[70]. The potency of innate immunity relies on the ability of the pathway to keenly differentiate signature molecules and peptides coming from pathogens. However, mitochondria, owing to their α-protobacterial origin, presents a problem for the innate immunity. Damage associated molecular patters (DAMPs) originating from mitochondria robustly activate innate immune responses[71]. Furthermore, mtDNA released into the cytosol triggers the activation of STING, which is a key node in the double-stranded DNA antiviral defense pathway, which in turn results in the expression of interferon-stimulated genes[72]. STING is a dimeric ER-localized protein which is activated by cGAMP, a compound generated via the binding of

cGAS with cytosolic double-stranded DNA[73]. Thus, mitochondrial damage can lead to the release of DAMPs and mtDNA into the cytosol, triggering STING-mediated inflammation[72,74].

It was recently reported that defective mitophagy in vivo results in the activation of STING, which in turn activates inflammatory responses, such as elevated IL-6[74]. Remarkably, ablation of STING in the mutator/Parkin-null mice, a well-characterized in vivo model of PD[75], rescues not only the inflammation observed in these mice but also various PD-related symptoms, such as loss of dopaminergic neurons within the substantia nigra and motor deficits[74]. Of note, a study revealed that patients with mutations in Park2 and Park6 display elevated circulating mtDNA compared to healthy controls[76]. Furthermore, IL-6 is also increased in the serum of these PD patients[76]. Thus, this human study recapitulated the inflammatory phenotype observed in a mitophagy deficient mice triggered by the escape of mtDNA from impaired mitochondria further highlighting the role of mitophagy in preventing unmitigated innate immune response to cytosolic mtDNA[74]. Therefore, a possible pathological hallmark of Parkinson's disease is the prolonged activation of innate immunity due to mitophagy defects, leading to neurodegeneration (**Fig 3**).

The impact of dysregulated mitophagy in disease pathogenesis is highlighted by the fact that mutations in genes central to the initiation of quality control mitophagy, *Pink1* and *Park2* (encodes for PINK1 and Parkin, respectively), result in familial Parkinson's Disease[77,78]. Studies performed in

Drosophila revealed an epistatic relationship between PINK1 and Parkin, with PINK1 functioning upstream of Parkin[79,80]. Other constituents of the mitophagic pathway are also implicated in neurodegenerative disorders, such as Amyotrophic Lateral Sclerosis[81]. It is possible that neurons are intrinsically sensitive to mitochondrial dyshomeostasis since neuronal activity requires the maintenance of plasma membrane chemical gradients, a bioenergetically demanding process requiring the maintenance of healthy mitochondria[82]. Lastly, the complex morphology of axons and dendrites presents another layer of spatial complexity for mitochondrial upkeep since assembly of mitochondria requires the coordinated expression of both nuclear- and mitochondrial-encoded genes[83–85]. These demands may in part contribute to the sensitivity of certain neuronal subpopulations to defects in mitophagy (**Fig 3**).

[H1] Lysophagy

Lysosomes, the last organelle to reach the end of membrane transport, have various hydrolytic enzymes and, as the name suggested, are organelles that degrade. Lysosome contains about 50 hydrolytic enzymes capable of breaking down proteins, lipids, polynucleotides, and carbohydrates. The lumen of the lysosome is acidified to around pH5 and plays an important role as a site of intracellular digestion[86]. When the lysosome is damaged, hydrolytic enzymes leak into the cytoplasm and cause cell death[87]. It has been reported that lysosome membranes can be damaged by extracellular materials that are introduced into cells, such as cholesterol, uric acid crystals, human beta-

amyloid peptide aggregates, and fine particles such as silica and asbestos[87,88]. When the lysosomal membrane is damaged, which causes inflammation due to loss of lysosomal homeostasis, cells attempt to isolate/repair the lysosomal membrane damage by autophagy and other mechanisms to prevent cell death[89]. Damaged lysosomes are the target of autophagy and named "lysophagy"[88,90] (**Fig. 4**). It has been suggested that damage to lysosomal membranes may lead to lifestyle-related diseases such as type II diabetes, atherosclerosis, gout, and neurodegenerative diseases. Therefore, the mechanism to repair and remove damaged lysosomes is attracting attention. How do cells respond to lysosomal membrane damage? We will outline what is currently known on lysosome repair/removal machinery.

Lysosomes are artificially damaged by using a drug called LLOMe, di-peptide L-leucyl-L-leucine methyl ester that becomes membranolytic when cleaved by cathepsin D, and examine the repair mechanism[88]. Galectin-3 (Gal3) is a lectin-binding protein that is normally found in the cytoplasm, but when organelle membranes are damaged, gal3 accesses the lumen and binds to the N-glycans of proteins. Accordingly, lysosomal damage caused by exposure to LLOMe is indicated by co-localization of lysosomes with Gal3, ubiquitin and LC3-II. Once LLOMe has been washed-out, localization of Gal3, ubiquitin, and LC3-II is back to cytoplasmic pattern and returned to the pre-treatment state, indicating the repair of the damaged lysosome[88]. The difference in the reduction of Gal3-positive lysosomes between control cells and autophagy-deficient cells indicates that autophagy is involved in the repair.

However, in autophagy-deficient cells, the percentage of Gal3-positive lysosomes is also reduced, suggesting that repair is carried out by means other than autophagy.

Recently, it has been reported that ESCRT-III complex is recruited to repair smaller lysosome damages[91]. Alix, a component of ESCRT-III complex is recruited to damaged lysosomes very rapidly, just 1 min after LLoMe treatment, where Gal3 recruitment starts to be seen after 30 min. Ca^{2+} leakage from lysosomal damage may trigger the recruitment of ESCRT-III and membrane repair. The authors believe the ESCRTs work to repair the lysosomes and keep them normal while the damage is not so severe that Gal3 is recruited. When damage is not fully repaired or large enough to be recognizable by Gal3, lysophagy is induced to clear the damaged lysosome.

[H2] Mechanisms of lysophagy

One of the common features of selective autophagy is that the many targets become ubiquitinated[92]. Lysophagy is no exception, and the lysosome is ubiquitinated upon damage. Similar to Gal3 recruitment, ubiquitination on damaged lysosomes does not appear until about 30 min after LLOMe treatment[88]. How does ubiquitination of damaged lysosomes occur? Among more than 600 E3 ubiquitin ligases in humans, recent paper showed the recruitment of TRIM16 as E3 Ub ligase to the damaged lysosome by binding through Gal3[93]. Since TRIM16 interacts with ULK1, Beclin 1 and Atg16, it

functions to bridge between damaged lysosome and Atg proteins like a receptor. It is involved at the initial stage to recruit Atg proteins to damaged lysosomes; however, Gal3 is only a marker of damaged lysosomes and not a necessary factor for lysophagy, to which degrees TRIM16 is required is not clear.

The involvement of another E3 ubiquitin ligase was reported, FBXO27, a substrate-recognition subunit of the SCF (SKP1/CUL1/F-box), in lysophagy[94]. FBXO27 colocalizes with Gal3 upon LLOMe treatment and FBXO27 KO reduced repair of damaged lysosomes by roughly 20% compared to control. In FBXO27 over-expressing cells, LAMP1 and especially LAMP2 is highly ubiquitinated upon lysosome damage. However, FBXO27 is mainly expressed in muscle and adipose tissue and is not ubiquitously expressed, suggesting the existence of other E3 ubiquitin ligases.

Lysophagy might have several backup systems to recognize/repair/remove damaged lysosomes. Lysosomes are important organelle to degrade yet they can be damaged by many extracellular particles up taken by cells and perhaps level of damages is different. When damages are small, ESCRT machinery tries to repair but when damages are too large detected by Gal3, autophagy removes them. Once damaged lysosomes are cleared, biogenesis of lysosomes kicks in through a control of TFEB.

The types of ubiquitination occurring on damaged lysosomes are K48 and K63[95]. K63 ubiquitin chains are seen from the early stages of damage, whereas the K48 ubiquitin chain peaks later at 2-4 h after LLOMe treatment. In addition, ELDR (endo-lysosomal damage response) complexes containing deubiquitinating enzymes (YOD1) and p97 (or VCP, Valosin-containg protein) are added to K48 ubiquitinated damaged lysosomes, resulting in K48 specific deubiquitination and LC3 recruitment to initiate lysophagy (**Fig. 4)**. Mutations in p97 have been reported to cause neurodegenerative diseases, and damaged lysosomes with K48 ubiquitination remain unremoved in the tissues of actual disease patients. Further study is required to know the role of each type of ubiquitination/deubiquitination on damaged lysosomes.

Recently, it was reported that UBE2QL1 is an E2 ligase required for lysophagy after screening approximately 40 E2 ligases in humans[96]. UBE2QL1 is involved in K48, not in K63, ubiquitin chains and appears 2-3 hours after LLoMe treated damaged lysosomes. The absence of UBE2Q1 significantly reduces the recruitment of p97, p62, and LC3 to the damaged lysosomes. However, since the time of recruitment to damaged lysosomes is as late as 2 hours after LLoMe treatment, UBE2Q1 may also work for the clearance of more severely damaged lysosomes. Also, UBE2QL1 recruits p97 to damaged lysosomes in a K48 ubiquitin-dependent manner, while p97 is responsible for pulling out and degrading proteins on the K48 ubiquitinated membrane by ERAD. In fact, it has been reported that mitophagy prevents damaged mitochondria from fission by degrading mitofusin from the outer membrane of

mitochondria. It is interesting to note that there may be a protein on the lysosome that prevents lysophagy from occurring unless it is removed, but the details will not be known until the protein is identified. The common denominator of several E3 ligases is that ligases come to the damaged lysosomes, are involved in K48-type ubiquitination, and ubiquitination occurs in the lumen of the lysosome.

In selective autophagy, most targets are ubiquitinated and receptors with ubiquitin binding sites and LC3-interacting regions (LIRs), collectively called SARS (selective autophagy receptors), bind to LC3 and recruit autophagosome membranes building factors[97]. The receptor involved in lysophagy is reported to be p62[95], however, recent study show TAX1BP1 is sufficient to promote lysophagy[98] (**Fig. 4**). p62 recruitment is observed in FBXO27-mediated ubiquitin[94] and the recently discovered UBE2QL1-mediated ubiquitin[96]. Further studies are needed.

[H2] Lysophagy and disease

When autophagy was suppressed in the proximal tubules of mice, hypouricemic nephropathy was aggravated[88]. This may be due to the lack of removal of damaged lysosomes by uric acid crystals. In addition, since the factors that cause damage to lysosomes are causative factors of lifestyle-related diseases such as gout and type 2 diabetes, lysophagy may be useful in improving lifestyle-related diseases. If left untreated, lysosomal damage can affect lysosomal homeostasis and lead to neurodegenerative diseases.

Lysosomal damage is also caused by factors known to be causative of neurodegenerative diseases, such as α-synuclein, amyloid-β, tau, and abnormal huntingtin protein[99]. When these causative factors are released into the cytoplasm by damage to the lysosomal membrane and form aggregates, they can be released from the cell and spread to other cells by causing cell death, leading to neurodegenerative diseases. Similar case was seen with prion-like proteins[100]. It is also said that Cathepsin D leaked from damaged lysosomes leads to the release of cytochrome C from mitochondria, resulting in apoptosis[87]. In fact, it has been observed that cathepsin D is released into the cytoplasm of aging rat neurons.

Since lysosomes, like the ER, are reservoirs of calcium, damage to the lysosomal membrane can cause calcium to leak out. It has been reported that this leads to the collapse of calcium homeostasis, leading to Alzheimer's disease[101]. Calcium efflux activates calpain, which inhibits autophagy and leads to further lysosomal damage, leading to necrosis. Mutation in mucolipin1/TRPML1, a calcium channel on lysosomes, have been reported to cause mucolipidosis type 4[102], a neurodegenerative disease. On the other hand, calcium efflux activates calcineurin, a phosphatase, which phosphorylates TFEB, a transcription factor EB, and causes transcription factors necessary for autophagy and lysosome biogenesis to maintain healthy lysosomes[103]. Recently, it was reported that LC3-II is recruited onto lysosomes during lysosomal damage via an interaction with TRPML1[104]. This interaction further enhances calcium efflux and leads to the activation of TFEB. In order for

lysosomes to function normally, cells are thought to have various defense systems in place: including regulation by TFEB, initial repair responses by ESCRT, and clearance by lysophagy as a last resort[105].

[H1] Aggrephagy

[H2] p62 and other ubiquitin-dependent receptors of aggrephagy

The clearance of aggregated protein by selective autophagy is called aggrephagy[106,107]. p62/SQSTM1 is a critical aggrephagy receptor and its function was elucidated along with the initial characterization of the LIR motif[108,109]. Recent work revealed that the ULK1 complex is recruited to ubiquitin-p62/SQSTM1 condensates through a direct association of p62/SQSTM1 with FIP200[110], resulting in the de novo autophagosome formation leading to the engulfment of the protein condensates. The association between FIP200 and p62/SQSTM1 is mediated by the C-terminal claw-domain of FIP200 binding the disordered region of p62 overlapping with the LIR motif[110]. Interestingly, in contrast to NDP52, the interaction of p62/SQSTM1 with FIP200 requires an intact LIR[110]. Lastly, the FIP200-interacting region of p62/SQSTM1 is phosphorylated at various sites, and phosphorylation at these sites enhances the interaction between p62/SQSTM1 and FIP200[110], although the kinase/s phosphorylating p62/SQSTM1 at these sites remain unknown. Interestingly, TBK1 is also involved in facilitating aggrephagy by phosphorylating p62/SQSTM1 at serine 403 to enhance its interaction with ubiquitin and mediate receptor oligomerization[111]. However, whether TBK1 is

involved in the interaction between p62/SQSTM1 and FIP200 is currently not known (**Fig 5**).

There are two major pathways to degrade protein aggregates within cells - the ubiquitin proteasome pathway (UPS) and autophagy. The solubility of the aggregated proteins and size of the aggregates may determine whether the UPS or aggrephagy is mobilized for their degradation[112,113]. Oligomerization of p62/SQSTM1 was demonstrated to be important for the proper targeting of the phagophore to ubiquitinated substrates[60,61] in line with the previous finding that p62/SQSTM1 oligomerization is critical for its receptor function[109]. Indeed, the ubiquitin-mediated oligomerization of p62/SQSTM1 drives the formation of liquid-like membraneless condensates via the multivalent interactions between the ubiquitin chains and p62/SQSTM1 multimers [114]. Moreover, mutations that prevent ubiquitin-mediated p62/SQSTM1 phase separation into condensates reduce the autophagic degradation of p62/SQSTM1[115]. Apart from ubiquitin, ALFY and WDR81 were previously shown to facilitate the phase separation and clearance of p62/SQSTM1 condensates [116,117]. Furthermore, NBR1, which was previously identified as an aggrephagy receptor[118], aids in the oligomerization and phase separation of p62/SQSTM1 via its PB1 and UBA domain[119]. Thus, the hetero-oligomeric complex of p62/SQSTM1 and NBR1 may possess a higher affinity for ubiquitinated substrates compared to p62/SQSTM1 oligomers alone[119]. This is supported by the previous findings that the UBA domain of NBR1 binds more tightly to ubiquitin relative to the UBA domain of p62/SQSTM1[120,121].

Apart from p62/SQSTM1, it was also recently shown that TAX1BP1 plays an important role in the clearance of Poly-Q Htt aggregates in various models, including in iPSC-derived cortical neurons[122]. Indeed, TAX1BP1 was shown also to be important for degradation of NBR1-positive protein aggregates[123]. Furthermore, TAX1BP1, much like NDP52, can associate with FIP200 via its SKICH domain[123]. The association between TAX1BP1 and FIP200 allows for the clearance of NBR1 condensates independently from LC3 lipidation[123]. Surprisingly, the LC3-independent clearance of NBR1 by TAX1BP1 does not appear to require the ubiquitin-binding capacity of TAX1BP1, as deletion of the UBZ domain of the protein does not impair its function[123]. Thus, TAX1BP1, much like p62/ SQSTM1, is able localize the ULK1 complex to protein aggregates to promote their clearance via its association with FIP200 (**Fig. 5**).

[H2] Aggrephagy in neurodegeneration

A variety of neurodegenerative disorders are characterized by the age-dependent accumulation of protein aggregates[141]. Some of these proteins display prion-like properties and have been identified as substrates of selective autophagy. Hyperphosphorylated tau fibrils[125], amyloid-β[126], huntingtin[127], α-synuclein[128], RNA-binding protein transactive response DNA binding protein 43[112,129] (TDP-43), and Fused in Sarcoma[129] (FUS), have all been shown to be aggrephagy substrates. Indeed, it is thought that the trans-synaptic propagation of some misfolded proteins induces the aggregation of natively folded proteins in naïve neurons[130,131]. The stereotypic spreading of these prion-like proteins

within discrete neuroanatomical networks is correlated with the disease progression and clinical presentation of various neurodegenerative disorders[124,132]. Indeed, the postmitotic nature of neurons may confer their sensitivity to pathologic proteins. Thus, a critical pathomechanism involved in neurodegeneration is the aggregation and the network-dependent spreading of prion-like proteins, which may be exacerbated by inefficient autophagic clearance of such proteins.

[H1] Xenophagy in anti-bacterial defense

Xenophagy is a mode of selective autophagy in which autophagosomes sequester and eliminate pathogens invading the cytoplasm (**Fig. 6**). Although the initial barrier against pathogens is an organized response by the immune system, even non-phagocytic cells (e.g. epithelial cells) can counteract pathogens via xenophagy[133]. In addition to bacteria, xenophagy can also target a variety of infecting viruses through a process called virophagy[134]. The case of virophagy, antiviral function of autophagy proteins does not always need autophagosome maturation, suggesting that the mode of actions of each autophagy protein in virophagy often differs from xenophagy of bacteria[134]. Although the mechanism by which host cells recognize the targets of xenophagy is shared with other forms of selective autophagy, xenophagy is distinguished from other modes of selective autophagy since it targets invaders opposing host cells. While xenophagy limits the proliferation of bacteria in the host cells, many pathogens have the capacity to inhibit the formation of autophagosomes or neutralize lysosomal enzymes to prevent degradation (e.g.

Listeria RavZ protein inhibiting the recycling of LC3, *Shigella* IcsB protein that hampers recognition of bacterial VirG protein by ATG5, and Salmonella SopF disrupts infection-induced V-ATPase-ATG16L1 interaction)[135–138]. In some cases these pathologies even hijack and exploit the system of xenophagy to promote their own growth [134,139]. Nonetheless, xenophagy is an essential survival mechanism, as it targets many fatal pathogens such as Group A *streptococcus* (GAS)[9] and *Salmonella*[140] , which are often resistant to antibiotics.

[H2] Recognition of the bacteria for xenophagy

Although the mechanism of invasion varies among pathogens, the major key factors needed for the recognition system are the ubiquitin labelling of targets and receptor proteins that bind to both LC3 proteins and ubiquitinated targets (**Fig. 1**). When bacteria invade cells, they are surrounded by endosomal membranes, which are subject to degradation by the endosomal-lysosomal system. In case of *Salmonella*, they proliferate by forming a SCV (*Salmonella*-containing vacuole) to avoid lysosomal degradation[141]. A small but significant fraction of invading *Salmonella* is released into cytoplasm by damaging the membrane surrounding the bacteria, followed by their decoration with polyubiquitination[142]. Thus, membrane rupture works as a danger signal provoking following events for xenophagy. The ubiquitinated fraction of *Salmonella* with ruptured membrane becomes positive for LC3 and sequestered by an autophagosome[140]. It has been shown that incorporation of just polystyrene beads bearing a reagent that damages endosomal membranes is

sufficient to cause formation of autophagosome-like membranes formation surrounding the beads,[143] the rupture of host membranes works as an universal danger signal provoking following events for xenophagy. However, this does not necessarily mean that bacterial proteins are irrelevant during recognition. Indeed, recent reports show that several bacterial proteins are involved in the recognition process. *Mycobacterium tuberculosis* protein Rv1468c is directly bound to ubiquitin for sequestration by the autophagosomal membrane[144]. The GlcNAc side chains of the GAS surface carbohydrate structure is recognized by FBXO2, a component of the ubiquitin ligase complex SCF, promoting the ubiquitination of the invading GAS [145]. The lipopolysaccharide (LPS) of the invading *Salmonella* is ubiquitylated by ubiquitin ligase RNF213 that is needed for the restriction of bacterial growth in host cells. It supports the idea that non-proteinaceous ubiquitylation substrates derived from pathogens or host cells may play a pivotal role in xenophagy[146]. Thus, factors derived from both hosts and bacterium become targets for the recognition. Moreover, galectins are not merely used as markers for the ruptured membrane, they also play an essential role in pathogen recognition. Among several galectin subtypes, such as galectin-8, play a major role in the recruitment of NDP52, a receptor protein described below. Indeed, NDP52 binding to galectin-8 on ruptured SCVs suppresses the expansion of invading *Salmonella*[147] while other galectins such as galectin-1 and -7 may support xenophagy of invading GAS[148].

[H2] Polyubiquitination of bacteria and recruitment of receptor proteins

The ubiquitination of the targets for xenophagy requires several E3 ligases which promote polyubiquitin chains including K6-, K27-, K33-, K48-, K63- and linear polyubiquitin chains. Each E3 ligase may have distinct functions for restriction of the proliferation of invading bacteria. Parkin, an E3 ligase required for mitophagy, is needed for K63-linked ubiquitination and growth-limitation of *M. tuberculosis*[149]. By contrast, the E3 ligase Smurf1 facilitates K48-linked ubiquitination of bacteria[150]. Parkin is required for the recruitment of p62 to the invading *M. tuberculosis*, whereas Smurf1 is dispensable for this process. By contrast, Smurf1 is needed to target the proteasome to the bacteria, whereas Parkin is not. The LRR-containing RING E3 ligase LRSAM1, which shows E3 ligase activity for K6- and K27-linked polyubiquitin changes in vitro, is required for the ubiquitination of several types of bacteria[151]. RNF166 is recruited to bacteria and facilitates subsequent recruitment and catalyzes K33-linked ubiquitination of p62[152]. LUBAC generates linear polyubiquitin chains and is activated upon *Salmonella* infection[153–155]. Notably, LUBAC localizes onto bacteria that have been already coated with ubiquitin, suggesting that it amplifies and refashions the ubiquitin coat[154]. Because this polyubiquitin chain on invading bacteria recruits not only optineurin for xenophagy, but also Nemo for activation of NF-kB, LUBAC-dependent recognition of the bacteria coordinates the actions of the anti-bacterial response in higher eukaryotes[154]. Xenophagy is facilitated by tethering of bacteria with autophagosomal structures by receptor proteins which can simultaneously bind to LC3 and ubiquitin (**Fig. 6**) [156]. p62 is recruited to invading *Salmonella* and suppresses their growth in host cells in a manner dependent on its activity of ubiquitin

binding[157]. NDP52 plays a unique and essential role in xenophagy because it also has galectin-binding domains in addition to ubiquitin-binding motif[37]. Moreover, it has an another role in the expulsion of intracellular bacteria; NDP52 binds to LC3 and MYOSIN VI to facilitate the maturation of bacteria-containing autophagosome[158]. Furthermore, NDP52 is required to recruit ULK1 complex to the bacteria in the cytosol, supporting the idea that autophagosomal structure is formed on the targets rather than recruited from the distant compartments to the bacteria[38,52] . NDP52 and p62 can be recruited to invading *Salmonella* independently, but act in the same pathway as the simultaneous knockdown of both receptors results in no additive increase in *Salmonella* growth than each single knockdown[159]. It has been shown that OPTN promotes xenophagy as a receptor protein and suppresses the proliferation of *Salmonella*[58]. Knockdown of CALCOCO family protein TAX1BP1 causes an increase in the number of ubiquitin-positive *Salmonella* and their hyper-proliferation[160]. Together with upstream regulators, LAMTOR1 and LAMTOR2, TAX1BP1 facilitates maturation of autophagosome containing invading GAS, and suppresses survival rate of GAS [161]. Tollip may also play a major role in xenophagy of GAS, as it facilitates recruitment of galectin-7 and other receptor proteins to invading GAS[148].

In summary, the coordinated ubiquitination of factors derived from both host and bacteria is critical for the recognition of targets for xenophagy. However, it should be noted that the ubiquitination could not be always essential for xenophagy. For example, *Salmonella* is co-localized with either diacylglycerol

(DAG) or ubiquitination, suggesting that DAG and ubiquitination pathway work independently [162].

[H1] Autophagy of other cellular structures

In the following sections, we will provide a brief overview of some of the other autophagy pathways, with a particular focus on receptor proteins involved in each process.

[H2] ER-Phagy

The degradation of endoplasmic reticulum (ER) fragments by selective autophagy is called ER-phagy or reticulophagy. In mammalian cells, there are a number of ER-phagy receptor proteins. FAM134B, is an ER resident protein containing a C-terminal LIR motif to specify the targeting of autophagic membranes on ER[163]. RTN3, a member of the reticulon protein family, is another ER-phagy receptor possessing multiple N-terminal LIR motifs and functions independently of FAM134B[164]. In addition, SEC62[165], TEX264[166,167], atlastin-3[168], CCPG1[169], and CALCOCO1[170] have all been recently identified as ER-phagy receptors. Additionally, p62/SQSTM1 also aid in the removal of excess ER from hepatocytes[171]. Furthermore, p62/SQSTM1 has been shown to associate with K63-ubiquitinated TRIM13 to facilitate ER-phagy[172]. Amongst the various ER-phagy receptors, CCPG1 is particularly interesting due to its capacity to bind both LC3 proteins and FIP200 via distinct motifs and interaction with both ATG proteins is essential for CCPG1-mediated ER-phagy[169]. It is

important to note that the ER-phagy receptors discussed above are already localized on the ER, and therefore do not require ubiquitin to function as receptors.

Recently, a genome-wide CRISPR/Cas9 screen revealed that UFMylation, a ubiquitin-like posttranslational modification, is a critical regulator of ER-phagy. The group found that UFL1 ligase translocated to the ER during stress to UFMylate ER-resident proteins[173], akin to the role of PINK1/Parkin in tagging damaged mitochondria during mitophagy. In addition to this, another group identified a highly conserved cytosolic ER-phagy receptor, called C53[174]. C53 associates with autophagosomes during ER stress via a non-canonical LIR motif. C53 is also recruited to the ER through UFL1 ligase and DDRGK1, thus linking the recently discovered UFMylation pathway with the delivery of phagophores to the ER to facilitate ER-phagy[174].

[H2] Ribophagy

Ribosomes may be degraded by autophagy through ribophagy[175]. Pharmacologic inhibition of mTOR, starvation, and arsenite were all shown to elicit ribophagy[176]. Nuclear FMR1 Interacting Protein 1 (NUFIP1) was demonstrated to function as a ribophagy receptor in mammals. Indeed, NUFIP1 can directly interact with LC3B and ribosomes to facilitate ribophagy, and reduction of NUFIP1 inhibits ribophagy[177]. However, recent work demonstrated that knocking out NUFIP1 did not perturb ribophagy and using proteomics

revealed that ribosomal delivery to lysosomes contributed very little to ribosomal abundance during starvation and mTOR inhibition[178]. Overall, more work is required to clarify the molecular components and role of mammalian ribophagy.

[H2] Ferritinophagy

Selective autophagy can also modulate iron homeostasis through specific degradation of ferritin, an iron sequestering protein. This process is aptly termed ferritinophagy. Although iron is required for many biological processes, high levels free iron can generate ROS. Ferritin is able to sequester free iron and ensure intracellular iron homeostasis is within tolerated levels[179]. However, when iron levels are low, ferritinophagy is initiated to release iron[180].

Nuclear receptor coactivator 4 (NCOA4) is the receptor protein mediating ferritinophagy[181]. NCOA4 associates with the heavy and light chains of ferritin, as well as LC3 proteins[181], and is required for erythropoiesis[182]. Interestingly, NCOA4 was shown to interact with TAX1BP1 to facilitate the delivery of ferritin to the lysosome, even in the absence of FIP200[183]. Additionally, the researchers revealed that TBK1 is responsive to iron levels, and along with TAX1BP1 and ATG9A, mediated the lysosomal delivery of ferritin in FIP200 KO cells[183].

[H2] Pexophagy

Pexophagy is the selective autophagic degradation of surplus or damaged peroxisomes. Both p62/SQSTM1 and NBR1 have been shown to participate in pexophagy[184,185]. PEX2, a peroxisomal E3 ligase, was reported to ubiquitinate peroxisomal membrane proteins upon starvation to induce pexophagy[186]. Additionally, PEX2 activation and subsequent pexophagy induction requires NBR1[186]. Peroxisomes generate ROS as a by-product of fatty acid β-oxidation. Recently, ataxia-telangiectasia mutated kinase (ATM) was shown to translocate to peroxisomes due to increased ROS production. ATM binds to and phosphorylates the peroxisome import receptor PEX5, leading to PEX5 ubiquitination, which in turn targets p62/SQSTM1 to peroxisomes to facilitate pexophagy[187].

[H1] Therapeutic opportunities

Since a common pathologic feature of many neurodegenerative diseases is the accumulation of various pathogenic protein aggregates, there are many therapeutic strategies focused on increasing autophagy flux in neurons that are being developed to clear these aggregates[188]. Moreover, there are many ongoing efforts to improve the clearance of damaged mitochondria by activating mitophagy to aid Parkinson's diseases. Two examples include, inhibiting USP30, a deubiquitinase that disassembles ubiquitin chains placed by Parkin on OMM to stimulate the PINK1/Parkin pathway[189], and upregulating bulk autophagy[190]. Since a common pathologic feature of many neurodegenerative diseases is the accumulation of various pathogenic protein aggregates, there

757 are many therapeutic strategies focused on increasing autophagy flux in
758 neurons that are being developed to clear these aggregates[188].
759
760 In addition to these strategies, directing the autophagic machinery
761 directly to detrimental cargo may be a viable therapeutic approach (**Fig. 5**).
762 AMPK activates ULK1 during starvation-induced autophagy, while mTOR
763 inhibits ULK1[191]. However, mitochondrial tethering of ULK1 still induces
764 mitophagy even in AMPK KO cells or in cells overexpressing mTOR suggesting
765 these bioenergetic inputs can be bypassed during selective autophagy once
766 enough ULK1 is localized on cargo[41]. Indeed, this model was first proposed and
767 demonstrated for Atg1 in yeast cytosolic-to-vacuole targeting pathway[192,193],
768 suggesting this is a conserved mode of ULK1 activation during selective
769 autophagy. Recently, Atg11 dimerization was demonstrated to cluster Atg1,
770 resulting in the cis-autophosphorylation of Atg1, further suggesting clustering of
771 Atg1 and ULK1 is sufficient to elicit its kinase activation[194]. These observations
772 suggest that selective autophagy initiation can be decoupled from energy
773 sensors that normally activate or repress bulk autophagy. Thus, a new strategy
774 to enhance cargo selective autophagy is to identify chemical compounds that
775 mimic the role of receptor proteins without the need to alter AMPK or mTOR
776 signaling. Compounds that mimic receptors may be able to induce not just
777 mitophagy, but also the degradation of various toxic intracellular targets, such
778 as prion-like proteins, known to cause neurodegenerative diseases. The design
779 of these compounds is similar to PROTACs[195], but instead of targeting a E3
780 ligase to a substrate to engage the proteasome, these compounds instead

781 bridge cargo organelle and autophagy components. For example, a compound
782 able to simultaneously bind LC3 and huntingtin can diminish the levels of
783 aggregated huntingtin in vitro and in vivo[196], which in turn effectively decreased
784 huntingtin's disease-related pathologies, at least in flies[196]. Furthermore, a
785 compound known as AUTAC, which is composed of an organelle-localizing
786 molecule fused with a guanine-derivative, is able to induce mitophagy[197]. A
787 promising therapeutic strategy is to develop permutations of "double-headed"
788 compounds able to link different cargo with various autophagy proteins to
789 pathogens, such as protein aggregates, damaged organelles, or bacteria.
790 These receptor-like compounds would have a distinct advantage over
791 increasing bulk autophagy by potentially avoiding the wholesale autophagic
792 degradation of healthy organelles and intracellular components. Thus, in the
793 foreseeable future, a repertoire of receptor-like compounds may hold the
794 promise for ameliorating various diseases by degrading disease-related
795 pathogens with great precision (**Fig. 5**).
796
797 **[H1] Conclusions and Perspectives**
798
799 The newly defined capacity of receptor proteins to associate with
800 upstream autophagy components provides a mechanism for the spatiotemporal
801 control of selective autophagosome biogenesis. This model allows for the
802 rational design of multi-specific compounds that can target various disease-
803 relevant pathogenic cargos for autophagic disposal. There are, however, still
804 many open questions with respect to selective autophagy and its receptors. For
805 instance, an aspect of selective autophagy which is not well-understood is

whether various receptors that work to eliminate the same cargo can provide context-dependent control of selective autophagy by being activated only during certain biological stimuli. Furthermore, understanding the cellular contexts and molecular players that remodel the ubiquitylome on cargo organelles may offer another layer of control for cargo selection due to the varying affinities of ubiquitin-dependent receptors to various ubiquitin moieties. Thus, precisely how various receptors are spatiotemporally coordinated, what restricts their function only to certain cargos, and the physiologic relevance of the overlapping function of some receptors, remain to be elucidated. Unraveling the processes governing selective autophagy may help to generate pharmacologically viable approaches to address several diseases.

Conflicts of interest

J.N.S.V, M.H, T.K, **R.J.Y and T.Y.** declare no conflict of interest. This work was supported by the Intramural Program of the National Institute of Neurological Disorders and Stroke.

Author Contributions

M.H, T.K, and T.Y wrote and edited the sections on introduction, lysophagy and xenophagy, and created the figures and a table associated with these sections. **J.N.S.V** and **R.J.Y** wrote and edited the sections on mitophagy, aggrephagy, autophagy of other cellular structures, therapeutic opportunities, and conclusions and perspectives as well as created the figures associated with these sections.

Figure Legends

Table 1. Receptor proteins involved in mammalian selective autophagy

Figure 1. Schematics of non-selective autophagy and Selective autophagy

Autophagy degrades cytoplasmic components sequestered by a double-membrane structure called autophagosome in manners both non-selective and selective. Isolation membrane is generated at the autophagosome formation sites upon a range of cues such as nutrient starvation. In the case of non-selective autophagy, the isolation membrane/phagophore is expanded to form autophagosomes and sequester cytoplasmic components randomly, followed by fusion with a lysosome that allows the contents to be digested by hydrolytic enzymes. In the case of selective autophagy, autophagosomes are formed on specific targets. Ubiquitination is a major, but not a prerequisite, factor for the recognition of the targets to be degraded by selective autophagy. It facilitates the recruitment of receptor proteins and tethering of the isolation membranes with the targets, promoting the sequestration of them by autophagosomes that are often bigger than regular autophagosomes generated by the non-selective autophagy pathway.

Figure 2. Receptor protein initiates de novo autophagosome formation and expansion during PINK1/Parkin mitophagy

(1) Damage to mitochondria, such as loss of membrane potential, induces the stabilization of PINK1, leading to ubiquitin phosphorylation and the recruitment and activation of Parkin leading to increased conjugation of ubiquitin chains on outer mitochondrial membrane proteins. (2) These ubiquitin chains then recruit and stabilize receptor protein complexes on the damaged mitochondria through their respective ubiquitin-binding domains. Here shown for instance, NDP52 and OPTN. TBK1 is recruited and activated on the mitochondria by virtue of its interaction with NDP52, as well as OPTN, leading to TBK1 autoactivation and corollary phosphorylation of NDP52 and OPTN (3) NDP52/TBK1 interacts with FIP200 and thereby recruits and stimulates ULK1 activation by autophosphorylation directly on the mitochondria. Furthermore, OPTN can associate with ATG9A-positive vesicles and recruit these membranes to the

mitochondria. (4) Activated ULK1 complex can then recruit downstream autophagy components to foster the de novo biogenesis of the phagophore studded with lipidated-LC3 on the mitochondria (5) More receptor proteins are recruited to the growing phagophore through their interaction with LC3 proteins via their LC3-interacting regions, promoting the recruitment and activation of more ULK1 complex to facilitate the expansion and maturation of the phagosome. (6) The feedforward recruitment of ULK1 complex by NDP52/TBK1 and of ATG9A by OPTN/TBK1 allows efficient enclosure of cargo organelle by the autophagosome followed by the subsequent formation of autolysosomes and the degradation of the damaged mitochondria.

Figure 3. Mitophagy in health and disease

A) The upkeep of the mitochondrial network requires a balance between mitochondrial biogenesis and mitophagy to ensure that the requisite number of optimally functioning mitochondria is maintained. Many factors can contribute to mitochondrial damage, for example exposure to compounds that depolarize the mitochondria. The bioenergetic requirements of neurons may also contribute mitochondrial stress. Furthermore, normal aging may also result in various pathways involved in mitochondrial biogenesis or mitophagy to become less efficient. PINK1/Parkin-dependent mitophagy can specifically identify and degrade suboptimal or damaged mitochondria, whilst sparing health ones to preserve optimal mitochondrial function. However, mutations in various genes known to facilitate mitophagy can lead to a block in the clearance of damaged mitochondria resulting in their accumulation, which is a hallmark of various neurodegenerative diseases, such as Parkinson’s disease and Amyotrophic Lateral Sclerosis (ALS). B) The buildup of damaged mitochondria can initiate various pathomechanisms which are toxic to the cell. For instance, damaged mitochondria can release mtDNA, which then triggers the cGAS/STING pathway. The unmitigated activation of STING by mtDNA can lead to aberrant inflammatory response and cell death. Furthermore, mitochondrial impairments can lead to the release of cytochrome-c from the mitochondria to the cytosol triggering apoptosis. Lastly, mitophagic defects results in the increase of reactive oxygen species (ROS) and loss of ATP which then leads to bioenergetic defects that cause accelerated aging.

Figure 4. Schematic of Lysophagy

Various factors listed in the figure could cause lysosome membrane damage. Damaged lysosomes are labelled with Galectins, poly ubiquitinated, ELDR complex removes K48 ubiquitin chain then recruitment of receptors & Atgs to form autophagosome membranes.

Figure 5. Receptor recruitment during aggrephagy promotes de novo autophagosome biogenesis

A) During aggrephagy, p62 binds ubiquitinated misfolded proteins to form condensates. NBR1 is then recruited by p62 filaments via its PB1 domain resulting in larger ubiquitin-dense condensates due to the higher affinity UBA domain of NBR1. Furthermore, the recruitment of another receptor, TAX1BP1, to these condensates is facilitated by NBR1, leading to the delivery of the FIP200/ULK1 complex. B) Ubiquitination of pathogenic aggregated proteins, such as prion-like proteins that form insoluble fibrils and protein condensates initiates selective autophagy by recruiting various receptor proteins. Of particular importance, both p62 and TAX1BP1 recruit the ULK1 complex to these aggregates through their association with FIP200. This event leads to the clustering and the autoactivation of ULK1. FIP200 also serves as a platform for the recruitment of various ATG components, such as ATG9A-containing vesicles and the PI3K complex, which in turn promotes the de novo biogenesis of autophagosomes directly on these aggregated protein substrates. Another receptor protein, TOLLIP, is also recruited to protein aggregates via ubiquitin-binding to facilitate aggrephagy [198]. Lastly, although not receptor protein, ALFY has been proposed to be important for the clearance of protein aggregates [199]. C) Schematic of double-headed compounds that mimic receptor protein function to target the autophagy machinery to specific intracellular cargos. Designer molecules with multispecific affinity towards autophagy-related proteins and organelle or proteotoxic aggregates, for example, can be used to localized autophagy machinery to target cargos. The targeting of upstream autophagy machinery, ULK1 complex for instance, may be sufficient to stimulate the de novo formation of autophagosome around the cargo, prompting their degradation through the autophagic pathway. p62: sequestosome-1; NBR1: Neighbor of BRCA1 Gene 1 protein; PB1 domain: Phox and Bem1 domain; UBA: Ubiquitin-associated domain; TAX1BP1: Tax1-binding protein 1; FIP200:

FAK-interacting protein 200 kilodalton (also referred to RB1CC1; ULK1: Unc-51 Like Autophagy Activating Kinase 1; ATG9A: Autophagy-Related Protein 9A; ALFY: autophagy-linked FYVE protein; TOLLIP: Toll-interacting protein.

Figure 6. Schematics of Xenophagy

Bacteria invading into host cells are accompanied by host membrane, sometimes generating niche structure for bacterial growth such as SCV (*Salmonella*-containing vacuole) in case of *Salmonella* infection. Entering cytoplasm by rupturing the membrane, bacteria are labeled by galectin and ubiquitin, provoking recruitments of receptor proteins and machinery facilitating autophagosome formation. Receptor proteins tether bacteria and isolation membranes by binding both LC3 on the isolation membrane and ubiquitin on the bacteria. After the closure of the edge of the double membrane structure, the bacteria-containing double-membrane structure is fused with lysosomes, followed by a break-down of the contents by lysosomal enzymes.

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Glossary (to be ordered as it appears within the manuscript, not alphabetically)

TIM/TOM complex
Translocase of the inner membrane (TIM) & Translocase of the outer membrane (TOM) complex. Mitochondrial protein complexes that facilitate the translocation of cytosolic proteins containing a mitochondrial targeting sequence into the mitochondria.

p97
A protein, member of the AAA-ATPase, also called VCP or cdc48.

ATG9A
Autophagy-related protein 9A. A transmembrane protein with a phospholipid scramblase activity which plays a key role in the initiation of autophagy through the delivery of membranes to growing autophagosomes.

MAVS
Mitochondrial antiviral-signaling protein. Localized on the outer membrane of the mitochondria and activated by viral RNA leading to increased levels of pro-inflammatory cytokines.

DAMPs

Damage-associated molecular pattern. Various molecules released during cell death via infection or damage. For instance, mtDNA released by apoptotic cells act as a DAMP and is recognized by Toll-like receptor 9 expressed by other cells, leading to inflammatory response.

LLoMe

L-Leucyl-L-Leucine methyl ester is a dipeptide that gets activated by lysosome enzyme like cathepsin and ruptures lysosomal membrane.

ELDR

Endo-lysosomal damage response**.** Cellular response triggered by lysosomal damage. ELDR complex contains ubiquitin-directed AAA-ATPase p97/VCP, deubiquitinating enzyme YOD1, cofactors UBXD1, PLAA.

E3 ligase

E3 ubiquitin ligases selectively modify proteins by covalently attaching ubiquitin.

Transcription factor EB (TFEB)

Master regulator for lysosomal biogenesis.

Prion-like proteins

Proteins like prions, self-replicating protein aggregates. Causative for various neurodegenerative

Calpain

Calcium-dependent non-lysosomal cysteine proteases.

Tau

Protein functions to stabilize microtubules in axons. When hyperphosphorylated, it becomes insoluble aggregates, causative of dementias of nervous system such as Alzheimer’s diseases and Parkinson’s diseases.

Amyloid β peptide aggregates

amyloid plaques found in the brain of patients with Alzheimer’s disease. Accumulated amyloid beta peptide takes sheet structure and forms an amyloid plaque.

Huntingtin
Protein involves in axonal transport. Mutants are causative of Huntington's diseases.

Alpha synuclein
Neuronal protein that regulates synaptic vesicle trafficking and neurotransmitter release. Aggregates of alpha-synuclein is insoluble fibrils found in patients with Parkinson's disease.

TDP-43
RNA-binding protein transactive response DNA binding protein 43. An RNA-binding protein which is mutated in amyotrophic lateral sclerosis (ALS). Furthermore, the aggregation of this protein is the neuropathological hallmark of ALS and frontotemporal dementia.

FUS
Fused in Sarcoma. A protein that functions as an RNA-binding protein. Mutations in FUS lead to early onset ALS.

β-oxidation
The process of breaking down fatty-acids, which in eukaryotes, is facilitated by the mitochondria.

LPS
Lipopolysaccharide. A major component of outer membranes of gram-negative bacteria. It consists of lipid A, oligosaccharide and the O-antigen. The structure of lipid A and oligosaccharide is shared among many bacteria, but O-antigen is variable.

Galectins
Proteins termed S-type lectins which bind β-galactoside carbohydrates. They bind to glycoproteins on the inner membrane of endosomes, so endosomal membrane rupture causes the exposure of galectins to cytoplasm which works as a danger signal provoking selective autophagy.

PROTACS

PROteolysis TArgeting Chimeras. Heterobifunctional molecules that target E3 ligase complexes to specific substrates to induce the ubiquitination and subsequent proteasomal degradation of the target.

Table 1. Receptors involved in mammalian selective autophagy

Pathway	*Substrate*	*Size*	*Mammalian autophagy receptors*	*E3*	*Refs*	*Disease related*
Ub-dependent Mitophagy	Mitochondria	1-2 μm	NDP52, OPTN, p62, TAX1BP1, Tollip	Parkin	[31-32],[35],[40-41],[53],[64], [111]	Neurodegenerative diseases, in particular Parkinson's disease and Amyotrophic Lateral Sclerosis, cancer, accelerated aging, heart defects
Ub-independent Mitophagy	Mitochondria		NIX, BNIP3, FUNDC1, FKBP8, PHB2, NLRX1, AMBRA1, cardiolipin, ceramide, NIPSNAP1/2		Reviewed in detail in [42]	Neurodegenerative diseases, cancer, heart defects
Lysophagy	Lysosome	~1 μm	TAX1BP1, p62	FBXO27	[90-94]	Hypouricemic nephropathy, neurodegenerative diseases
Aggrephagy	Protein aggregate	~200 nm	p62, NBR1, OPTN, Tax1bp1		[108-110],[118],[123]	Implicated in many neurodegenerative disorders characterized by the accumulation of prion-like proteins
Xenophagy	Bacteria	1-5 μm	NDP52, p62, OPTN, TAX1BP1, Tollip	LRSAM1, Parkin, Smurf1, LUBAC, RNF166	[9],[38], [58], [140], [149-161]	Infectious diseases (e.g. Streptococcal infection and Shigellosis)
ERphagy	ER	1-5 μm	FAM134B, SEC62, RTN3, CCPG1, ATL3, TEX264		[163-174]	spastic paraplegia, autosomal-dominant hereditary sensory neuropathy
Ribophagy	Ribosomes	~500 nm	NUFIP1	UFL1	[175-178]	
Ferritinophagy	Ferritin	≥12 nm	NCO4A		[181-183]	Implicated with iron-dyshomeostasis in neurodegenerative diseases, cancer
Ub-dependent Pexophagy	Peroxisome	~500 nm	NBR1, p62		[184-187]	

Fig 1. Model of non-selective autophagy vs selective autophagy

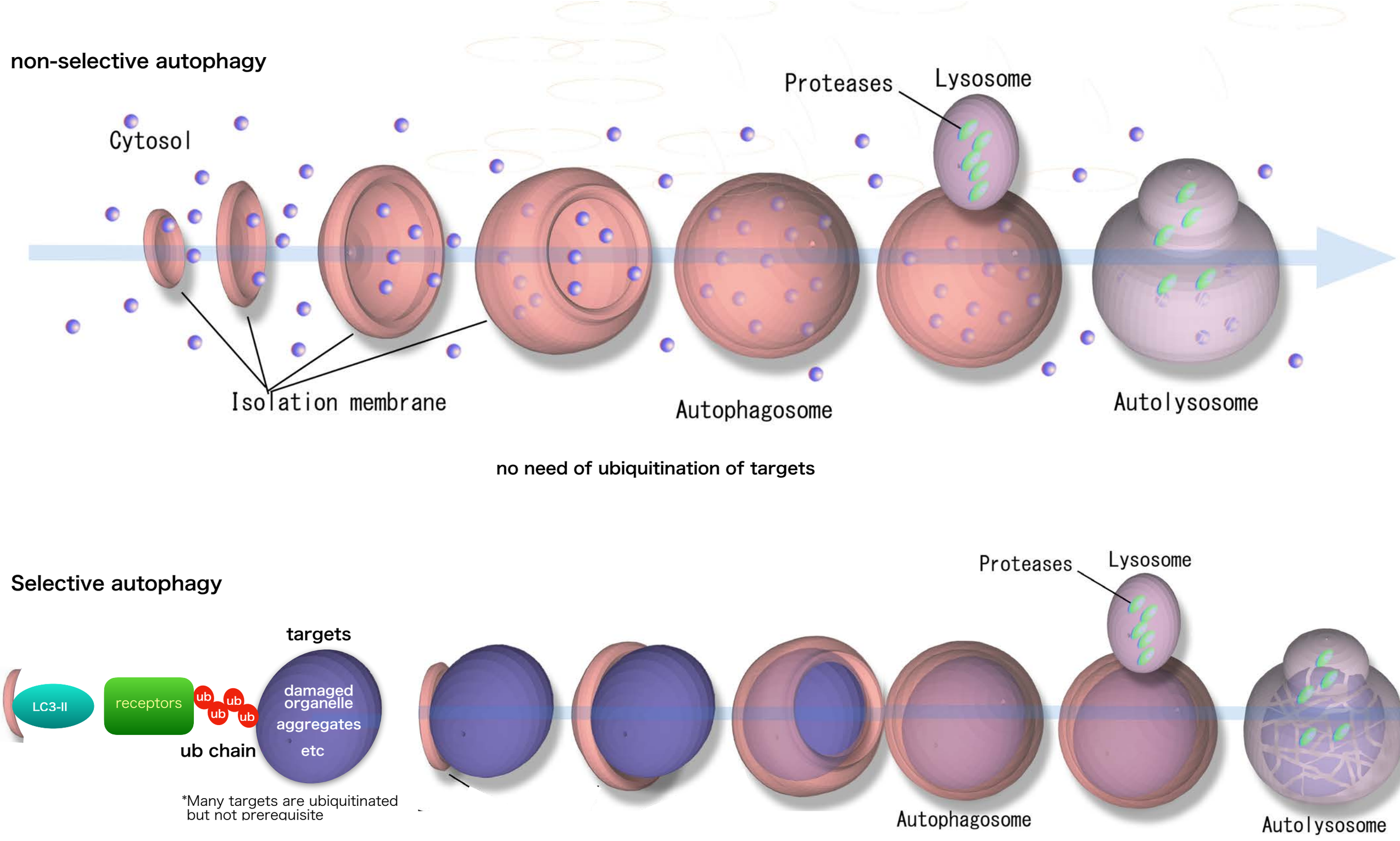
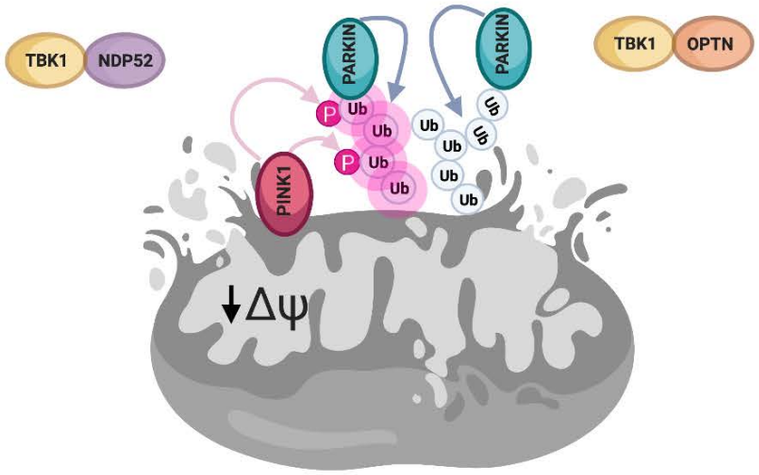
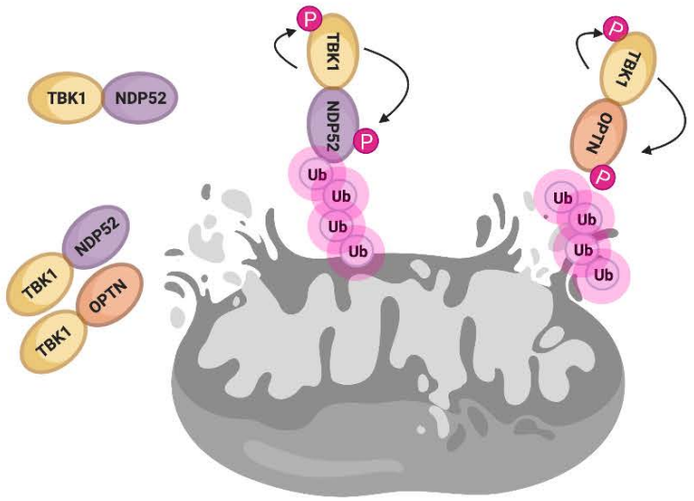


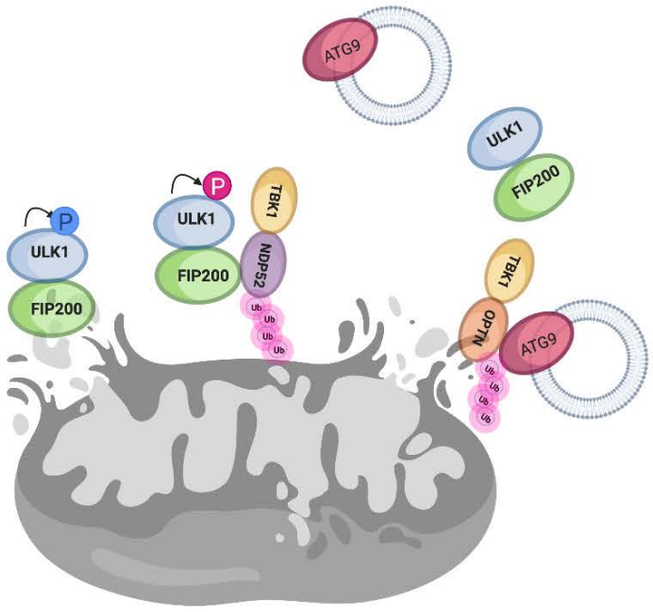
Fig 2. Receptor protein initiates de novo autophagosome formation and expansion during PINK1/Parkin mitophagy



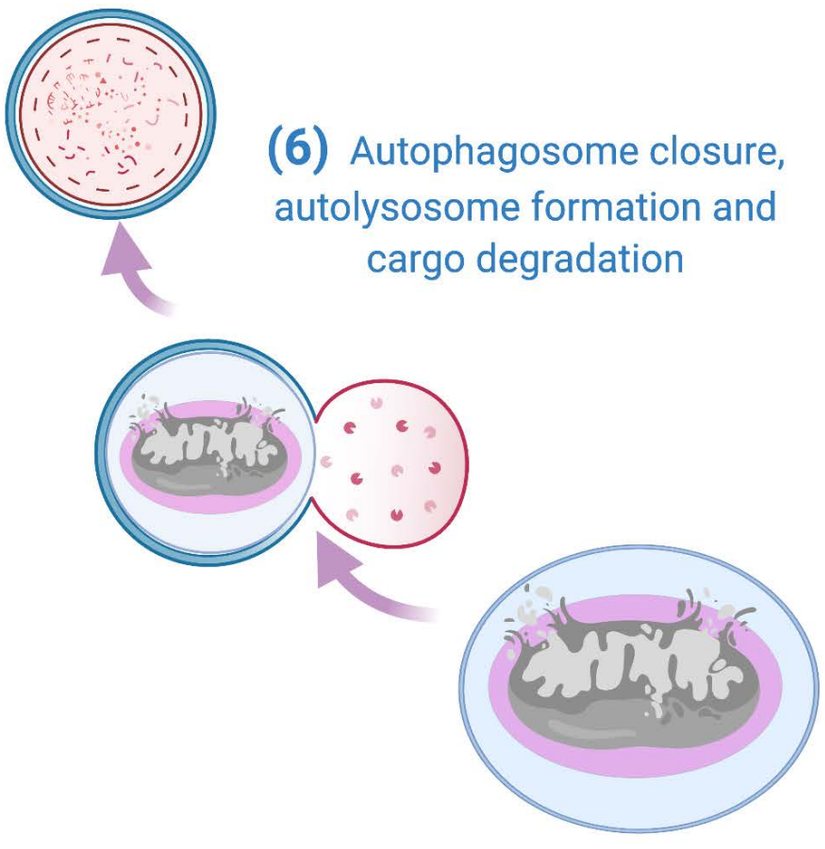
(1) PINK1/Pakin recruitment to damaged mitochondria and generation of S65-PO4 ubiquitin chains on OMMs



(2) Recruitment of NDP52/TBK1 proteins to mitochondria by S65-PO4 ubiquitin chains

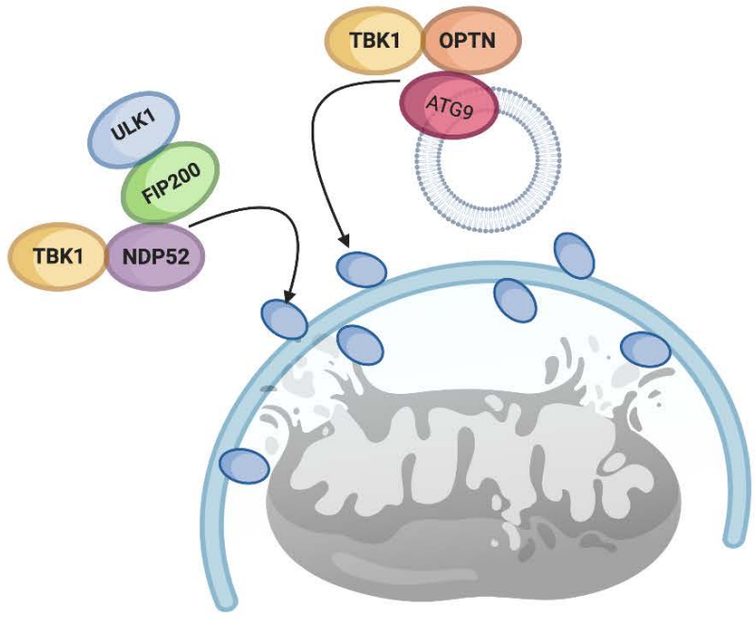


(3) Recruitment of ULK1 complex though interation between FIP200 and NDP52/TBK1 and ATG9A by OPTN



(6) Autophagosome closure, autolysosome formation and cargo degradation

(5) LC3-dependent recruitment of NDP52 and OPTN to maturing phagosome to facilitate membrane expansion



(4) De novo phagophore biogenesis, downstream ATG recruitment and LC3-lipidation

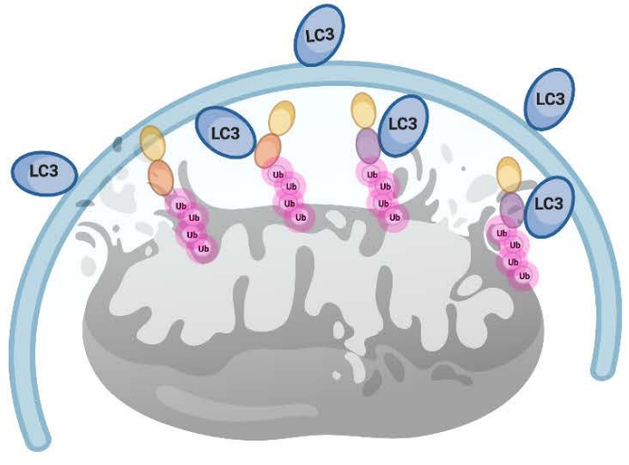


Fig 3. Mitophagy in health and disease

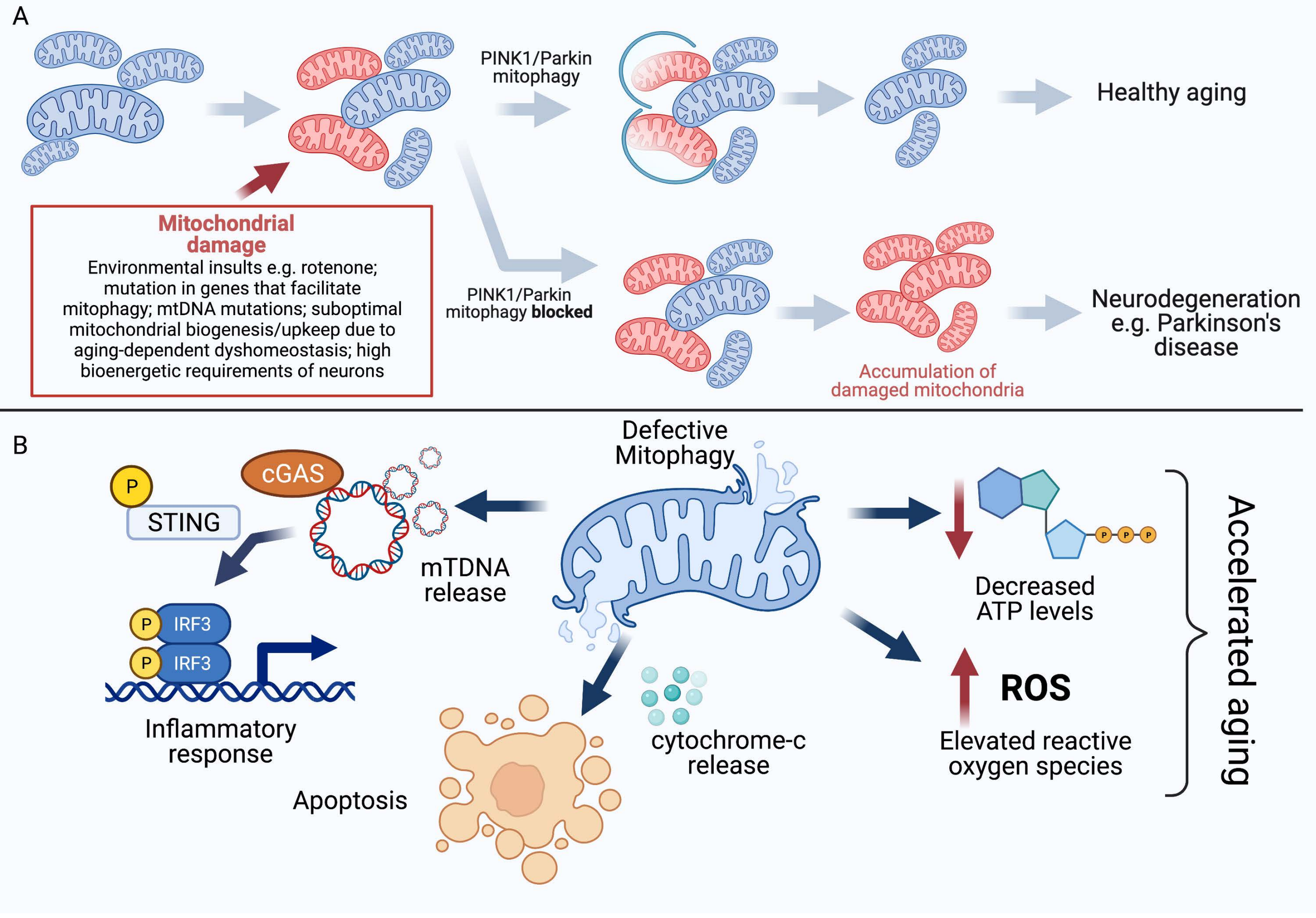


Fig 4. Schmatic of lysophagy

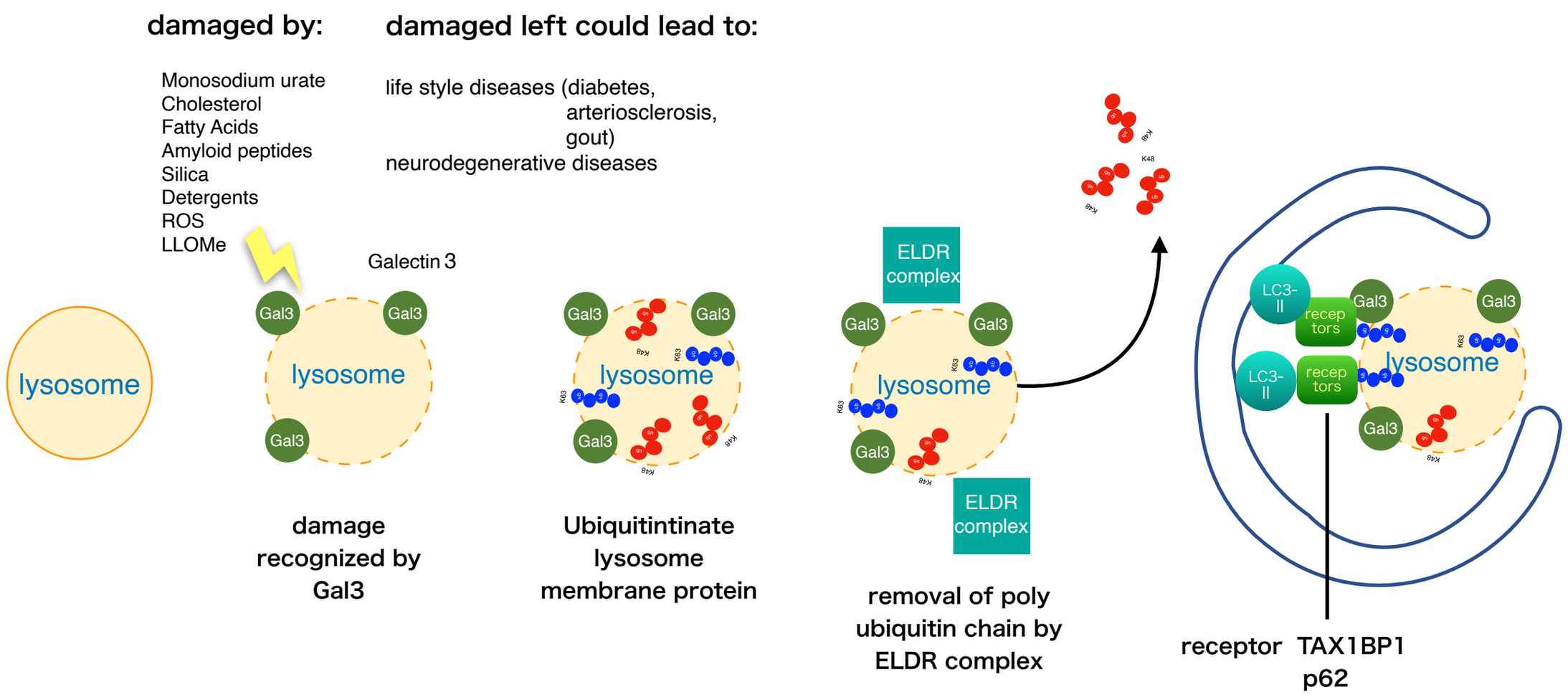


Fig 5. Receptor recruitment during aggrephagy promotes de novo autophagosome biogenesis

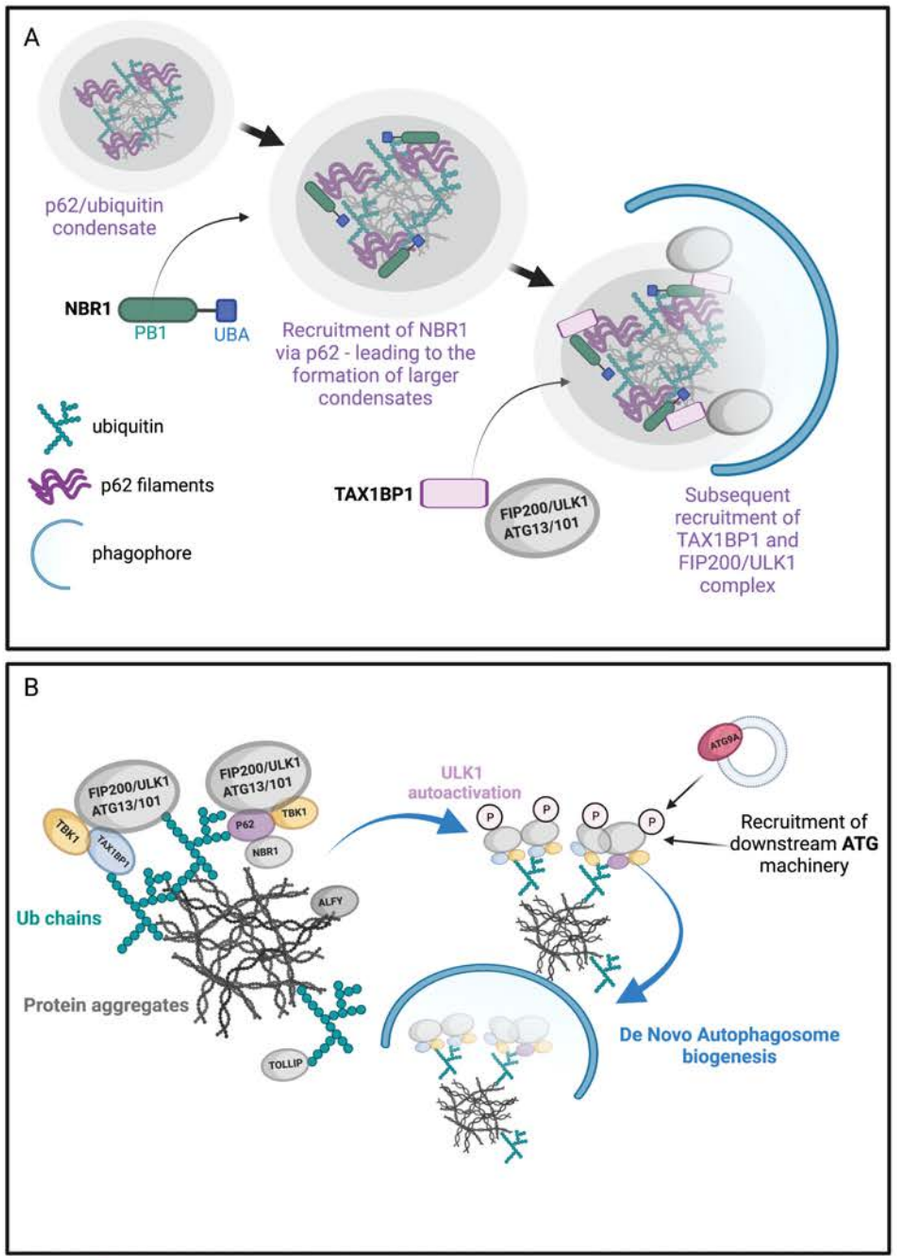


Fig 6. Schematics of enophagy