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Autophagy: supporting cellular and organismal homeostasis by self-eating

Running title: Autophagy supports homeostasis

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Abbreviations:

ALS, amyotropic lateral sclerosis; AMPK, adenosine monophosphate-activated protein kinase; ATP13A2, lysosomal type 5 ATPase; CMA, chaperone-mediated autophagy; DMC, 4,4′-dimethoxychalcone; ER, endoplasmic reticulum; GBA, glucocerebrosidase; LAMP2A, lysosome-associated membrane protein 2A; LRRK2, leucine-rich repeat kinase 2; PI3K, phosphoinositide 3-kinase; PI3P, phosphatidyl inositol 3-phosphate; PINK1, PTEN-induced putative kinase 1; SLE, systemic lupus erythematosus; TDP-43, Tar-DNA binding protein 43; TBK1, tank binding kinase 1; TFEB, Transcription factor EB; VCP, valosin-containing protein

Abstract

Autophagy is a conserved catabolic process that delivers cytoplasmic components and organelles to lysosomes for degradation and recycling. This pathway serves to degrade nonfunctional organelles and aggregate-prone proteins, as well as to produce substrates for energy production and biosynthesis. Autophagy is especially important for the maintenance of stem cells, and for the survival and homeostasis of post-mitotic cells like neurons. Functional autophagy promotes longevity in several model organisms. Autophagy regulates immunity and inflammation at several levels and has both anti- and pro-tumorigenic roles in cancer. This review provides a concise overview of autophagy and its importance in cellular and organismal homeostasis, with emphasis on aging, stem cells, neuronal cells, immunity, inflammation, and cancer.

1. Introduction

In autophagy, cells transport their own cytoplasmic material and organelles to lysosomes for degradation and recycling. Basal autophagy functions in intracellular quality control by degrading defective organelles and aggregate-prone proteins. Induced autophagy is initiated as a survival mechanism by stress such as starvation; by degrading redundant components, cells can produce nutrients and building blocks such as amino acids. Cytoplasmic material can be transported to lysosomes via three different paths (Galluzzi et al., 2017a). In macroautophagy, the first step is the engulfment of cytosolic cargo into membrane-bound autophagosomes (Figure 1). Autophagosomes then fuse with lysosomes and deliver their cargo for degradation and recycling (Mercer et al., 2018). In microautophagy, the endosomal or lysosomal limiting membrane internalizes the cytoplasmic cargo in a process topologically similar to endocytosis. The intraendosomal or intralysosomal cargo-containing vesicles are then degraded by the lysosomal hydrolases (Tekirdag and Cuervo, 2018). The third autophagic pathway is called chaperone-mediated autophagy (CMA), since it is assisted by cytoplasmic and lysosomal chaperones. The cargo proteins of CMA contain a signal sequence similar to the canonical KFERQ-sequence, which is recognized by the cytosolic chaperone HSC70 and its co-chaperones. The cargo-chaperone complex is recognized by a lysosomal receptor, the lysosome-associated membrane protein 2A (LAMP2A). LAMP2A and cytoplasmic as well as lysosomal chaperones mediate the unfolding and transport of the cargo protein through the lysosomal membrane (Kaushik and Cuervo, 2018).

The macroautophagic pathway is presented in Figure 2. Autophagosomes are formed by flat membrane cisterns called phagophores or isolation membranes. When the phagophore seals to engulf the cytoplasmic cargo, the resulting autophagosome has two lipid bilayers around it. The outer limiting membrane of the autophagosome then fuses with endosomes and finally with lysosomes. After fusion with endosomes, autophagosomes become amphisomes. Fusion with lysosomes produces autolysosomes. The cytoplasmic cargo, still surrounded by the inner limiting membrane of the autophagosome, is delivered to the lysosome. The limiting membrane must be degraded or at least permeabilized before the lysosomal hydrolases will be able to degrade the cargo. Macromolecules liberated in the degradation process are transported back to cytoplasm by pumps on the lysosomal membrane. Autolysosomes have at least two alternative clearance possibilities which are not mutually exclusive. Autolysosomes may fuse with the plasma membrane and empty their contents to the extracellular space (Medina et al., 2011). Another possibility is that lysosomes reform from autolysosomes (Yu et al., 2010).

2. Autophagy proteins regulate autophagosome biogenesis

Autophagy (atg) genes and proteins were originally discovered using yeast mutants (Baba et al., 1997; Thumm et al., 1994; Tsukada and Ohsumi, 1993), and corresponding genes and proteins were later found to function in mammalian cells. Upon autophagy initiation, ULK1 kinase complex, consisting or ULK1, ATG13, RB1CC1/FIP200 and ATG101, becomes active and translocates to the endoplasmic reticulum (ER) (Figure 3). The next step is the recruitment of the autophagy-specific phosphoinositide 3-kinase (PI3K) complex, containing the class III PI3-kinase PIK3C3/VPS34, PIK3R4/VPS15, Beclin1, ATG14, and other proteins. This leads to the production of PI3P and formation of omegasomes, specific ER subcompartments where autophagosome biogenesis occurs (Axe et al., 2008). Omegasomes are characterized by the PI3P-binding marker protein ZFYVE1/DFCP1. PI3P also recruits WIPI proteins to the forming phagophores. ATG12-ATG5 conjugates, which form larger complexes by binding to ATG16, are also recruited to the phagophores. WIPI proteins and the ATG12-ATG5-ATG16 complex promote lipidation of ATG8 homologs including LC3. LC3 is a widely used autophagosome marker protein, and its lipidated, phagophore-associated form is called LC3-II. The mammalian ATG8 protein family contains three LC3 forms (A, B, and C), GABARAP, GABARAPL1 and GABARAPL2/GATE-16. ATG9 is the only transmembrane protein among mammalian core autophagy proteins. ATG9 vesicles are known the play a role in autophagosome biogenesis, but the details of this role are not fully understood. ATG9 is recruited to the site of autophagosome formation either from the Golgi complex or from recycling endosomes. Recent review articles describe the current knowledge on autophagy proteins in more detail (Dikic and Elazar, 2018; Mercer et al., 2018; Wen and Klionsky, 2016).

Origin of autophagosome membranes has been investigated since autophagy was first described in late 1950's. Current view is that phagophores acquire membrane from several sources including ER, ER exit sites, mitochondria, ER-Golgi intermediate compartment, Golgi complex, recycling endosomes and plasma membrane. Membrane contact sites with any of the above organelles may also be involved in phagophore biogenesis. Origin of phagophore membranes is discussed in detail in several excellent reviews (Ktistakis and Tooze, 2016; Mari et al., 2011; Soreng et al., 2018; Yu et al., 2018). Maturation of autophagosomes to degradative autolysosomes depends on the small GTPase RAB7, its guanine nucleotide exchange factor CCZ1-MON1, the HOPS complex as well as syntaxin 17 and other SNARE proteins. Details of autophagosome maturation to autolysosomes are described in several recent reviews (Ktistakis and Tooze, 2016; Soreng et al., 2018; Yu et al., 2018; Zhao and Zhang, 2018; Zhao and Zhang, 2019).

Autophagy is stimulated by different stress conditions, of which amino-acid starvation is currently best understood. Lack of amino acids, oxygen, energy or growth factors inactivate the nutrient sensing protein kinase mTORC1, and as a consequence of this, mTORC1 sites of ULK1 become dephosphorylated. ULK1 then undergoes autophosphorylation. ULK1 also phosphorylates ATG13 and FIP200, the other components of the ULK1 complex, which stimulates the ULK1 kinase activity and the translocation of the ULK1 complex to the omegasome. Transcription factor EB (TFEB) is a key regulator of autophagy and lysosome biogenesis. TFEB is negatively regulated by mTORC1 activity, and during amino-acid starvation, TFEB is released from the inhibition to enhance the expression of autophagy and lysosomal genes. Autophagy is also induced by decreasing energy levels, e.g. during glucose starvation, which is sensed via ATP/AMP ratio by AMPK (AMP-activated protein kinase) as well as the serine/threonine-protein kinase LKB1 (also called STK11). AMPK can mediate autophagy induction either via mTORC1, or directly by inducing phosphorylation of ULK1,

VPS34, and Beclin1. A recent study revealed a new aspect in autophagy regulation. Autophagy induction was shown to depend on the eukaryotic translation initiation factor 5A (eIF5A), which is necessary for the translation of ATG3 (Lubas et al., 2018). ATG3 is one of the E2-like enzymes that mediate lipid conjugation to LC3B and other ATG8 family proteins. mTORC1 inhibition was shown to enhance the association of eIF5A with ribosomes. Autophagy signaling in described in more detail in several reviews (Damme et al., 2015; Gallagher et al., 2016; Rabanal-Ruiz et al., 2017; Zachari and Ganley, 2017).

Starvation-induced macroautophagy is considered to be unselective with respect to the cytoplasmic cargo. However, recent studies have revealed several selective modes of macroautophagy, including mitophagy (selective for mitochondria), aggrephagy (aggregates), reticulophagy or ER-phagy (endoplamic reticulum, ER), ribophagy (ribosomes), lipophagy (lipid droplets), lysophagy (damaged lysosomes), pexophagy (peroxisomes), and xenophagy (intracellular pathogens). The selectivity is mediated by autophagy receptors that have domains binding to one or more of the ATG8 homologs localized on the phagophore membrane, as well as domains binding to the cargo (Figure 4). Part of autophagy receptors recognize ubiquitin on the cargo, while others bind the cargo independent of ubiquitination (Khaminets et al., 2016). Ubiquitin-dependent autophagy receptors include SQSTM1/p62, NBR1, OPTN (optineurin) and CALCOCO2/NDP52, while ubiquitin-independent receptors include NIX, BNIP3, FUNDC1, RETREG1/FAM134B and galectin 8. One autophagy receptor can play a role in several types of selective autophagy, and one type of selective autophagy can be mediated by several receptors. A more complete description of autophagy receptors is presented in (Khaminets et al., 2016).

3. Autophagy supports cellular and organismal homeostasis

Autophagy maintains intracellular energy homeostasis and protects cells against stress. Post-mitotic cells like neurons and muscle cells are particularly dependent on autophagic clearance of defective organelles and aggregated proteins, since they are not able to renew their cytoplasm by cell division (Damme et al., 2015). Autophagy has been shown to support the health of both cells and organisms, and defects in autophagy lead to diseases including neurodegeneration, muscle diseases, cancer, immunological disorders and metabolic diseases (Dikic and Elazar, 2018; Levine and Kroemer, 2008; Levine and Kroemer, 2019). Several neurodegenerative diseases are connected to defective autophagy including Parkinson's, Alzheimer's, and Huntington's diseases and amyotropic lateral sclerosis (ALS) (Damme et al., 2015; Dikic and Elazar, 2018; Nixon, 2013; Wong and Holzbaur, 2015). Further, several studies have shown that functional autophagy can extend lifespan in different model organisms (Fernandez et al., 2018; Madeo et al., 2015; Melendez et al., 2003). However, the role of autophagy in cancer is context dependent. By clearing defective mitochondria that are a source of reactive oxygen species, autophagy inhibits tumor formation by decreasing oxidative stress (White et al., 2015). In addition, autophagy inhibits tumorigenesis by regulating inflammation and immunity (Zhong et al., 2016a). On the other hand, cancer cells can utilize autophagy to support their energy balance in order to survive stress, and increased autophagy has been connected to metastasis (Mowers et al., 2016; White et al., 2015). Figure 5 summarizes the functions of autophagy at cellular and organismal levels. The current knowledge on the role of autophagy in aging, neurodegeneration, immunity and cancer is discussed in more detail in the following paragraphs.

4. Aging, lifespan and stem cells

During aging, cells accumulate genetic and oxidative damage, which ultimately leads to the death of the organism. Several studies with model systems including yeast, Caenorhabditis elegans, Drosophila melanogaster and mice have shown that autophagy-related genes are required for lifespan extension under different longevity conditions, while autophagy-deficiency has less effect on normal lifespan (Hansen et al., 2018; Melendez et al., 2003; Nakamura and Yoshimori, 2018). Further, long-lived mutant animals display increased steady-state levels of autophagy proteins, suggesting increased autophagy activity. Both macroautophagy and chaperone-mediated autophagy activities decline when animals age, due to decrease in autophagy gene expression. On the other hand, overexpression of autophagy genes has been shown to extend the lifespan in several species. For example, overexpression of Atg8a in the nervous system of Drosophila extends the lifespan of the flies (Simonsen et al., 2008). Further, overexpression of the Drosophila transcription factor hlh-30 (TFEB in mammals), which regulates many autophagy and lysosomal genes, extends lifespan of the animals (Lapierre et al., 2013).

Specific constitutive activation of basal autophagy was recently studied in mice. The activation was achieved by introducing a point mutation, F121A, in Beclin1. The mutation impairs the binding of Beclin1 to BCL2, which would prevent Beclin1 function in autophagy. Remarkably, the Beclin1 mutation increased basal autophagic flux and prolonged the median survival of both male and female mice by 12% (Fernandez et al., 2018). Further, age-related renal and cardiac pathologies and spontaneous tumors were decreased in the mutant mice. Thus, increased basal autophagy increased both lifespan and healthspan in mice. Another recent study demonstrated the longevity-promoting effects of a natural flavonoid, 4,4′-dimethoxychalcone (DMC), in several species (Carmona-Gutierrez et al., 2019). DMC induces autophagy, and this induction was shown to be essential for its cytoprotective effects. DMC induced a conserved, systemic change in metabolism, which was independent of mTORC1, but instead depended on GATA transcription factors.

It has been established that autophagy activity declines with aging, but until recently, the underlying mechanisms of the decline were not known. A recent study showed that the expression of Rubicon, a negative regulator of autophagy, increases at both mRNA and protein levels in tissues of aged C. elegans, Drosophila, and mouse (Nakamura et al., 2019). Knockdown of Rubicon increased the lifespan of worms and flies, and in addition, several age-associated phenotypes decreased. Notably, knockdown of Rubicon in neurons was most effective in extending the lifespan. Rubicon knockout mice showed reduced fibrosis in the kidneys and decreased accumulation of α-synuclein in the brain. The authors conclude that inhibition of autophagy by increased levels of Rubicon is one of the signatures of aging.

A recent study showed that autophagy induction in hippocampal neurons is required to promote memory in mice (Glatigny et al., 2019). Autophagy was shown to promote activity-dependent structural and functional synaptic plasticity. Further, hippocampal autophagy was observed to decline with aging, and remarkably, restoring autophagy activity in old mice was sufficient to reverse age-related memory decline. Of note, the bone-derived molecule osteocalcin was identified as a direct hormonal inducer of hippocampal autophagy.

Stem cells have the ability to undergo both self-renewal and differentiation into different cell types. Like all cells, stem cell undergo aging and can lose their ability for self-renewal and/or differentiation, and this is associated with decline of organ functions during aging of the

organism. Basal autophagy is very active in different types of stem cells (Pan et al., 2013), and it is required for quality control, energy production, and metabolic reprogramming (Levine and Kroemer, 2019). Stem cells utilize autophagy to maintain their regenerative capacity, and autophagy is also activated during differentiation (Boya et al., 2018; Garcia-Prat et al., 2016a; Garcia-Prat et al., 2017; Guan et al., 2013). The regenerative capacity of muscle stem cells declines with aging, when the cells transition from quiescence to irreversible senescence (Garcia-Prat et al., 2016b). Basal autophagy was shown to be essential for the maintenance of quiescence in mice, and failure of autophagy caused senescence by mitochondrial dysfunction, oxidative stress, and loss of proteostasis. Similarly, autophagy is indispensable for the maintenance of hematopoietic stem cells (Mortensen et al., 2011). Interestingly, in hematopoietic stem cells, autophagy was shown to suppress metabolism by degrading healthy, active mitochondria, in order to maintain quiescence and stemness, while loss of autophagy caused metabolic activation and loss of stemness (Ho et al., 2017). Neural stem cells also depend on autophagy for both self-renewal and differentiation (Boya et al., 2018).

5. Neurodegeneration

Under physiological conditions, neurons have a relatively high level of basal autophagy (Nikoletopoulou et al., 2015). One of the hallmarks of several neurodegenerative diseases is the accumulation of unfolded or misfolded proteins in neuronal cells, which disrupts cell functions and eventually leads to cell death (Boland et al., 2018). The role of autophagy in neurons has been demonstrated using neural-cell-specific knockout of autophagy proteins (ATG5, ATG7 or FIP200/RB1CC1) that are indispensable for autophagosome formation (Hara et al., 2006; Komatsu et al., 2006; Liang et al., 2010). Shortened lifespan and progressive motor and behavioral defects were observed in the mutant mice. The animals showed severe neurodegeneration and histological analysis revealed accumulation of ubiquitin-positive aggregates in neurons.

Dysfunctional mitochondria are another major cause for neurodegeneration, since they produce reactive oxygen species that damage proteins, lipids, carbohydrates, and nucleic acids (Birben et al., 2012; Joshi and Mochly-Rosen, 2018). Several proteins with neurodegenerative disease-causing mutations have been connected to autophagy, especially mitophagy, or lysosomal function (Gan-Or et al., 2015; Levine and Kroemer, 2019; Trinh and Farrer, 2013). Accumulating evidence indicates that active autophagy is beneficial in preventing neurodegeneration. Accordingly, autophagy induction is explored as a way to treat or prevent neurodegenerative diseases (Boland et al., 2018; Dikic and Elazar, 2018). The role of autophagy in three major neurodegenerative diseases, Parkinson's disease, Alzheimer's disease, and amyotropic lateral sclerosis, is discussed in more detail below.

5.1. Parkinson's disease

Increasing evidence shows that lysosomal and autophagosomal dysfunction and the development of Parkinson's disease are closely linked (Lynch-Day et al., 2012). Two proteins that function in mitophagy, PTEN-induced putative kinase 1 (PINK1) and the ubiquitin ligase Parkin, are strongly associated with early-onset Parkinson's disease (Hernandez et al., 2016). Depolarization of mitochondria initiates a cascade on the mitochondrial surface, including PINK1-mediated phosphorylation and Parkin-mediated ubiquitination, which leads to recruitment of autophagy machinery to the mitochondrion (Pickles et al., 2018). Several other Parkinson's disease-associated proteins also function in autophagy or lysosomes including LRRK2, ATP13A2 and GBA (Hernandez et al., 2016). LRRK2 (leucine-rich repeat kinase 2) is a

large multi-domain protein implicated in several cellular functions including autophagy (Manzoni and Lewis, 2017), mitochondrial function, and vesicular trafficking. Disease-causing mutations of ATP13A2 (lysosomal type 5 ATPase) impair lysosomal acidification and proteolytic activity, thereby also decreasing autophagic flux and the clearance of α-synuclein aggregates, which typically accumulate in neurons in Parkinson's disease (Dehay et al., 2012). Aggregation of α-synuclein eventually disturbs neuronal function and leads to cell death. ATP13A2 was also recently shown to promote autophagosome-lysosome fusion (Wang et al., 2018). Glucocerebrosidase (GBA) is a lysosomal enzyme required for the degradation of glucocerebroside to ceramide. Knockdown of GBA in cortical neurons was shown to cause accumulation of α-synuclein (Mazzulli et al., 2011). Notably, homozygous or heterozygous GBA mutations are associated with 20-fold increase in the risk of Parkinson's disease (Schapira, 2015).

α-Synuclein contains the KFERQ-sequence that acts as a zip code for CMA, and accordingly, α-synuclein has been shown to be turned over via CMA (Cuervo et al., 2004). Further, other studies have shown that also macroautophagy is beneficial for cells expressing mutant α-synuclein. Induction of macroautophagy by overexpression of Beclin1 or rapamycin treatment could rescue α-synuclein degradation in neuronal cell lines overexpressing α-synuclein (Spencer et al., 2009). Lentivirus-mediated overexpression of Beclin1 also decreased the Parkinson's disease pathology of α-synuclein transgenic mice. These results suggest that both CMA and macroautophagy contribute to the turnover of α-synuclein. Prolyl oligopeptidase enzyme has the ability to accelerate α-synuclein aggregation, and an inhibitor of prolyl oligopeptidase activity, KYP-2047, was demonstrated to decrease the amount of α-synuclein aggregates in cell cultures and α-synuclein transgenic mice (Savolainen et al., 2014; Svarcbahs et al., 2016). Importantly, cell culture experiments indicated that KYP-2047 accelerated the clearance of α-synuclein aggregates by increasing autophagy (Savolainen et al., 2014).

5.2. Alzheimer's disease

Alzheimer's disease is characterized by the accumulation of amyloid β-peptide and Tau in neurons (Boland et al., 2018; Hamano et al., 2018; Xin et al., 2018). Both autophagy and proteasomes have been implicated in the normal intracellular clearance of these two proteins. A recent study analyzed transcriptomics data of post-mortem brains of Alzheimer's and type 2 diabetes patients. Data analysis indicated a principal role for autophagy dysfunction in both diseases (Caberlotto et al., 2019). The role of autophagy-related genes was confirmed using an Alzheimer mouse model. Cholesterol accumulation is another symptom common to many neurodegenerative diseases including Alzheimer's disease. High brain cholesterol levels in an Alzheimer mouse model were shown to enhance autophagosome formation but inhibit their fusion with endosomes and lysosomes, which resulted in impaired clearance of both amyloid β-peptide and Tau (Barbero-Camps et al., 2018). Hyperphosphorylation of Tau protein leads to the formation of aggregates called neurofibrillary tangles, and autophagy has been implicated in the removal of these aggregates. Selective autophagy was recently shown to protect cells against seeded Tau aggregation (Falcon et al., 2018). Tau assemblies move from cell to cell by exocytosis and endocytosis. The endocytosed Tau assemblies escape to the cytosol by damaging the endosomal membrane. However, the danger receptor galectin-8 detects the damaged endosomes and initiates selective autophagy, thus limiting the release of Tau assemblies into the cytosol where they would act as seeds for larger aggregates. Another study showed that

Tau has the potential to inhibit mitophagy by reducing the recruitment of Parkin to damaged mitochondria (Cummins et al., 2018).

Amyloid precursor protein is processed in cells by BACE1 and γ-secretase. The cleavage by BACE1, followed by γ-secretase, produces the harmful amyloid β 40 and 42 peptides. A recent study asked how γ-secretase processing of amyloid precursor protein affects autophagy and lysosomal functions in monogenic Alzheimer's disease (Hung and Livesey, 2018). Neurons with mutations in amyloid precursor protein and presenilin1, another protein linked to Alzheimer's disease, were demonstrated to have defects in lysosomal proteolysis and autophagosome clearance. The rapid appearance of these defects was interpreted to indicate that they are causes, rather than consequences, of neuronal dysfunction. When BACE1 enzyme was inhibited, lysosome function was restored in both amyloid precursor protein and presenilin1 mutant neurons. Further, presenilin1 mutant phenotype was rescued by deletion of amyloid precursor protein. Another recent study showed that expression of Alzheimer's disease mutant amyloid precursor protein in primary mouse hippocampal neurons induced defects in autophagy, mitophagy and mitochondrial functions (Reddy et al., 2018). Further, mutations in presenilin1 have been implicated in impaired lysosomal acidification, due to disturbed transport of a v-ATPase subunit from the ER to lysosomes (Lee et al., 2010). Impaired lysosomal acidification causes accumulation of autolysosomes in the cytoplasm, which disturbs neuronal functions.

5.3. Huntington's disease

Huntington's disease is a hereditary disorder caused by expanded GAG trinucleotide repeats in the gene encoding Huntingtin protein. Huntingtin is a large protein with several proposed functions including endocytosis, vesicle transport and autophagy (Harjes and Wanker, 2003). The expanded polyglutamine repeats in Huntingtin make the protein prone to aggregation. Polyglutamine-containing Huntingtin is normally turned over via autophagy (Ravikumar et al., 2002; Yamamoto et al., 2006), and autophagy induction has been shown to reduce toxicity of polyglutamine proteins in Huntington animal models (Ravikumar et al., 2004). Huntingtin has been demonstrated to function as an adaptor protein in selective autophagy (Rui et al., 2015). Huntingtin was shown to participate in SQSTM1-mediated cargo recognition by facilitating the binding of SQSTM1 to polyubiquitinated proteins. Further, by interacting with ULK1, Huntingtin was able to dissociate ULK1 from its inhibitory interaction with mTORC1. Another study showed that ULK1-mediated autophagy induction is disturbed in a Huntington mouse model (Wold et al., 2016). Further, polyglutamine extension in Huntingtin was shown to competitively disturb the interaction of Beclin1 with the deubiquitinase ataxin3. This disruption lead to proteasomal degradation of Beclin1, which decreased autophagosome formation (Ashkenazi et al., 2017).

To summarize the studies described above, aggregated polyglutamine-containing Huntingtin is less able to carry out its functions in autophagy, which enhances its accumulation in cells. In agreement with this, a recent study demonstrated that aggregated Huntingtin inhibits autophagy in neuronal cells. This lead to accumulation of Argonaute-2, a protein that executes microRNA functions. Thus, impaired autophagy due to Huntingtin aggregation caused a global dysregulation of microRNAs in neurons (Pircs et al., 2018). The deubiquitinase USP12 was recently shown to induce autophagy and protect neurons in Huntington's disease models (Aron et al., 2018). USP12 overexpression was demonstrated to increase autophagic flux in neurons approximately six-fold, while suppression of endogenous USP12 inhibited

autophagy. Notably, catalytic activity of USP12 was dispensable for its neuroprotective and autophagy-inducing functions.

5.4. Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a neuromuscular disease that involves loss of motor neurons in the spinal cord and brain. Deficiency of autophagy and/or mitophagy has been implicated in this disease (Evans and Holzbaur, 2018). ALS is characterized by accumulation of protein aggregates containing Tar-DNA binding protein 43 (TDP-43) as well as abnormal mitochondria in motor neurons (Taylor et al., 2016). A large number of different genes have been implicated in the hereditary forms of ALS. These genes are associated with differing cellular functions including ribosome/RNA function, proteostasis, mitochondrial function, cytoskeleton, and intracellular traffic. Notably, several of the ALS-associated proteins have connections to autophagy and/or mitophagy, including autophagy receptors SQSTM1, optineurin and ubiquilin2, as well as TBK1 (tank binding kinase 1) that functions in mitophagy and xenophagy (Damme et al., 2015; Ravenhill et al., 2019; van Beek et al., 2018). A recent study showed that the autophagy receptor NDP52 binds TBK1, and this complex targets ULK1 to mitochondria, in order to initiate mitophagy (Vargas et al., 2019). In addition to their autophagy cargo receptor function, SQSTM1, optineurin and ubiquilin2 also act in the degradation of substrates via the proteasome system.

The most common genetic cause of ALS and the related disorder, frontotemporal dementia (FTD), is the expansion of a hexanucleotide repeat in a non-coding region of the gene C9orf72. The C. elegans orthologue of this gene product was shown to function in degradation of endosomal and lysosomal content and in lysosome reformation, and defects in its function lead to defects in the clearance of autophagosomal cargo (Corrionero and Horvitz, 2018). Another protein mutated in TDP-43 proteinopathies is the valosin-containing protein (VCP). VCP is a member of the AAA^{+}-ATPase (ATPase associated with diverse cellular activities) protein super family (Johnson et al., 2010). Mutations in VCP lead to impaired fusion of autophagosomes with lysosomes (Ju et al., 2009; Tresse et al., 2010).

6. Immunity, infection and inflammation

Autophagy has been implicated in several immune functions including removal of intracellular pathogens, cytokine secretion, inflammation, antigen presentation and lymphocyte development. Xenophagy, a type of selective autophagy, participates in innate immunity by targeting certain intracellular pathogens for degradation in lysosomes (Gkikas et al., 2018). The first observations on xenophagy were reported for intracellular group A Streptococcus, which were shown to be selectively targeted by autophagy (Nakagawa et al., 2004). Other intracellular bacteria including Listeria, Salmonella, Legionella and Shigella are degraded by a similar xenophagy mechanism (Gomes and Dikic, 2014). Similar to other types of selective autophagy, xenophagy is mediated by autophagy receptor proteins including SQSTM1, NBR1, NDP52 and optineurin. Some pathogens are able to modify the xenophagic or phagocytic processes in a way that allows them to survive and multiply inside these cellular compartments. Mycobacterium tuberculosis persists inside phagosomes in phagocytic cells by interfering with the biogenesis of degradative phagolysosomes. This interference could be rescued by stimulating autophagy in macrophages (Gutierrez et al., 2004). Autophagy induction resulted in the recruitment of the autophagy protein LC3 to the bacteria-containing phagosomes, which facilitated fusion of the phagosomes with lysosomes. This type of phagocytosis is called LC3-associated phagocytosis (LAP) (Martinez, 2018).

The molecular mechanisms of xenophagy and mitophagy are remarkably similar, including participation of autophagy receptors and the Parkin ubiquitin ligase (Gkikas et al., 2018). Mitophagy also plays an important role in inflammation. By removing damaged mitochondria, mitophagy prevents the accumulation of depolarized mitochondria that are a source of reactive oxygen species and oxidized mitochondrial DNA, which would activate inflammatory signaling, leading to chronic inflammation (Gkikas et al., 2018; Nakahira et al., 2011; Zhong et al., 2016b). Autophagy can also selectively degrade inflammasome components (Deretic and Levine, 2018). TRIM proteins are autophagy receptors that have been demonstrated to play a role in autophagic degradation of several inflammasome proteins (Kimura et al., 2015). Autophagy is also involved in antigen presentation by MHC-II molecules in macrophages, dendritic cells and thymic epithelial cells. Autophagosomes containing degraded pathogens or intracellular antigens fuse with the cellular compartments where MHC-II loading occurs (Kinsella et al., 2018; Paludan et al., 2005; Schmid et al., 2007). A recent study revealed yet another aspect in the interplay between autophagy and immunity. CD4+ T cells upregulate autophagy in response to activation. T cells unable to induce autophagy after T cell receptor activation showed defective signaling, leading to T cell anergy, a state of functional inactivation. In a mouse model of autoimmune disease, the inability of T cells to upregulate autophagy decreased the severity of the disease (Mocholi et al., 2018). Finally, autophagy genes have been demonstrated to play different roles during the development of both B cells and T cells (Kinsella et al., 2018).

Autophagy acts as an anti-inflammatory pathway, and defective autophagy has been associated with susceptibility to autoimmune and chronic inflammatory diseases (Bonam et al., 2018; Deretic and Levine, 2018; Levine and Kroemer, 2019; Yin et al., 2018). For example, polymorphisms of autophagy genes are associated with susceptibility to the inflammatory bowel disease called Crohn's disease, and to the autoimmune disorder called systemic lupus erythematosus (SLE). ATG16L1 is an autophagy protein that functions during autophagosome biogenesis. Mutations in ATG16L1, especially T300A point mutation, are linked with Crohn's disease. ATG16L1 has a caspase-cleavage motif, and the T300A variant significantly increases the susceptibility of the protein for caspase3 cleavage (Murthy et al., 2014). Mouse models of Crohn's disease were used to show that ATG16L1 can control inflammasome activation (Cadwell et al., 2008; Saitoh et al., 2008). Mutations in ATG16L1 are also associated with defects in innate immune response against enteric bacteria (Kinsella et al., 2018; Strisciuglio et al., 2013). Further, a missense mutation in the autophagy receptor NDP52 is also associated with Crohn's disease (Ellinghaus et al., 2013). The mutation was shown to impair the function of NDP52 in inhibiting the activation of inflammatory genes by NF-κB, and to have an effect on the stability of Toll-like receptor pathway proteins. IRGM is another established risk factor for Crohn's disease. IRGM was recently shown to inhibit NLRP3 inflammasome activation in order to reduce inflammation (Mehto et al., 2019). Mechanistically, IRGM was demonstrated to mediate selective autophagic elimination of the NLRP3 inflammasome.

Polymorphisms in ATG5, another protein that functions in autophagosome formation, are associated with susceptibility to SLE, and several lines of evidence show that autophagy contributes to the development of the disease (Ciccacci et al., 2018; Liu et al., 2016). The pathogenesis of SLE is not understood, but there are numerous ways how autophagy could influence the disease, and several autophagy-modulating drugs are used in clinical trials for SLE (Liu et al., 2016). Of note, chaperone-mediated autophagy has been observed to be hyperactivated in a subset of lymphocytes of SLE model mice. A peptide called P140 targets this autophagy pathway, and treatment with P140 resulted in weaker signaling of

autoreactive T cells and reduced symptoms in SLE model mice. The effect on T cell signaling was confirmed using T cells of SLE patients (Monneaux et al., 2005; Monneaux et al., 2003). Notably, in phase II clinical trials, P140 was able to significantly diminish the clinical manifestations of SLE (Zimmer et al., 2013).

7. Cancer

The role of autophagy in cancer is complex and highly context dependent; autophagy can both suppress and promote cancer progression (Dikic and Elazar, 2018; Yun and Lee, 2018). During cancer initiation autophagy is considered anti-tumoral due to its role in protection against metabolic, oxidative and inflammatory stress (Liang et al., 1999; Qu et al., 2003; Takamura et al., 2011). At later stages of tumorigenesis and metastasis, both anti- and pro-tumoral roles of autophagy have been reported, depending on the context.

The first findings connecting autophagy with cancer showed that monoallelic deletion of the autophagy gene BECN1 are associated with breast and ovarian cancer (Levine and Kroemer, 2019; Liang et al., 1999). BECN1 heterozygous mice showed decreased autophagy and increased incidence of tumors (Qu et al., 2003; Yue et al., 2003). Further, HER2, the oncogenic receptor tyrosine kinase that is often overexpressed in aggressive tumors, was shown to interact with Beclin1, and this interaction was shown to inhibit autophagy (Vega-Rubin-de-Celis et al., 2018). A recent study demonstrated another role for autophagy in tumor suppression. Replicative crisis prevents oncogenic transformation by eliminating pre-cancerous cells that have lost their cell-cycle checkpoints. Autophagy was shown to play a major role in the cell death during replicative crisis (Nassour et al., 2019). When autophagy was suppressed, the cells were able to bypass the crisis, continued to proliferate, and accumulated genome instability. Further, telomere dysfunction was demonstrated to trigger autophagy.

Human cancers with activity-increasing HRAS and KRAS mutations often have increased levels of basal autophagy, which maintains functional mitochondria and cellular metabolism. Autophagy also supports survival during starvation that often occurs in the center of solid tumors (Guo et al., 2011). The status of the tumor suppressor p53 was reported to determine the role of autophagy in pancreatic tumorigenesis in mice (Rosenfeldt et al., 2013). The mice had an oncogenic allele of KRAS in the pancreas, which lead to the appearance of a small number of pre-cancerous lesions that proceeded to cancer over time. The progression to cancer was not observed in mice lacking essential autophagy genes. However, if the mice lacked p53, loss of autophagy did not block tumor progression. Another recent study revealed a mechanism for the autophagy-dependency of KRAS-driven liver tumorigenesis: autophagy was shown to control asparagine homeostasis (Lin et al., 2018). Autophagy-deficient tumors suffered from asparagine deficiency and therefore grew more slowly, and the tumor cells also showed reduced mitochondrial function. Further, another study showed that host-specific autophagy deficiency impairs tumor growth due to reduction of circulating arginine (Poillet-Perez et al., 2018). Glioblastoma is one of the most malignant forms of brain cancer due to resistance to chemotherapy. This tumor type utilizes oxidative phosphorylation, aerobic glycolysis, as well as autophagy to maintain its energy homeostasis (Zou et al., 2014). A recent study showed that autophagy inhibition prior to chemotherapy was able to impair the mitochondrial function and energy balance of the cancer cells, leading to apoptotic cell death (Kriel et al., 2018).

Autophagy also has a dual role in metastasis (Kenific et al., 2010). At early stages of metastasis, autophagy is mainly anti-metastatic due to limitation of necrosis and inflammation, while at later stages autophagy promotes metastasis due to promotion of cancer cell survival. Autophagy enables extracellular-matrix-detached cancer cells to avoid anoikis, cell death due to loss of anchorage (Guadamillas et al., 2011). Autophagy has also been shown to assist the migration of metastatic tumor cells by recycling of focal adhesion proteins (Sharifi et al., 2016). Autophagy inhibition was demonstrated to inhibit tumor cell migration and invasion in vitro and retard metastasis in vivo. Another study showed that autophagy inhibition decreased metastasis of osteosarcoma cells (Zhang et al., 2018). In oncogenic-RAS-transformed epithelial cells, depletion of autophagy genes inhibited invasion in vitro and metastasis in vivo (Lock et al., 2014). In the latter study, the increased invasive capacity was shown to be due to autophagy-dependent secretion of the pro-migratory cytokine interleukin 6.

Many forms of cancer therapy induce autophagy in tumor cells, which helps them to survive stress caused by the treatment. Accordingly, inhibition of autophagy at the time of therapy has been suggested to be beneficial for the treatment (Apel et al., 2008; Dikic and Elazar, 2018; Shingu et al., 2009). However, in other contexts, autophagy activation can be used to enhance the effect of cancer therapy, as shown recently for glioblastoma (Kriel et al., 2018). As discussed above, autophagy plays several roles in immunity, and activation of autophagy has been suggested to be a way to enhance the effect of cancer immunotherapy (Galluzzi et al., 2017b; Michaud et al., 2011). Cancer treatments can also activate a lethal type of autophagy called autophagic cell death (Armstrong et al., 2015; Fulda, 2018). Finally, as also discussed above, autophagy plays a role in maintaining the fitness and pluripotency of stem cells, including cancer stem cells, which contribute to chemoresistance (Sharif et al., 2017; Smith and Macleod, 2018).

8. Conclusions

The significance of autophagy has been widely recognized in recent years, as evidenced by the Nobel prize in medicine or physiology 2016, awarded to Yoshinori Ohsumi for his work on the molecular mechanisms of autophagy (Mohammadi, 2016). Recent decades have increased our understanding on the numerous roles of autophagy in aging, stem cell maintenance, neuronal function, immunity, and inflammation. A growing number of studies support the view that autophagy is beneficial for neurons, and induction of autophagy has potential in treatment of neurodegenerative diseases. However, the role of autophagy in initiation, establishment and metastasis of cancer is more complex and strongly context-dependent. Further studies are needed in order to understand whether, and how, autophagy could be exploited in cancer treatment.

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References

Apel, A., I. Herr, H. Schwarz, H.P. Rodemann, and A. Mayer. 2008. Blocked autophagy sensitizes resistant carcinoma cells to radiation therapy. Cancer Res. 68:1485-1494.

Armstrong, J.L., D.S. Hill, C.S. McKee, S. Hernandez-Tiedra, M. Lorente, I. Lopez-Valero, M. Eleni Anagnostou, F. Babatunde, M. Corazzari, C.P.F. Redfern, G. Velasco, and P.E. Lovat. 2015. Exploiting cannabinoid-induced cytotoxic autophagy to drive melanoma cell death. J Invest Dermatol. 135:1629-1637.

Aron, R., P. Pellegrini, E.W. Green, D.C. Maddison, K. Opoku-Nsiah, J.S. Wong, A.C. Daub, F. Giorgini, and S. Finkbeiner. 2018. Deubiquitinase Usp12 functions noncatalytically to induce autophagy and confer neuroprotection in models of Huntington's disease. Nature communications. 9:3191.

Ashkenazi, A., C.F. Bento, T. Ricketts, M. Vicinanza, F. Siddiqi, M. Pavel, F. Squitieri, M.C. Hardenberg, S. Imarisio, F.M. Menzies, and D.C. Rubinsztein. 2017. Polyglutamine tracts regulate beclin 1-dependent autophagy. Nature. 545:108-111.

Axe, E.L., S.A. Walker, M. Manifava, P. Chandra, H.L. Roderick, A. Habermann, G. Griffiths, and N.T. Ktistakis. 2008. Autophagosome formation from membrane compartments enriched in phosphatidylinositol 3-phosphate and dynamically connected to the endoplasmic reticulum. J Cell Biol. 182:685-701.

Baba, M., M. Osumi, S.V. Scott, D.J. Klionsky, and Y. Ohsumi. 1997. Two distinct pathways for targeting proteins from the cytoplasm to the vacuole/lysosome. J Cell Biol. 139:1687-1695.

Barbero-Camps, E., V. Roca-Agujetas, I. Bartolessis, C. de Dios, J.C. Fernandez-Checa, M. Mari, A. Morales, T. Hartmann, and A. Colell. 2018. Cholesterol impairs autophagy-mediated clearance of amyloid beta while promoting its secretion. Autophagy. 14:1129-1154.

Birben, E., U.M. Sahiner, C. Sackesen, S. Erzurum, and O. Kalayci. 2012. Oxidative stress and antioxidant defense. World Allergy Organ J. 5:9-19.

Boland, B., W.H. Yu, O. Corti, B. Mollereau, A. Henriques, E. Bezard, G.M. Pastores, D.C. Rubinsztein, R.A. Nixon, M.R. Duchen, G.R. Mallucci, G. Kroemer, B. Levine, E.L. Eskelinen, F. Mochel, M. Spedding, C. Louis, O.R. Martin, and M.J. Millan. 2018. Promoting the clearance of neurotoxic proteins in neurodegenerative disorders of ageing. Nat Rev Drug Discov. 17:660-688.

Bonam, S.R., F. Wang, and S. Muller. 2018. Autophagy: A new concept in autoimmunity regulation and a novel therapeutic option. J Autoimmun. 94:16-32.

Boya, P., P. Codogno, and N. Rodriguez-Muela. 2018. Autophagy in stem cells: repair, remodelling and metabolic reprogramming. Development. 145.

Caberlotto, L., T.P. Nguyen, M. Lauria, C. Priami, R. Rimondini, S. Maioli, A. Cedazo-Minguez, G. Sita, F. Morroni, M. Corsi, and L. Carboni. 2019. Cross-disease analysis of Alzheimer's disease and type-2 Diabetes highlights the role of autophagy in the pathophysiology of two highly comorbid diseases. Sci Rep. 9:3965.

Cadwell, K., J.Y. Liu, S.L. Brown, H. Miyoshi, J. Loh, J.K. Lennerz, C. Kishi, W. Kc, J.A. Carrero, S. Hunt, C.D. Stone, E.M. Brunt, R.J. Xavier, B.P. Sleckman, E. Li, N. Mizushima, T.S. Stappenbeck, and H.W.t. Virgin. 2008. A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. Nature. 456:259-263.

Carmona-Gutierrez, D., A. Zimmermann, K. Kainz, F. Pietrocola, G. Chen, S. Maglioni, A. Schiavi, J. Nah, S. Mertel, C.B. Beuschel, F. Castoldi, V. Sica, G. Trausinger, R. Raml, C. Sommer, S. Schroeder, S.J. Hofer, M.A. Bauer, T. Pendl, J. Tadic, C. Dammbrueck, Z. Hu, C. Ruckenstuhl, T. Eisenberg, S. Durand, N. Bossut, F. Aprahamian, M. Abdellatif, S. Sedej, D.P. Enot, H. Wolinski, J. Dengjel, O. Kepp, C. Magnes, F. Sinner, T.R. Pieber, J. Sadoshima, N. Ventura, S.J. Sigrist, G. Kroemer, and F. Madeo. 2019. The flavonoid 4,4'-dimethoxychalcone promotes autophagy-dependent longevity across species. Nature communications. 10:651.

Ciccacci, C., C. Perricone, C. Alessandri, A. Latini, C. Politi, F. Delunardo, M. Pierdominici, F. Conti, G. Novelli, E. Ortona, and P. Borgiani. 2018. Evaluation of ATG5 polymorphisms in Italian patients with systemic lupus erythematosus: contribution to disease susceptibility and clinical phenotypes. Lupus. 27:1464-1469.

Corrionero, A., and H.R. Horvitz. 2018. A C9orf72 ALS/FTD Ortholog Acts in Endolysosomal Degradation and Lysosomal Homeostasis. Curr Biol. 28:1522-1535 e1525.

Cuervo, A.M., L. Stefanis, R. Fredenburg, P.T. Lansbury, and D. Sulzer. 2004. Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy. Science. 305:1292-1295.

Cummins, N., A. Tweedie, S. Zuryn, J. Bertran-Gonzalez, and J. Gotz. 2018. Disease-associated tau impairs mitophagy by inhibiting Parkin translocation to mitochondria. EMBO J.

Damme, M., T. Suntio, P. Saftig, and E.L. Eskelinen. 2015. Autophagy in neuronal cells: general principles and physiological and pathological functions. Acta Neuropathol. 129:337-362.

Dehay, B., A. Ramirez, M. Martinez-Vicente, C. Perier, M.H. Canron, E. Doudnikoff, A. Vital, M. Vila, C. Klein, and E. Bezard. 2012. Loss of P-type ATPase ATP13A2/PARK9 function induces general lysosomal deficiency and leads to Parkinson disease neurodegeneration. Proc Natl Acad Sci U S A. 109:9611-9616.

Deretic, V., and B. Levine. 2018. Autophagy balances inflammation in innate immunity. Autophagy. 14:243-251.

Dikic, I., and Z. Elazar. 2018. Mechanism and medical implications of mammalian autophagy. Nat Rev Mol Cell Biol. 19:349-364.

Ellinghaus, D., H. Zhang, S. Zeissig, S. Lipinski, A. Till, T. Jiang, B. Stade, Y. Bromberg, E. Ellinghaus, A. Keller, M.A. Rivas, J. Skieceviciene, N.T. Doncheva, X. Liu, Q. Liu, F. Jiang, M. Forster, G. Mayr, M. Albrecht, R. Hasler, B.O. Boehm, J. Goodall, C.R. Berzuini, J. Lee, V. Andersen, U. Vogel, L. Kupcinskas, M. Kayser, M. Krawczak, S. Nikolaus, R.K. Weersma, C.Y. Ponsioen, M. Sans, C. Wijmenga, D.P. Strachan, W.L. McArdle, S. Vermeire, P. Rutgeerts, J.D. Sanderson, C.G. Mathew, M.H. Vatn, J. Wang, M.M. Nothen, R.H. Duerr, C. Buning, S. Brand, J. Glas, J. Winkelmann, T. Illig, A. Latiano, V. Annese, J. Halfvarson, M. D'Amato, M.J. Daly, M. Nothnagel, T.H. Karlsen, S. Subramani, P. Rosenstiel, S. Schreiber, M. Parkes, and A. Franke. 2013. Association between variants of PRDM1 and NDP52 and Crohn's disease, based on exome sequencing and functional studies. Gastroenterology. 145:339-347.

Evans, C.S., and E.L.F. Holzbaur. 2018. Autophagy and mitophagy in ALS. Neurobiology of disease.

Falcon, B., J. Noad, H. McMahon, F. Randow, and M. Goedert. 2018. Galectin-8-mediated selective autophagy protects against seeded tau aggregation. J Biol Chem. 293:2438-2451.

Fernandez, A.F., S. Sebti, Y. Wei, Z. Zou, M. Shi, K.L. McMillan, C. He, T. Ting, Y. Liu, W.C. Chiang, D.K. Marciano, G.G. Schiattarella, G. Bhagat, O.W. Moe, M.C. Hu, and B. Levine. 2018. Disruption of the beclin 1-BCL2 autophagy regulatory complex promotes longevity in mice. Nature. 558:136-140.

Fulda, S. 2018. Targeting autophagy for the treatment of cancer. Biological Chemistry. 399:673-677.

Gallagher, L.E., L.E. Williamson, and E.Y. Chan. 2016. Advances in Autophagy Regulatory Mechanisms. Cells. 5.

Galluzzi, L., E.H. Baehrecke, A. Ballabio, P. Boya, J.M. Bravo-San Pedro, F. Cecconi, A.M. Choi, C.T. Chu, P. Codogno, M.I. Colombo, A.M. Cuervo, J. Debnath, V. Deretic, I. Dikic, E.L. Eskelinen, G.M. Fimia, S. Fulda, D.A. Gewirtz, D.R. Green, M. Hansen, J.W. Harper, M. Jaattela, T. Johansen, G. Juhasz, A.C. Kimmelman, C. Kraft, N.T. Ktistakis, S. Kumar, B. Levine, C. Lopez-Otin, F. Madeo, S. Martens, J. Martinez, A. Melendez, N. Mizushima, C. Munz, L.O. Murphy, J.M. Penninger, M. Piacentini, F. Reggiori, D.C. Rubinsztein, K.M. Ryan, L. Santambrogio, L. Scorrano, A.K. Simon, H.U. Simon, A. Simonsen, N. Tavernarakis, S.A. Tooze, T. Yoshimori, J. Yuan, Z. Yue, Q. Zhong, and G. Kroemer. 2017a. Molecular definitions of autophagy and related processes. EMBO J. 36:1811-1836.

Galluzzi, L., J.M. Bravo-San Pedro, S. Demaria, S.C. Formenti, and G. Kroemer. 2017b. Activating autophagy to potentiate immunogenic chemotherapy and radiation therapy. Nat Rev Clin Oncol. 14:247-258.

Gan-Or, Z., P.A. Dion, and G.A. Rouleau. 2015. Genetic perspective on the role of the autophagy-lysosome pathway in Parkinson disease. Autophagy. 11:1443-1457.

Garcia-Prat, L., M. Martinez-Vicente, and P. Munoz-Canoves. 2016a. Autophagy: a decisive process for stemness. Oncotarget. 7:12286-12288.

Garcia-Prat, L., M. Martinez-Vicente, E. Perdiguero, L. Ortet, J. Rodriguez-Ubreva, E. Rebollo, V. Ruiz-Bonilla, S. Gutarra, E. Ballestar, A.L. Serrano, M. Sandri, and P. Munoz-Canoves. 2016b. Autophagy maintains stemness by preventing senescence. Nature. 529:37-42.

Garcia-Prat, L., P. Sousa-Victor, and P. Munoz-Canoves. 2017. Proteostatic and Metabolic Control of Stemness. Cell stem cell. 20:593-608.

Gkikas, I., K. Palikaras, and N. Tavernarakis. 2018. The Role of Mitophagy in Innate Immunity. Front Immunol. 9:1283.

Glatigny, M., S. Moriceau, M. Rivagorda, M. Ramos-Brossier, A.C. Nascimbeni, F. Lante, M.R. Shanley, N. Boudarene, A. Rousseaud, A.K. Friedman, C. Settembre, N. Kuperwasser, G. Friedlander, A. Buisson, E. Morel, P. Codogno, and F. Oury. 2019. Autophagy Is Required for Memory Formation and Reverses Age-Related Memory Decline. Curr Biol. 29:435-448 e438.

Gomes, L.C., and I. Dikic. 2014. Autophagy in antimicrobial immunity. Mol Cell. 54:224-233.

Guadamillas, M.C., A. Cerezo, and M.A. Del Pozo. 2011. Overcoming anoikis--pathways to anchorage-independent growth in cancer. J Cell Sci. 124:3189-3197.

Guan, J.L., A.K. Simon, M. Prescott, J.A. Menendez, F. Liu, F. Wang, C. Wang, E. Wolvetang, A. Vazquez-Martin, and J. Zhang. 2013. Autophagy in stem cells. Autophagy. 9:830-849.

Guo, J.Y., H.Y. Chen, R. Mathew, J. Fan, A.M. Strohecker, G. Karsli-Uzunbas, J.J. Kamphorst, G. Chen, J.M. Lemons, V. Karantza, H.A. Coller, R.S. Dipaola, C. Gelinas, J.D. Rabinowitz, and E. White. 2011. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. Genes Dev. 25:460-470.

Gutierrez, M.G., S.S. Master, S.B. Singh, G.A. Taylor, M.I. Colombo, and V. Deretic. 2004. Autophagy is a defense mechanism inhibiting BCG and Mycobacterium tuberculosis survival in infected macrophages. Cell. 119:753-766.

Hamano, T., K. Hayashi, N. Shirafuji, and Y. Nakamoto. 2018. The Implications of Autophagy in Alzheimer's disease. Curr Alzheimer Res.

Hansen, M., D.C. Rubinsztein, and D.W. Walker. 2018. Autophagy as a promoter of longevity: insights from model organisms. Nat Rev Mol Cell Biol.

Hara, T., K. Nakamura, M. Matsui, A. Yamamoto, Y. Nakahara, R. Suzuki-Migishima, M. Yokoyama, K. Mishima, I. Saito, H. Okano, and N. Mizushima. 2006. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature. 441:885-889.

Harjes, P., and E.E. Wanker. 2003. The hunt for huntingtin function: interaction partners tell many different stories. Trends Biochem Sci. 28:425-433.

Hernandez, D.G., X. Reed, and A.B. Singleton. 2016. Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance. J Neurochem. 139 Suppl 1:59-74.

Ho, T.T., M.R. Warr, E.R. Adelman, O.M. Lansinger, J. Flach, E.V. Verovskaya, M.E. Figueroa, and E. Passegue. 2017. Autophagy maintains the metabolism and function of young and old stem cells. Nature. 543:205-210.

Hung, C.O.Y., and F.J. Livesey. 2018. Altered gamma-Secretase Processing of APP Disrupts Lysosome and Autophagosome Function in Monogenic Alzheimer's Disease. Cell Rep. 25:3647-3660 e3642.

Johnson, J.O., J. Mandrioli, M. Benatar, Y. Abramzon, V.M. Van Deerlin, J.Q. Trojanowski, J.R. Gibbs, M. Brunetti, S. Gronka, J. Wuu, J. Ding, L. McCluskey, M. Martinez-Lage, D. Falcone, D.G. Hernandez, S. Arepalli, S. Chong, J.C. Schymick, J. Rothstein, F. Landi, Y.D. Wang, A. Calvo, G. Mora, M. Sabatelli, M.R. Monsurro, S. Battistini, F. Salvi, R. Spataro, P. Sola, G. Borghero, I. Consortium, G. Galassi, S.W. Scholz, J.P. Taylor, G. Restagno, A. Chio, and B.J. Traynor. 2010. Exome sequencing reveals VCP mutations as a cause of familial ALS. Neuron. 68:857-864.

Joshi, A.U., and D. Mochly-Rosen. 2018. Mortal engines: Mitochondrial bioenergetics and dysfunction in neurodegenerative diseases. Pharmacol Res. 138:2-15.

Ju, J.S., R.A. Fuentealba, S.E. Miller, E. Jackson, D. Piwnica-Worms, R.H. Baloh, and C.C. Weihl. 2009. Valosin-containing protein (VCP) is required for autophagy and is disrupted in VCP disease. J Cell Biol. 187:875-888.

Kaushik, S., and A.M. Cuervo. 2018. The coming of age of chaperone-mediated autophagy. Nat Rev Mol Cell Biol. 19:365-381.

Kenific, C.M., A. Thorburn, and J. Debnath. 2010. Autophagy and metastasis: another double-edged sword. Curr Opin Cell Biol. 22:241-245.

Khaminets, A., C. Behl, and I. Dikic. 2016. Ubiquitin-Dependent And Independent Signals In Selective Autophagy. Trends Cell Biol. 26:6-16.

Kimura, T., A. Jain, S.W. Choi, M.A. Mandell, K. Schroder, T. Johansen, and V. Deretic. 2015. TRIM-mediated precision autophagy targets cytoplasmic regulators of innate immunity. J Cell Biol. 210:973-989.

Kinsella, R.L., E.M. Nehls, and C.L. Stallings. 2018. Roles for Autophagy Proteins in Immunity and Host Defense. Vet Pathol. 55:366-373.

Komatsu, M., S. Waguri, T. Chiba, S. Murata, J. Iwata, I. Tanida, T. Ueno, M. Koike, Y. Uchiyama, E. Kominami, and K. Tanaka. 2006. Loss of autophagy in the central nervous system causes neurodegeneration in mice. Nature. 441:880-884.

Kriel, J., K. Muller-Nedebock, G. Maarman, S. Mbizana, E. Ojuka, B. Klumperman, and B. Loos. 2018. Coordinated autophagy modulation overcomes glioblastoma chemoresistance through disruption of mitochondrial bioenergetics. Sci Rep-Uk. 8.

Ktistakis, N.T., and S.A. Tooze. 2016. Digesting the Expanding Mechanisms of Autophagy. Trends Cell Biol. 26:624-635.

Lapierre, L.R., C.D. De Magalhaes Filho, P.R. McQuary, C.C. Chu, O. Visvikis, J.T. Chang, S. Gelino, B. Ong, A.E. Davis, J.E. Irazoqui, A. Dillin, and M. Hansen. 2013. The TFEB orthologue HLH-30 regulates autophagy and modulates longevity in Caenorhabditis elegans. Nature communications. 4:2267.

Lee, J.H., W.H. Yu, A. Kumar, S. Lee, P.S. Mohan, C.M. Peterhoff, D.M. Wolfe, M. Martinez-Vicente, A.C. Massey, G. Sovak, Y. Uchiyama, D. Westaway, A.M. Cuervo, and R.A. Nixon. 2010. Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. Cell. 141:1146-1158.

Levine, B., and G. Kroemer. 2008. Autophagy in the pathogenesis of disease. Cell. 132:27-42.

Levine, B., and G. Kroemer. 2019. Biological Functions of Autophagy Genes: A Disease Perspective. Cell. 176:11-42.

Liang, C.C., C. Wang, X. Peng, B. Gan, and J.L. Guan. 2010. Neural-specific deletion of FIP200 leads to cerebellar degeneration caused by increased neuronal death and axon degeneration. J Biol Chem. 285:3499-3509.

Liang, X.H., S. Jackson, M. Seaman, K. Brown, B. Kempkes, H. Hibshoosh, and B. Levine. 1999. Induction of autophagy and inhibition of tumorigenesis by beclin 1. Nature. 402:672-676.

Lin, H.H., Y. Chung, C.T. Cheng, C. Ouyang, Y. Fu, C.Y. Kuo, K.K. Chi, M. Sadeghi, P. Chu, H.J. Kung, C.F. Li, K.H. Limesand, and D.K. Ann. 2018. Autophagic Reliance Promotes Metabolic Reprogramming in Oncogenic KRAS-driven Tumorigenesis. Autophagy.

Liu, X., H. Qin, and J. Xu. 2016. The role of autophagy in the pathogenesis of systemic lupus erythematosus. Int Immunopharmacol. 40:351-361.
Lock, R., C.M. Kenific, A.M. Leidal, E. Salas, and J. Debnath. 2014. Autophagy-dependent production of secreted factors facilitates oncogenic RAS-driven invasion. Cancer Discov. 4:466-479.
Lubas, M., L.M. Harder, C. Kumsta, I. Tiessen, M. Hansen, J.S. Andersen, A.H. Lund, and L.B. Frankel. 2018. eIF5A is required for autophagy by mediating ATG3 translation. EMBO Rep. 19.
Lynch-Day, M.A., K. Mao, K. Wang, M. Zhao, and D.J. Klionsky. 2012. The role of autophagy in Parkinson's disease. Cold Spring Harb Perspect Med. 2:a009357.
Madeo, F., A. Zimmermann, M.C. Maiuri, and G. Kroemer. 2015. Essential role for autophagy in life span extension. J Clin Invest. 125:85-93.
Manzoni, C., and P.A. Lewis. 2017. LRRK2 and Autophagy. Adv Neurobiol. 14:89-105.
Mari, M., S.A. Tooze, and F. Reggiori. 2011. The puzzling origin of the autophagosomal membrane. F1000 Biol Rep. 3:25.
Martinez, J. 2018. LAP it up, fuzz ball: a short history of LC3-associated phagocytosis. Curr Opin Immunol. 55:54-61.
Mazzulli, J.R., Y.H. Xu, Y. Sun, A.L. Knight, P.J. McLean, G.A. Caldwell, E. Sidransky, G.A. Grabowski, and D. Krainc. 2011. Gaucher disease glucocerebrosidase and alpha-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell. 146:37-52.
Medina, D.L., A. Fraldi, V. Bouche, F. Annunziata, G. Mansueto, C. Spampanato, C. Puri, A. Pignata, J.A. Martina, M. Sardiello, M. Palmieri, R. Polishchuk, R. Puertollano, and A. Ballabio. 2011. Transcriptional activation of lysosomal exocytosis promotes cellular clearance. Dev Cell. 21:421-430.
Mehto, S., K.K. Jena, P. Nath, S. Chauhan, S.P. Kolapalli, S.K. Das, P.K. Sahoo, A. Jain, G.A. Taylor, and S. Chauhan. 2019. The Crohn's Disease Risk Factor IRGM Limits NLRP3 Inflammasome Activation by Impeding Its Assembly and by Mediating Its Selective Autophagy. Mol Cell. 73:429-445 e427.
Melendez, A., Z. Talloczy, M. Seaman, E.L. Eskelinen, D.H. Hall, and B. Levine. 2003. Autophagy genes are essential for dauer development and lifespan extension in C. elegans. Science. 301:1387-1391.
Mercer, T.J., A. Gubas, and S.A. Tooze. 2018. A molecular perspective of mammalian autophagosome biogenesis. Journal of Biological Chemistry. 293:5386-5395.
Michaud, M., I. Martins, A.Q. Sukkurwala, S. Adjemian, Y. Ma, P. Pellegatti, S. Shen, O. Kepp, M. Scoazec, G. Mignot, S. Rello-Varona, M. Tailler, L. Menger, E. Vacchelli, L. Galluzzi, F. Ghiringhelli, F. di Virgilio, L. Zitvogel, and G. Kroemer. 2011. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science. 334:1573-1577.
Mocholi, E., S.D. Dowling, Y. Botbol, R.C. Gruber, A.K. Ray, S. Vastert, B. Shafit-Zagardo, P.J. Coffer, and F. Macian. 2018. Autophagy Is a Tolerance-Avoidance Mechanism that Modulates TCR-Mediated Signaling and Cell Metabolism to Prevent Induction of T Cell Anergy. Cell Rep. 24:1136-1150.
Mohammadi, D. 2016. 2016 Nobel prize in medicine goes to Japanese scientist. Lancet. 388:1870.
Monneaux, F., J. Hoebeke, C. Sordet, C. Nonn, J.P. Briand, B. Maillere, J. Sibillia, and S. Muller. 2005. Selective modulation of CD4+ T cells from lupus patients by a promiscuous, protective peptide analog. J Immunol. 175:5839-5847.
Monneaux, F., J.M. Lozano, M.E. Patarroyo, J.P. Briand, and S. Muller. 2003. T cell recognition and therapeutic effect of a phosphorylated synthetic peptide of the 70K snRNP protein administered in MR/lpr mice. Eur J Immunol. 33:287-296.
Mortensen, M., A.S. Watson, and A.K. Simon. 2011. Lack of autophagy in the hematopoietic system leads to loss of hematopoietic stem cell function and dysregulated myeloid proliferation. Autophagy. 7:1069-1070.
Mowers, E.E., M.N. Sharifi, and K.F. Macleod. 2016. Autophagy in cancer metastasis. Oncogene.
Murthy, A., Y. Li, I. Peng, M. Reichelt, A.K. Katakam, R. Noubade, M. Roose-Girma, J. DeVoss, L. Diehl, R.R. Graham, and M. van Lookeren Campagne. 2014. A Crohn's disease variant in Atg16l1 enhances its degradation by caspase 3. Nature. 506:456-462.
Nakagawa, I., A. Amano, N. Mizushima, A. Yamamoto, H. Yamaguchi, T. Kamimoto, A. Nara, J. Funao, M. Nakata, K. Tsuda, S. Hamada, and T. Yoshimori. 2004. Autophagy defends cells against invading group A Streptococcus. Science. 306:1037-1040.
Nakahira, K., J.A. Haspel, V.A. Rathinam, S.J. Lee, T. Dolinay, H.C. Lam, J.A. Englert, M. Rabinovitch, M. Cernadas, H.P. Kim, K.A. Fitzgerald, S.W. Ryter, and A.M. Choi. 2011. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol. 12:222-230.
Nakamura, S., M. Oba, M. Suzuki, A. Takahashi, T. Yamamuro, M. Fujiwara, K. Ikenaka, S. Minami, N. Tabata, K. Yamamoto, S. Kubo, A. Tokumura, K. Akamatsu, Y. Miyazaki, T. Kawabata, M. Hamasaki, K. Fukui, K. Sango, Y. Watanabe, Y. Takabatake, T.S. Kitajima, Y. Okada, H. Mochizuki, Y. Isaka, A. Antebi, and T.

Yoshimori. 2019. Suppression of autophagic activity by Rubicon is a signature of aging. Nature communications. 10:847.
Nakamura, S., and T. Yoshimori. 2018. Autophagy and Longevity. Mol Cells. 41:65-72.
Nassour, J., R. Radford, A. Correia, J.M. Fuste, B. Schoell, A. Jauch, R.J. Shaw, and J. Karlseder. 2019. Autophagic cell death restricts chromosomal instability during replicative crisis. Nature. 565:659-663.
Nikoletopoulou, V., M.E. Papandreou, and N. Tavernarakis. 2015. Autophagy in the physiology and pathology of the central nervous system. Cell Death Differ. 22:398-407.
Nixon, R.A. 2013. The role of autophagy in neurodegenerative disease. Nat Med. 19:983-997.
Paludan, C., D. Schmid, M. Landthaler, M. Vockerodt, D. Kube, T. Tuschl, and C. Munz. 2005. Endogenous MHC class II processing of a viral nuclear antigen after autophagy. Science. 307:593-596.
Pan, H., N. Cai, M. Li, G.H. Liu, and J.C. Izpisua Belmonte. 2013. Autophagic control of cell 'stemness'. EMBO Mol Med. 5:327-331.
Pickles, S., P. Vigie, and R.J. Youle. 2018. Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance. Curr Biol. 28:R170-R185.
Pircs, K., R. Petri, S. Madsen, P.L. Brattas, R. Vuono, D.R. Ottosson, I. St-Amour, B.A. Hersbach, M. Matusiak-Bruckner, S.H. Lundh, A. Petersen, N. Deglon, S.S. Hebert, M. Parmar, R.A. Barker, and J. Jakobsson. 2018. Huntingtin Aggregation Impairs Autophagy, Leading to Argonaute-2 Accumulation and Global MicroRNA Dysregulation. Cell Rep. 24:1397-1406.
Poillet-Perez, L., X. Xie, L. Zhan, Y. Yang, D.W. Sharp, Z.S. Hu, X. Su, A. Maganti, C. Jiang, W. Lu, H. Zheng, M.W. Bosenberg, J.M. Mehnert, J.Y. Guo, E. Lattime, J.D. Rabinowitz, and E. White. 2018. Autophagy maintains tumour growth through circulating arginine. Nature. 563:569-573.
Qu, X., J. Yu, G. Bhagat, N. Furuya, H. Hibshoosh, A. Troxel, J. Rosen, E.L. Eskelinen, N. Mizushima, Y. Ohsumi, G. Cattoretti, and B. Levine. 2003. Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. J Clin Invest. 112:1809-1820.
Rabanal-Ruiz, Y., E.G. Otten, and V.I. Korolchuk. 2017. mTORC1 as the main gateway to autophagy. Essays in biochemistry. 61:565-584.
Ravenhill, B.J., K.B. Boyle, N. von Muhlinen, C.J. Ellison, G.R. Masson, E.G. Otten, A. Foeglein, R. Williams, and F. Randow. 2019. The Cargo Receptor NDP52 Initiates Selective Autophagy by Recruiting the ULK Complex to Cytosol-Invading Bacteria. Mol Cell.
Ravikumar, B., R. Duden, and D.C. Rubinsztein. 2002. Aggregate-prone proteins with polyglutamine and polyalanine expansions are degraded by autophagy. Hum Mol Genet. 11:1107-1117.
Ravikumar, B., C. Vacher, Z. Berger, J.E. Davies, S. Luo, L.G. Oroz, F. Scaravilli, D.F. Easton, R. Duden, C.J. O'Kane, and D.C. Rubinsztein. 2004. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. Nat Genet. 36:585-595.
Reddy, P.H., X. Yin, M. Manczak, S. Kumar, J.A. Pradeepkiran, M. Vijayan, and A.P. Reddy. 2018. Mutant APP and amyloid beta-induced defective autophagy, mitophagy, mitochondrial structural and functional changes and synaptic damage in hippocampal neurons from Alzheimer's disease. Hum Mol Genet. 27:2502-2516.
Rosenfeldt, M.T., J. O'Prey, J.P. Morton, C. Nixon, G. MacKay, A. Mrowinska, A. Au, T.S. Rai, L. Zheng, R. Ridgway, P.D. Adams, K.I. Anderson, E. Gottlieb, O.J. Sansom, and K.M. Ryan. 2013. p53 status determines the role of autophagy in pancreatic tumour development. Nature. 504:296-300.
Rui, Y.N., Z. Xu, B. Patel, Z. Chen, D. Chen, A. Tito, G. David, Y. Sun, E.F. Stimming, H.J. Bellen, A.M. Cuervo, and S. Zhang. 2015. Huntingtin functions as a scaffold for selective macroautophagy. Nat Cell Biol. 17:262-275.
Saitoh, T., N. Fujita, M.H. Jang, S. Uematsu, B.G. Yang, T. Satoh, H. Omori, T. Noda, N. Yamamoto, M. Komatsu, K. Tanaka, T. Kawai, T. Tsujimura, O. Takeuchi, T. Yoshimori, and S. Akira. 2008. Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1beta production. Nature. 456:264-268.
Savolainen, M.H., C.T. Richie, B.K. Harvey, P.T. Mannisto, K.A. Maguire-Zeiss, and T.T. Myohanen. 2014. The beneficial effect of a prolyl oligopeptidase inhibitor, KYP-2047, on alpha-synuclein clearance and autophagy in A30P transgenic mouse. Neurobiology of disease. 68:1-15.
Schapira, A.H. 2015. Glucocerebrosidase and Parkinson disease: Recent advances. Mol Cell Neurosci. 66:37-42.
Schmid, D., M. Pypaert, and C. Munz. 2007. Antigen-loading compartments for major histocompatibility complex class II molecules continuously receive input from autophagosomes. Immunity. 26:79-92.
Sharif, T., E. Martell, C. Dai, B.E. Kennedy, P. Murphy, D.R. Clements, Y. Kim, P.W. Lee, and S.A. Gujar. 2017. Autophagic homeostasis is required for the pluripotency of cancer stem cells. Autophagy. 13:264-284.
Sharifi, M.N., E.E. Mowers, L.E. Drake, C. Collier, H. Chen, M. Zamora, S. Mui, and K.F. Macleod. 2016. Autophagy Promotes Focal Adhesion Disassembly and Cell Motility of Metastatic Tumor Cells through the Direct Interaction of Paxillin with LC3. Cell Rep. 15:1660-1672.

Shingu, T., K. Fujiwara, O. Bogler, Y. Akiyama, K. Moritake, N. Shinojima, Y. Tamada, T. Yokoyama, and S. Kondo. 2009. Inhibition of autophagy at a late stage enhances imatinib-induced cytotoxicity in human malignant glioma cells. Int J Cancer. 124:1060-1071.

Simonsen, A., R.C. Cumming, A. Brech, P. Isakson, D.R. Schubert, and K.D. Finley. 2008. Promoting basal levels of autophagy in the nervous system enhances longevity and oxidant resistance in adult Drosophila. Autophagy. 4:176-184.

Smith, A.G., and K.F. Macleod. 2018. Autophagy, cancer stem cells and drug resistance. J Pathol.

Soreng, K., T.P. Neufeld, and A. Simonsen. 2018. Membrane Trafficking in Autophagy. International Review of Cell and Molecular Biology, Vol 336. 336:1-92.

Spencer, B., R. Potkar, M. Trejo, E. Rockenstein, C. Patrick, R. Gindi, A. Adame, T. Wyss-Coray, and E. Masliah. 2009. Beclin 1 gene transfer activates autophagy and ameliorates the neurodegenerative pathology in alpha-synuclein models of Parkinson's and Lewy body diseases. J Neurosci. 29:13578-13588.

Strisciuglio, C., E. Miele, M.E. Wildenberg, F.P. Giugliano, M. Andreozzi, A. Vitale, F. Capasso, A. Camarca, M.V. Barone, A. Staiano, R. Troncone, and C. Gianfrani. 2013. T300A variant of autophagy ATG16L1 gene is associated with decreased antigen sampling and processing by dendritic cells in pediatric Crohn's disease. Inflamm Bowel Dis. 19:2339-2348.

Svarcbahs, R., U.H. Julku, and T.T. Myohanen. 2016. Inhibition of Prolyl Oligopeptidase Restores Spontaneous Motor Behavior in the alpha-Synuclein Virus Vector-Based Parkinson's Disease Mouse Model by Decreasing alpha-Synuclein Oligomeric Species in Mouse Brain. J Neurosci. 36:12485-12497.

Takamura, A., M. Komatsu, T. Hara, A. Sakamoto, C. Kishi, S. Waguri, Y. Eishi, O. Hino, K. Tanaka, and N. Mizushima. 2011. Autophagy-deficient mice develop multiple liver tumors. Genes Dev. 25:795-800.

Taylor, J.P., R.H. Brown, Jr., and D.W. Cleveland. 2016. Decoding ALS: from genes to mechanism. Nature. 539:197-206.

Tekirdag, K., and A.M. Cuervo. 2018. Chaperone-mediated autophagy and endosomal microautophagy: Joint by a chaperone. J Biol Chem. 293:5414-5424.

Thumm, M., R. Egner, B. Koch, M. Schlumpberger, M. Straub, M. Veenhuis, and D.H. Wolf. 1994. Isolation of autophagocytosis mutants of Saccharomyces cerevisiae. FEBS Lett. 349:275-280.

Tresse, E., F.A. Salomons, J. Vesa, L.C. Bott, V. Kimonis, T.P. Yao, N.P. Dantuma, and J.P. Taylor. 2010. VCP/p97 is essential for maturation of ubiquitin-containing autophagosomes and this function is impaired by mutations that cause IBMPFD. Autophagy. 6:217-227.

Trinh, J., and M. Farrer. 2013. Advances in the genetics of Parkinson disease. Nat Rev Neurol. 9:445-454.

Tsukada, M., and Y. Ohsumi. 1993. Isolation and characterization of autophagy-defective mutants of Saccharomyces cerevisiae. FEBS Lett. 333:169-174.

van Beek, N., D.J. Klionsky, and F. Reggiori. 2018. Genetic aberrations in macroautophagy genes leading to diseases. Biochim Biophys Acta Mol Cell Res. 1865:803-816.

Wang, R., J. Tan, T. Chen, H. Han, R. Tian, Y. Tan, Y. Wu, J. Cui, F. Chen, J. Li, L. Lv, X. Guan, S. Shang, J. Lu, and Z. Zhang. 2018. ATP13A2 facilitates HDAC6 recruitment to lysosome to promote autophagosome-lysosome fusion. J Cell Biol.

Vargas, J.N.S., C. Wang, E. Bunker, L. Hao, D. Maric, G. Schiavo, F. Randow, and R.J. Youle. 2019. Spatiotemporal Control of ULK1 Activation by NDP52 and TBK1 during Selective Autophagy. Mol Cell.

Vega-Rubin-de-Celis, S., Z. Zou, A.F. Fernandez, B. Ci, M. Kim, G. Xiao, Y. Xie, and B. Levine. 2018. Increased autophagy blocks HER2-mediated breast tumorigenesis. Proc Natl Acad Sci U S A. 115:4176-4181.

Wen, X., and D.J. Klionsky. 2016. An overview of macroautophagy in yeast. J Mol Biol. 428:1681-1699.

White, E., J.M. Mehnert, and C.S. Chan. 2015. Autophagy, Metabolism, and Cancer. Clin Cancer Res. 21:5037-5046.

Wold, M.S., J. Lim, V. Lachance, Z. Deng, and Z. Yue. 2016. ULK1-mediated phosphorylation of ATG14 promotes autophagy and is impaired in Huntington's disease models. Mol Neurodegener. 11:76.

Wong, Y.C., and E.L. Holzbaur. 2015. Autophagosome dynamics in neurodegeneration at a glance. J Cell Sci. 128:1259-1267.

Xin, S.H., L. Tan, X. Cao, J.T. Yu, and L. Tan. 2018. Clearance of Amyloid Beta and Tau in Alzheimer's Disease: from Mechanisms to Therapy. Neurotox Res. 34:733-748.

Yamamoto, A., M.L. Cremona, and J.E. Rothman. 2006. Autophagy-mediated clearance of huntingtin aggregates triggered by the insulin-signaling pathway. J Cell Biol. 172:719-731.

Yin, H., H. Wu, Y. Chen, J. Zhang, M. Zheng, G. Chen, L. Li, and Q. Lu. 2018. The Therapeutic and Pathogenic Role of Autophagy in Autoimmune Diseases. Front Immunol. 9:1512.

Yu, L., Y. Chen, and S.A. Tooze. 2018. Autophagy pathway: Cellular and molecular mechanisms. Autophagy. 14:207-215.

Yu, L., C.K. McPhee, L. Zheng, G.A. Mardones, Y. Rong, J. Peng, N. Mi, Y. Zhao, Z. Liu, F. Wan, D.W. Hailey, V. Oorschot, J. Klumperman, E.H. Baehrecke, and M.J. Lenardo. 2010. Termination of autophagy and reformation of lysosomes regulated by mTOR. Nature. 465:942-946.

Yue, Z., S. Jin, C. Yang, A.J. Levine, and N. Heintz. 2003. Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor. Proc Natl Acad Sci U S A. 100:15077-15082.

Yun, C.W., and S.H. Lee. 2018. The Roles of Autophagy in Cancer. Int J Mol Sci. 19.

Zachari, M., and I.G. Ganley. 2017. The mammalian ULK1 complex and autophagy initiation. Essays in biochemistry. 61:585-596.

Zhang, F., T. Yan, W. Guo, K. Sun, S. Wang, X. Bao, K. Liu, B. Zheng, H. Zhang, and T. Ren. 2018. Novel oncogene COPS3 interacts with Beclin1 and Raf-1 to regulate metastasis of osteosarcoma through autophagy. J Exp Clin Cancer Res. 37:135.

Zhao, Y.G., and H. Zhang. 2018. Formation and maturation of autophagosomes in higher eukaryotes: a social network. Curr Opin Cell Biol. 53:29-36.

Zhao, Y.G., and H. Zhang. 2019. Autophagosome maturation: An epic journey from the ER to lysosomes. J Cell Biol. 218:757-770.

Zhong, Z., E. Sanchez-Lopez, and M. Karin. 2016a. Autophagy, Inflammation, and Immunity: A Troika Governing Cancer and Its Treatment. Cell. 166:288-298.

Zhong, Z., A. Umemura, E. Sanchez-Lopez, S. Liang, S. Shalapour, J. Wong, F. He, D. Boassa, G. Perkins, S.R. Ali, M.D. McGeough, M.H. Ellisman, E. Seki, A.B. Gustafsson, H.M. Hoffman, M.T. Diaz-Meco, J. Moscat, and M. Karin. 2016b. NF-kappaB Restricts Inflammasome Activation via Elimination of Damaged Mitochondria. Cell. 164:896-910.

Zimmer, R., H.R. Scherbarth, O.L. Rillo, J.J. Gomez-Reino, and S. Muller. 2013. Lupuzor/P140 peptide in patients with systemic lupus erythematosus: a randomised, double-blind, placebo-controlled phase IIb clinical trial. Ann Rheum Dis. 72:1830-1835.

Zou, Y.H., Q. Wang, B.L. Li, B. Xie, and W.M. Wang. 2014. Temozolomide induces autophagy via ATM-AMPK-ULK1 pathways in glioma. Molecular Medicine Reports. 10:411-416.

Figures

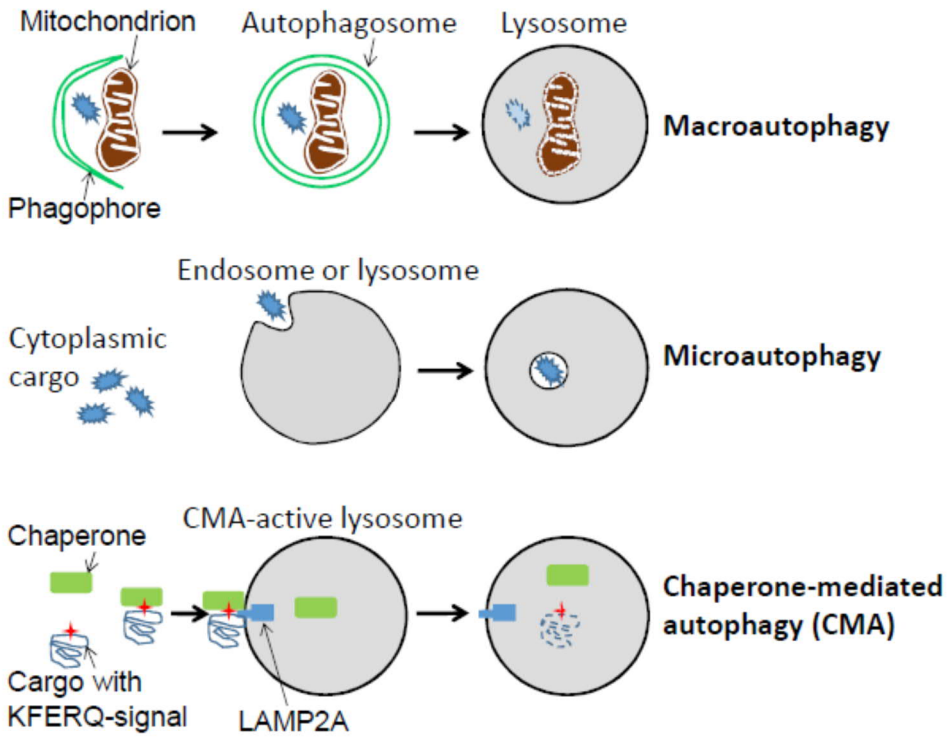

Figure 1

Figure 1. Schematic representation of the three autophagic pathways that deliver cargo from cytoplasm to lysosomes.

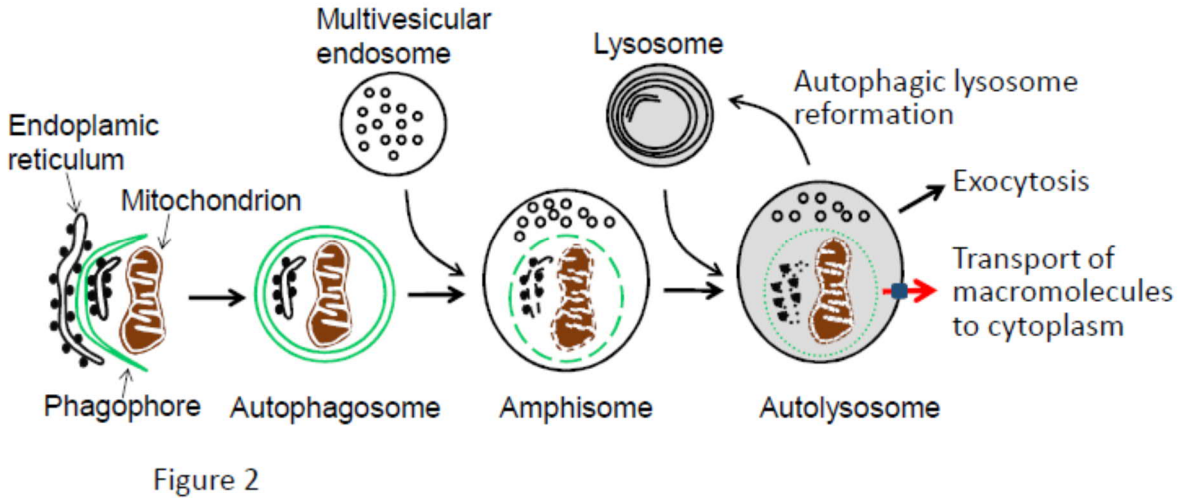

Figure 2

Figure 2. Schematic drawing of the macroautophagy pathway. Phagophores emerge between two endoplasmic reticulum cisternae, and close to form autophagosomes. Autophagosomes fuse with endosomes and lysosomes to mature into autolysosomes, which are the main degradative compartment of the pathway. Lysosomes can reform from autolysosomes, and autolysosomes can also fuse with the plasma membrane and empty their contents to the extracellular space.

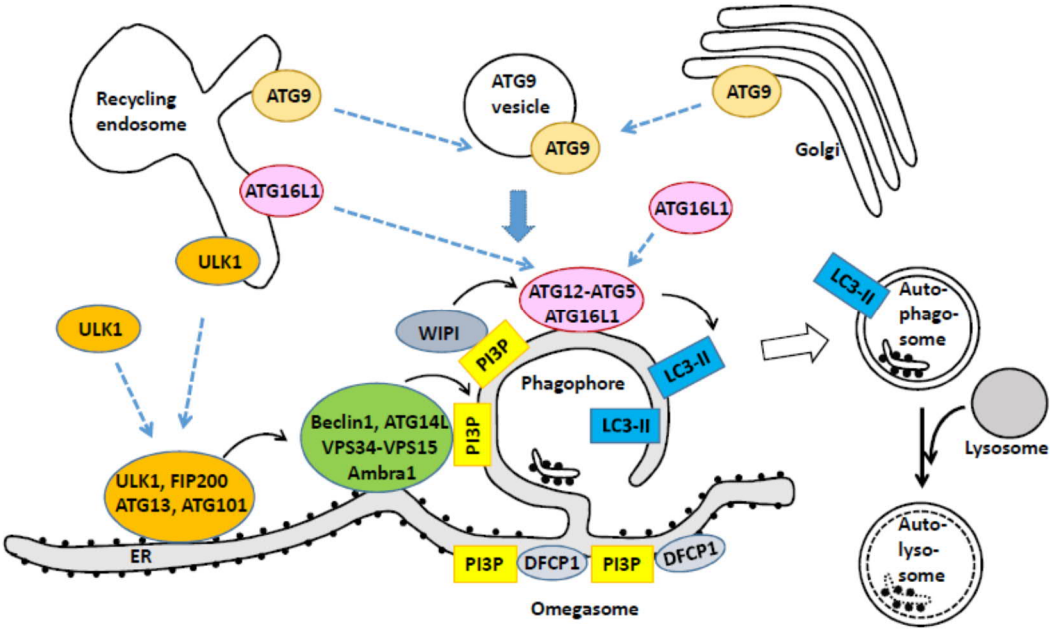

Figure 3. Overview of proteins, protein complexes and organelles that participate in autophagosome formation. See text for further details.

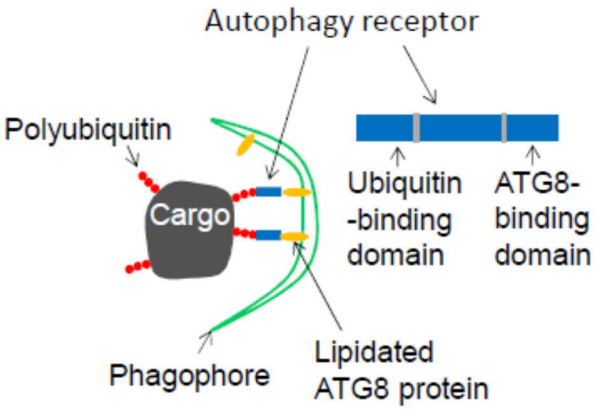

Figure 4. Schematic drawing of ubiquitin-dependent selective autophagy. Note that part of the autophagy receptors are independent of cargo ubiquitination.

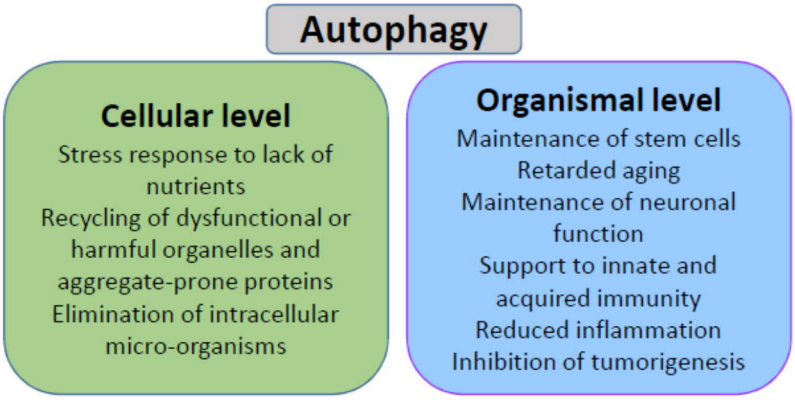

Figure 5. Summary of the functions of autophagy at cellular and organismal levels.