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Autophagy: A Lysosome-Dependent Process with Implications in Cellular Redox Homeostasis and Human Disease

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Abstract

Significance: Autophagy, a lysosome-dependent homeostatic process inherent to cells and tissues, has emerging significance in the pathogenesis of human disease. This process enables the degradation and turnover of cytoplasmic substrates *via* membrane-dependent sequestration in autophagic vesicles (autophagosomes) and subsequent lysosomal delivery of cargo.
Recent Advances: Selective forms of autophagy can target specific substrates (*e.g.*, organelles, protein aggregates, and lipids) for processing. Autophagy is highly regulated by oxidative stress, including exposure to altered oxygen tension, by direct and indirect mechanisms, and contributes to inducible defenses against oxidative stress. Mitochondrial autophagy (mitophagy) plays a critical role in the oxidative stress response, through maintenance of mitochondrial integrity.
Critical Issues: Autophagy can impact a number of vital cellular processes including inflammation and adaptive immunity, host defense, lipid metabolism and storage, mitochondrial homeostasis, and clearance of aggregated proteins, all which may be of significance in human disease. Autophagy can exert both maladaptive and adaptive roles in disease pathogenesis, which may also be influenced by autophagy impairment. This review highlights the essential roles of autophagy in human diseases, with a focus on diseases in which oxidative stress or inflammation play key roles, including human lung, liver, kidney and heart diseases, metabolic diseases, and diseases of the cardiovascular and neural systems.
Future Directions: Investigations that further elucidate the complex role of autophagy in the pathogenesis of disease will facilitate targeting this pathway for therapies in specific diseases. *Antioxid. Redox Signal.* 30, 138–159.

Keywords: autophagy, lysosome, selective autophagy, mitophagy, oxidative stress

Introduction

MACROAUTOPHAGY, COMMONLY ABBREVIATED as autophagy (meaning ''self-eating''), is a cellular homeostatic process that facilitates the turnover of cellular proteins and organelles, through a lysosome-dependent mechanism (111). In this dynamic process, cytoplasmic materials are sequestered into double-membraned vesicles called autophagosomes, which subsequently fuse to lysosomes where their contents are enzymatically degraded (Fig. 1). Autophagy may catabolize numerous cytoplasmic substrates, including protein aggregates, damaged organelles, carbohydrates, lipids, nucleic acids, and pathogens, which, in turn, regenerates metabolic precursors such as amino acids, fatty acids, and nucleotides, for reutilization in biosynthetic pathways (111).

The autophagy program is highly evolutionarily conserved and genetically regulated. Many proteins crucial for the regulation of autophagy, termed autophagy-related (ATG) proteins, have been identified in higher mammals, with homologous cognate proteins originally identified in yeast (35). In addition to macroautophagy, two other autophagy subtypes have been characterized. Microautophagy describes a

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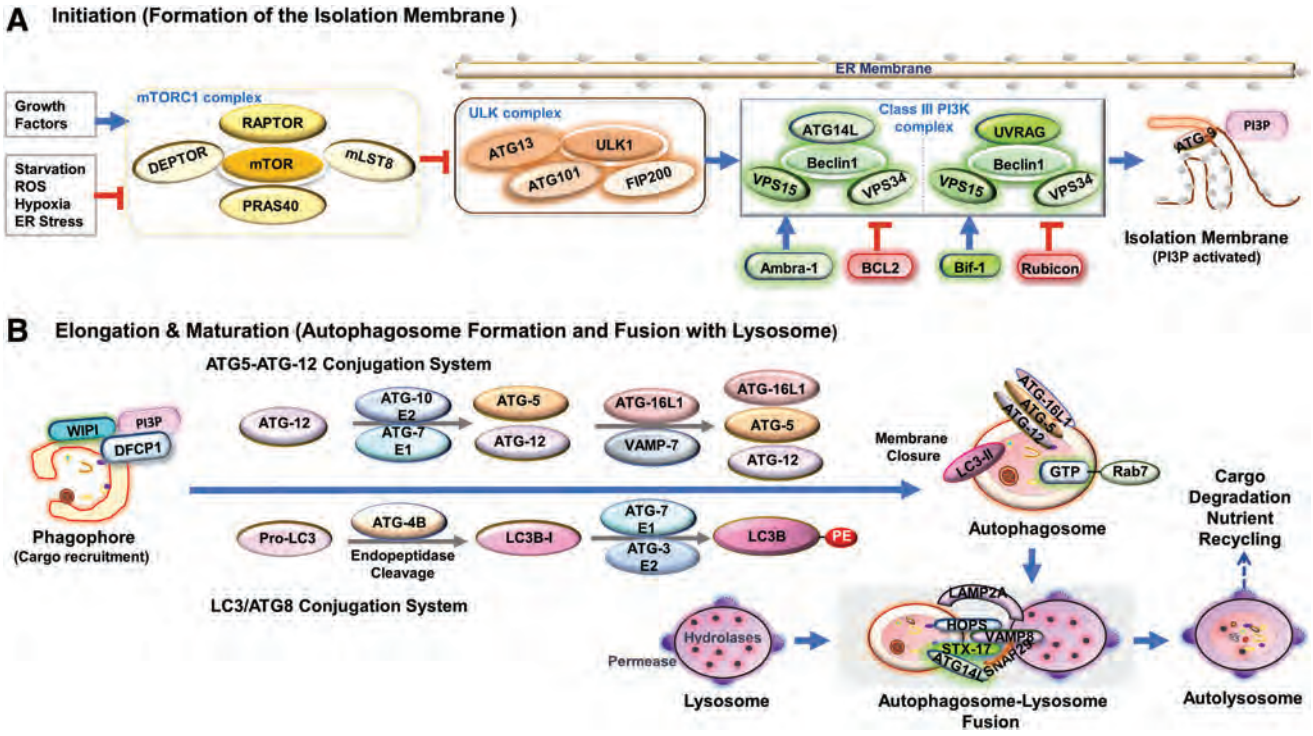

FIG. 1. Molecular regulation of autophagy. The autophagy pathway progresses through a series of sequential steps: **(A)** Initiation (formation of the isolation membrane) (*upper panel*). Growth factors or nutrient signals stimulate mTORC1, whereas starvation, ROS, or hyperoxia inhibit mTORC1 activity. mTORC1 inhibition leads to activation of ULK1. ULK1 resides in a macromolecular complex containing various regulatory proteins: FIP200, ATG13, and ATG101. Formation of the isolation membrane requires the Beclin 1 macromolecular complex, which includes VPS34/PIK3C3, p150/Vps15, and ATG14L. ULK1 positively regulates autophagy by activating Beclin1 *via* phosphorylation of Beclin1 or ATG14L. UVRAG can exchange for ATG14L. AMBRA-1 positively whereas BCL2 negatively regulates the Beclin1 complex. Bif-1 acts as a positive whereas Rubicon acts as a negative regulator of Beclin1–UVRAG complex. VPS34 activity generates PI3P, which promotes the formation of the isolation membrane. ATG9 also facilitates lipid recruitment to the nascent autophagosome membrane. **(B)** Elongation and maturation of the phagophore to form autophagosomes (*lower panel*). PI3P recruits regulatory proteins, including DFCP1 and WIPI, to the phagophore. The elongation of the phagophore involves two ubiquitin-like conjugation systems: (i) ATG5–ATG12 conjugation system. ATG12 is conjugated to ATG5 by ATG7 (E1 ubiquitin activating enzyme-like) and Atg10 (E2 ubiquitin-conjugase-like) enzymes. ATG5–ATG12 complex associates with Atg16L1 with the assistance of VAMP7. (ii) LC3/ATG8 conjugation system, ATG4B endopeptidase cleaves pro-LC3 to generate LC3B-I. Conjugation of PE with LC3-I is catalyzed by Atg7 (E1-like) and Atg3 (E2-like) activities. Both conjugation systems are involved in autophagosome formation. Rab7 in its GTP bound form also regulates the maturation of autophagosome. The HOPS-tethering complex that includes VPS33A and VPS16 promotes autophagosome–lysosome fusion through interaction with the autophagosomal Qa-SNARE, syntaxin-17 (STX-17). STX-17 is localized on the outer membrane of the mature autophagosome, interacts with ATG14L and SNAP29. The SNARE complex involved in autophagosome–lysosome fusion is composed of STX-17, SNAP29, and VAMP8. LAMP-2A helps in recruitment of STX-17. The fusion results in cargo degradation by lysosomal acid hydrolases and recycling of nutrients through lysosomal efflux permeases. AMBRA-1, autophagy/Beclin 1 regulator; ATG, autophagy-related; Bif-1, Bax-interacting factor-1; DFCP1, double FYVE-containing protein-1; ER, endoplasmic reticulum; FIP200, focal adhesion kinase family interacting protein of 200 kDa; HOPS, homotypic fusion and protein sorting; LAMP-2A, lysosome-associated membrane protein-2A; LC3B, microtubule-associated protein-1 light chain 3B; mTOR, mechanistic/mammalian target of rapamycin; mTORC1, mTOR complex 1; PE, phosphatidylethanolamine; PI3P, phosphatidylinositol-3-phosphate; PIK3C3, phosphatidylinositol 3-kinase Class III; ROS, reactive oxygen species; Rubicon, run-domain Beclin-1 interacting and cysteine-rich containing protein; SNARE, soluble *N*-ethylmaleimide-sensitive factor attachment receptor; STX-17, syntaxin-17; ULK1, unc-51-like autophagy activating kinase-1; UVRAG, ultraviolet radiation resistance-associated gene protein; VPS, vacuolar protein sorting; WIPI, WD-repeat protein interacting with phosphoinositides. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

process wherein cytoplasmic components are directly assimilated *via* membrane invagination into the lysosome (87). In chaperone-mediated autophagy (CMA), proteins bearing a KFERQ motif are recognized by heat shock cognate (hsc70) protein, a cytoplasmic chaperone. The protein–chaperone complexes are subsequently internalized into the lysosomes *via* interaction with the lysosome-associated membrane protein-2A (LAMP-2A) (22).

Autophagy serves as a protective process associated with cell survival, in particular during nutrient or energy-deficient states (*i.e.*, starvation) (111). Like many adaptive processes, autophagy constitutes an inducible response that can be triggered by cellular stimulation with stress agents, including reactive oxygen species (ROS), endoplasmic reticulum (ER) stress, and hypoxia (25). Observations of the occurrence of autophagosomes in dying cells led to defining autophagy as

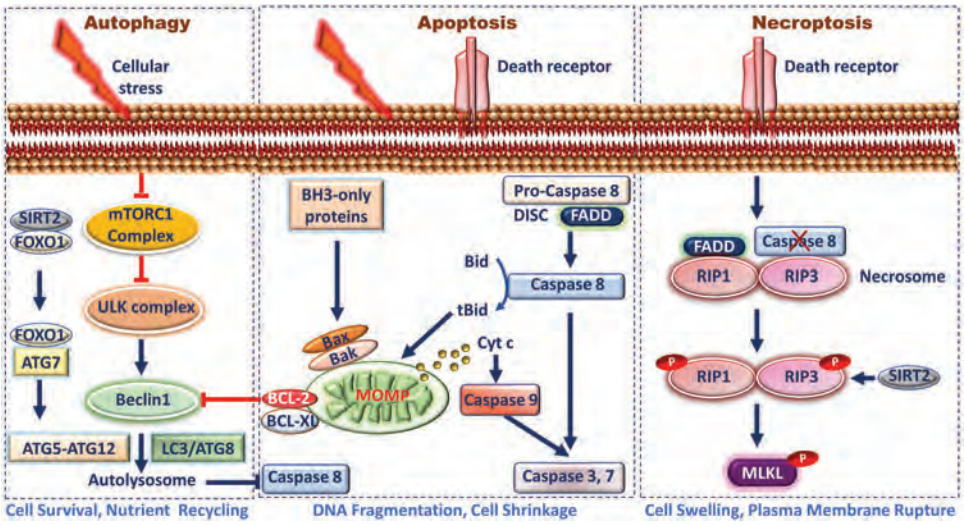

FIG. 2. Signaling pathways and cross talk between autophagy, apoptosis, and necroptosis. Autophagy is a cellular homeostatic program associated with cell survival, which can interact with the major programmed cell death pathways (*i.e.*, apoptosis and necroptosis). Both autophagy and apoptosis can be triggered in response to cellular stress or nutrient deprivation. Apoptosis is activated by extrinsic signals (*e.g.*, binding of TNF-α, FASL, or TRAIL to the death receptor) or intrinsic stimuli (*e.g.*, BH3-only protein-induced release of Cyt c by mitochondria). Internalization of TNF-α by the death receptor (TNFR1) stimulates the formation of the cytoplasmic DISC and subsequent activation of caspase 8. DISC formation involves recruitment of FADD, TRADD, and RIP1. Caspase 8 plays a critical role in both apoptosis and necroptosis. Caspase 8 cleaves Bid into t-Bid and promotes apoptosome formation by activation of caspase 7 and caspase 3. In addition, intrinsic stimuli induce MOMP and release of apoptotic mediators including Cyt c, which promotes caspase 9-dependent activation of caspase 7 and caspase 3. These signaling events culminate in DNA fragmentation associated with apoptosis. The cross talk between apoptosis and autophagy includes inhibition of Beclin 1 by apoptotic proteins Bcl-2 and Bcl-XL. The cleaved c-terminal portion of Beclin 1 triggers apoptotic signaling events in mitochondria. The proteolytic cleavage of caspase 8 from the complex containing RIP1, RIP3, TRADD, and FADD induces the formation of the RIP1–RIP3 necrosome complex. This complex phosphorylates (activates) mixed lineage kinase domain-like protein (MLKL) and promotes necroptosis. The relationship between autophagy and necroptosis remains incompletely understood. SIRT2 (orthologues of silent information regulator) promotes RIP1–RIP3 complex formation by deacetylation of RIP1. However, in response to oxidative stress, the transcription factor FOXO1 dissociates from SIRT2 and, in its acetylated form, stimulates autophagy through binding to ATG7. Cyt c, cytochrome c; DISC, death-inducing signaling complex; FADD, FAS-associated protein with death domain; MOMP, mitochondrial outer membrane permeabilization; RIP, receptor-interacting protein; SIRT2, Sirtuin 2; TNF-α, tumor necrosis factor-alpha; TNFR1, TNF receptor 1; TRADD, TNFR1-associated death domain protein . To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

an alternative form of programmed cell death (144). Although this definition is now obsolete, it remains evident that signaling processes governing the regulation of autophagy can overlap those regulating cell death programs such as apoptosis and necroptosis (Fig. 2) (45).

Furthermore, the concept that autophagy is always related to beneficial outcomes has been challenged by findings that excessive autophagy can be associated with increased apoptosis and/or necroptosis (17, 18, 110). In recent years, autophagy has gained recognition as a regulator of innate and adaptive immunity, which impacts the regulation of inflammation and immune responses, antigen presentation, and pathogen (*i.e.*, bacterial, viral, and parasite) clearance (86).

The 2016 Nobel Prize in Physiology or Medicine was awarded to Dr. Yoshinori Ohsumi for his discoveries of the basic mechanisms of autophagy that laid the groundwork for studies on the role of autophagy and its link to human disease. This review examines the importance of redox-dependent processes in the molecular regulation and function of autophagy, as they relate to cellular homeostasis and the oxidative stress response. Furthermore, the significance of autophagy in major organ diseases involving oxidative stress or inflammation is discussed, with an emphasis on human diseases of the lung, kidney, liver, cardiovascular, and neural systems.

Regulation of Autophagosome Formation

Autophagy progresses through sequential steps. Autophagosome formation begins with the nucleation step leading to the formation of an isolation membrane or phagophore. In the elongation step, the phagophore extends to engulf a cargo (*e.g.*, misfolded proteins or damaged organelles). Subsequently, the maturation step results in autophagosome completion and cargo sequestration. In the fusion step, the autophagosome merges with the lysosome, with subsequent degradation of contents by lysosomal enzymes (111).

The nucleation step is regulated primarily by unc-51-like autophagy activating kinase-1 (ULK1; homologue of yeast Atg1) (184). ULK1 resides in a macromolecular complex that includes the focal adhesion kinase family interacting protein of 200 kDa (FIP200), and the ATG-13 and ATG-101 proteins (184). The regulation of autophagosome formation requires another macromolecular complex, named for its key component, the autophagy regulator Beclin 1 (BECN1, homologue of yeast Atg6), a tumor suppressor protein (49).

The Beclin 1 complex contains the vacuolar protein sorting (VPS) 34/phosphatidylinositol 3-kinase Class III (PIK3C3), p150/Vps15, and ATG14L. (49). ULK1 may positively regulate autophagy by regulating the Beclin1 complex *via* phosphorylation of Beclin 1 (138), or ATG14L (123). The intrinsic VPS34/PIK3C3 activity of the BECN1 complex generates phosphatidylinositol-3-phosphate (PI3P), which is required for the formation of the autophagosome (49). PI3P acts as a second messenger that recruits WD-repeat protein interacting with phosphoinositides (WIPI) proteins, which regulate autophagosome assembly (31). BECN1 interacts with Bcl-2 family members (*e.g.*, Bcl-2 and Bcl-X_L), resulting in inhibition of autophagy-associated cell death (90). The BECN1 complex is also negatively regulated by the Class I phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which phosphorylates BECN1 (180).

The ultraviolet radiation resistance-associated gene protein (UVRAG) can interchange for ATG14L by competition for BECN1 (49). The UVRAG–BECN1 complex functions in autophagosome formation, whereas UVRAG may also function in endocytic trafficking and autophagosome maturation (74). Additional proteins positively or negatively regulate autophagy through interaction with BECN1. For example, the autophagy/Beclin 1 regulator (AMBRA-1) positively regulates the BECN1 complex (49). Furthermore, Bax-interacting factor-1 (Bif-1) activates, whereas Rubicon (run-domain Beclin-1 interacting and cysteine-rich containing protein) inhibits Beclin 1–UVRAG complexes (49). The transmembrane protein ATG9 facilitates lipid recruitment to the nascent autophagosome membrane, and cycles between the autophagosome, endosome, and the Golgi apparatus (35).

Downstream of autophagosome nucleation, the elongation of the phagophore to generate the mature autophagosome involves two ubiquitin-like conjugation systems (35, 111). In the ATG5–ATG12 conjugation system, the ubiquitin-like protein ATG12 is conjugated to ATG5. The ATG5–ATG12 complex associates with Atg16L1, which is required for autophagosome assembly. In the LC3/ATG8 conjugation system, the ubiquitin-like protein microtubule-associated protein-1 light chain 3B (LC3B) (encoded by the *MAP1LC3B* gene), and related ATG8 homologues serve as mediators of autophagosome formation (35, 111). The ATG4B endopeptidase cleaves pro-LC3 to generate LC3B-I. In mammals, the conversion of LC3B-I (free form) to its phosphatidylethanolamine (PE)-conjugated form LC3B-II represents a marker of autophagosome biogenesis (35, 111).

Recent genetic studies suggest that LC3B/Atg8 may not be absolutely essential in autophagosome biogenesis, but rather critical in autophagosome–lysosome fusion (118). Soluble *N*-ethylmaleimide-sensitive factor attachment receptor (SNARE) proteins serve as factors important for autophagosome biogenesis (113) and autophagosome–lysosome fusion. The SNARE VAMP7 recruits ATG16L1 to the isolation membrane (113). The homotypic fusion and protein sorting (HOPS)-tethering complex including vacuolar protein sorting 33A (VPS33A) and VPS16 interacts with the autophagosomal SNARE, syntaxin-17 (63). Syntaxin-17, localized on the outer membrane of the mature autophagosome, interacts with ATG14L and SNAP29, and with the lysosomal SNARE VAMP8, to facilitate autophagosome–lysosome fusion (26, 57).

Metabolic Regulation of Autophagy

Autophagy is tightly regulated by metabolic signals sensitive to energy levels, reducing equivalents, and nutrient status, including growth factors, glucose, and amino acid levels (111, 184). Growth factors negatively regulate autophagy through the mechanistic/mammalian target of rapamycin (mTOR) pathway. The mTOR protein participates in a macromolecular complex, mTOR complex 1 (mTORC1), that inhibits autophagy, and includes the regulatory-associated protein of mTOR (RAPTOR), PRAS40/AKT1 substrate 1 (AKT1S1), and the mTOR-associated protein, LST8 homologue (MLST8) (64). Furthermore, mTORC1 is regulated by additional interactive proteins such as DEPTOR (dishevelled, egl-10, and pleckstrin-domain-containing mTOR-interacting protein).

Growth factors (*e.g.*, insulin) that activate the Class I PI3K/Akt pathway activate mTORC1 through phosphorylation of regulatory proteins (*e.g.*, tuberous sclerosis-2 [TSC2] and AKT1S1) (64). The mTORC1 inhibits autophagy by phosphorylating ULK1 (Ser 757) and ATG13 (71), and inhibits the BECN1 complex through phosphorylation of AMBRA-1, ATG14L, or UVRAG (193).

The autophagy pathway is regulated by energy depletion through activation of the 5′-AMP activated protein kinase (AMPK), which senses cellular AMP levels (71, 111). AMPK can activate autophagy through several mechanisms, including the direct phosphorylation of ULK1 at Ser 317 and Ser 777 (71). AMPK can also phosphorylate BECN1 (Thr 388) leading to Vps34 activation (195). Depletion of cellular reducing equivalents regulates autophagy *via* activation of the NAD^+-dependent class III histone deactylase sirtuin 1 (SIRT1) (79). SIRT1 was reported to complex and catalyze the deacetylation of key autophagy regulator proteins, including ATG5, ATG7, and ATG8 (79).

Selective Autophagy

Autophagy can be targeted toward specific substrates in processes collectively known as ''selective autophagy'' (111, 154) (Fig. 3). The ubiquitination of subcellular targets represents a universal signal for identification of selective autophagy substrates (154). The selective targeting of autophagy substrates to the autophagosome is assisted by cargo adaptor proteins such as $p62^{SQSTM1}$ (p62, sequestosome, autophagy cargo adaptor protein) that can associate with ubiquitinated substrates and with ATG8 homologues at the autophagosome membrane *via* the LC3-interacting region (LIR) (154).

Mitophagy

The most widely studied selective autophagy pathway is mitophagy, a mechanism for the selective degradation of mitochondria (192) (Fig. 4). The regulation of mitophagy involves the activation of the transmembrane Ser/Thr kinase PINK1 [phosphatase and tensin homologue deleted in chromosome 10 (PTEN)-induced putative kinase 1], which is stabilized on damaged or depolarized mitochondria (116, 192). PINK1 recruits the E3: ubiquitin ligase Parkin, Parkinson protein-2 (PARK2) to the mitochondria, which ubiquitinates outer mitochondrial membrane proteins, including mitofusins (39, 116), which are then recognized and targeted to autophagosomes by the autophagic cargo adaptor protein

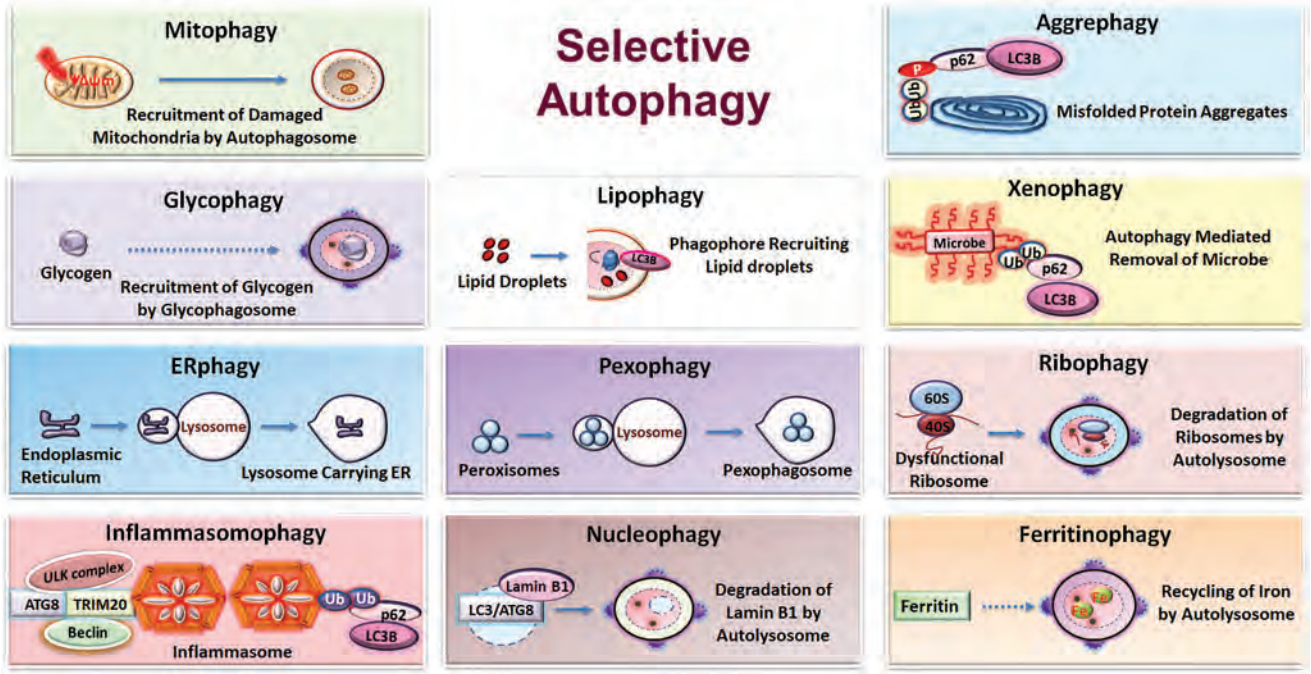

FIG. 3. Selective autophagy mediates the removal of dysfunctional or superfluous organelles, protein aggregates, accumulated glycogen, lipid droplets, or defective ribosomes, and contributes in maintaining cellular quality control, organelle function, and promotes cell survival under oxidative stress conditions. Mitophagy exerts protective functions in various diseases by removing dysfunctional mitochondria and suppressing mtROS-induced mtDNA damage. Aggrephagy removes aggregates of oxidized or misfolded proteins, and its impairment leading to the accumulation of protein aggregates has been implicated in disorders such as neurodegenerative diseases. Lipophagy removes lipid droplets, and its impairment has been associated with diseases such as atherosclerosis and hepatic steatosis. Glycophagy degrades accumulated glycogen, which is potentially important in diabetes. Xenophagy assists in immune responses by promoting clearance of foreign pathogens such as bacteria and viruses. ERphagy removes aggregate-prone proteins from the ER membrane. ERphagy may limit unfolded protein-induced ER stress responses. Pexophagy suppresses peroxisomal ROS production by recycling damaged peroxisomes. Ribophagy assists in the removal of nonfunctional ribosomes. Inflammasomophagy involves targeted destruction of inflammasomes either through binding of p62 to the ubiquitylated ASC subunit or *via* recognition of Nod like receptor protein–1 (NLRP1) or NLRP3 by TRIM20. TRIM20 promotes autophagy by recruiting ULK1, Beclin1, and ATG8 complexes. Nucleophagy involves autophagy-mediated degradation of nucleus or its components. The LC3/Atg8 conjugation system binds and degrades nuclear lamina protein lamin B1 during tumorigenic stress, such as by activated oncogenes. Ferritinophagy may contribute to the maintenance of iron homeostasis by shuttling of iron-bound ferritin to the lysosome for recycling. ASC, apoptosis-associated speck-like protein containing caspase-recruitment domain; ER, endoplasmic reticulum; mtDNA, mitochondrial DNA; mtROS, mitochondria-derived reactive oxygen species; NLRP, Nod like receptor protein; p62, sequestosome; TRIM20, tripartite motif-containing 20; UB, ubiquitin. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

p62 (192). Mutations in the *PINK1* and *PARK2* genes are associated with accumulation of dysfunctional mitochondria, and recessive familial forms of Parkinson's disease (PD) (168). PINK1 may directly phosphorylate ubiquitin, as a prerequisite for Parkin activation (76).

An alternatively regulated form of mitophagy governs the turnover of mitochondria in erythrocytes and reticulocytes. This form of mitophagy involves the BH3-only protein, Nix (Bnip3L). Nix localizes to the outer mitochondrial membrane and directly interacts with mammalian Atg8 homologues through its LIR (27).

Xenophagy

The selective autophagy processing of intracellular pathogens such as bacteria, viruses, and parasites is termed ''xenophagy,'' a process that may support cellular immune responses during infection (86). Invading bacteria are marked by ubiquitin, which is recognized by cargo adaptors, including p62, optineurin (OPTN), NBR1 (neighbor of *BRCA1* gene 1), and NDP52 (nuclear dot protein, 52-kDa), which facilitate the transfer and sequestration to autophagosomes (43). Xenophagy may also contribute to host defenses by enhancing immune recognition of infected cells through generation of antigenic bacterial peptides (86). Despite the protective functions of autophagy against pathogen invasion, some bacterial strains (*e.g.*, *Staphylococcus aureus*) can exploit host autophagosomes for replication (142). These bacteria can not only block autophagosome maturation and acidification but can also proliferate within autophagosomes (43, 142).

Aggrephagy

Aggrephagy refers to the selective autophagic degradation of protein aggregates, which may be significant in metabolic or neurodegenerative diseases that involve the accumulation

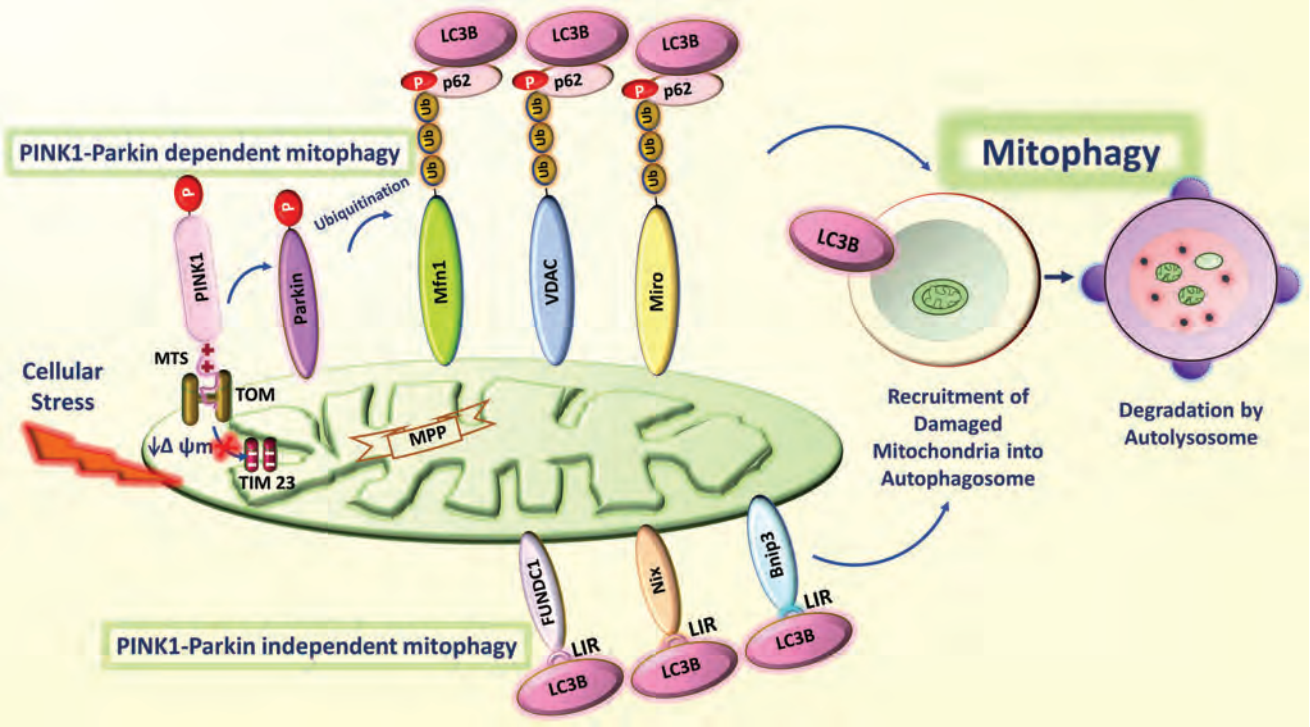

FIG. 4. Mechanisms of mitochondrial autophagy (mitophagy). Mitophagy can proceed *via* PINK1/Parkin-dependent and independent pathways. In the PINK1/Parkin-dependent pathway, healthy mitochondria permit PINK1 (a serine/threonine kinase) into the IMM *via* TOM and TIM-23 proteins. The matrix metalloprotease of mitochondria cleaves the MTS of PINK1. However, during severe oxidative stress, impaired mitochondria with declining mitochondrial membrane potential fail to import PINK1 into the IMM. Under these conditions, PINK1 associates with TOM and accumulates on the OMM. PINK1 promotes the recruitment and activation of Parkin from the cytoplasm to the OMM. Parkin ubiquitinates various OMM proteins (*e.g.*, mitofusin 1 and mitofusin 2, VDAC, and Miro). Subsequently, p62, a cargo adaptor protein, recognizes and binds to the ubiquitinated OMM proteins. Finally, p62 binds with LC3B and promotes autophagosome formation. PINK1/Parkin-independent mitophagy involves interaction of LC3B with OMM proteins: FUNDC1, Nix/Bnip3L, and Bnip3 through the LIR. This results in removal of mitochondria through mitophagy. Bnip3, Bcl-2/adenovirus E1B 19 kDa-interacting protein-3; FUNDC1, FUN14 domain containing 1; IMM, inner mitochondrial membrane; LIR, LC3-interacting region; MTS, mitochondral targeting signal; Nix/Bnip3L, NIP3-like protein X; OMM, outer mitochondrial membrane; PINK1, phosphatase and tensin homologue deleted in chromosome 10 (PTEN)-induced putative kinase 1; TIM, translocase of inner membrane; TOM, translocase of outer membrane; VDAC, voltage-dependent anion channel. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

of aberrantly folded proteins (189). p62 participates in direct protein–protein interactions with ubiquitinated proteins *via* its ubiquitin-associated domain, and with LC3 localized to the isolation membrane *via* an LIR motif, thus facilitating the sequestration of ubiquitinated proteins in the nascent autophagosome (154).

In addition to p62, the selective autophagy adaptor NBR1 is required for the formation of ubiquitin-positive protein aggregates, which facilitates their sequestration and removal by aggrephagy (189). Aggrephagy also requires the 400 kDa, PI3P-binding autophagy-linked FYVE domain protein (ALFY), a scaffolding protein that interacts directly with p62 (20). In addition, histone deacetylase 6 (HDAC6) recognizes and assists in dynein-mediated transport of ubiquitinated proteins (69). We have recently uncovered a novel role for HDAC6 in the autophagic processing of cilia proteins, in a process termed ''ciliophagy'' (78).

Other selective autophagy programs

Additional subtypes of selective autophagy and their specific cargo adaptors have been recently reviewed (33). For example, ''lipophagy'' regulates lipid metabolism through the clearance of lipid droplets (148). The processes of ''pexophagy'' and ''ribophagy'' refer to the autophagic turnover of peroxisomes and ribosomes, respectively. Still other forms include ''ERphagy,'' ''glycophagy,'' and ''RNAphagy'' for the selective degradation of membrane fragments, glycogen, and RNA, respectively, ''nucleophagy'' for the selective degradation of the nuclear lamina protein Lamin B1, and ''inflammasomophagy'' for the autophagic processing of inflammasome complexes (33). The autophagic degradation of ferritin or ''ferritinophagy'' utilizes the cargo adaptor nuclear receptor coactivator 4 (NCOA4), and may regulate intracellular iron levels (100).

Autophagy and Oxidative Stress

Oxidative cellular stress occurs when the metabolic production of ROS exceeds that required for physiological functions, and overwhelms the capacity of cellular antioxidant defenses, leading to mitochondrial dysfunction and damage to cellular macromolecules such as DNA, lipids, and

proteins. Mitochondria-derived ROS (mtROS), the major component of cellular ROS production, arises as a by-product of mitochondrial respiration, and increases in pathophysiological states. ROS may evolve from enzyme activities such as NADPH oxidases. The major ROS include the superoxide anion radical ($O_2^{\bullet -}$), and its dismutation product hydrogen peroxide (H_2O_2), which may lead to the formation of the reactive hydroxyl radical (from the iron-catalyzed decomposition of H_2O_2), or peroxynitrite (from the reaction of $O_2^{\bullet -}$ and NO) (32).

Activation of autophagy by cellular stimulation with H_2O_2, redox cycling compounds, and respiratory chain inhibitors suggests that autophagy represents a general response to oxidative stress (5, 141). Rotenone and thenoyltrifluoroacetone, which inhibit Complex I and Complex II, respectively, increase mtROS production in transformed cells, and induce a caspase-independent cell death associated with enhanced autophagy (15, 16). The mitochondrial uncoupling agent carbonyl cyanide *m*-chlorophenyl hydrazone (CCCP), which induces mitochondrial depolarization, can induce PINK1-dependent mitophagy (104, 177). The decline of mitochondrial membrane potential ($\Delta\psi_m$) and the increased production of mtROS represent initiating signals for mitophagy.

Autophagy may protect against oxidative stress by facilitating the turnover of damaged or oxidized macromolecules, including proteins and lipids (111, 199). Importantly, the removal of damaged or dysfunctional mitochondria by mitophagy may play a cardinal role in cellular antioxidant defenses, by insuring mitochondrial quality control and preventing pathological mtROS generation (192). Our studies suggest that autophagy can dampen inflammation *via* downregulating inflammasome-associated cytokines production (*e.g.*, interleukin [IL]-1β, IL-18) and maturation through the preservation of mitochondrial function and reduction of mtROS formation (114).

Genetic studies have confirmed the importance of autophagy in cellular resistance to oxidative stress and in mitochondrial maintenance. Oxidative stress generated by ultraviolet-A radiation induced the accumulation of p62-positive protein aggregates in human skin keratinocytes, and induced autophagy. Genetic interference of *ATG7* sensitized keratinocytes to ultraviolet-A radiation-induced protein aggregation and phospholipid peroxidation (199). Genetic interference of *ATG7* also rendered human keratinocytes susceptible to toxicity and DNA damage induced by the redox-cycling compound paraquat (149). Loss of PINK1 function can promote oxidative stress and trigger mitochondrial fragmentation and autophagy (24), whereas PINK1 overexpression leads to mitochondrial clustering and accumulation of autophagosomes (177). Deletion of *PINK1* or *PARK2* results in progressive mitochondrial damage and dysfunction (192).

Chemical inhibition of autophagic flux using chloroquine or bafilomycin in neurons resulted in impaired mitochondrial bioenergetics and significant alterations in mitochondrial metabolism (134).

Redox regulation of autophagy

The key autophagy protein ATG4B and its homologues may be subjected to direct redox regulation (141). A cysteine residue (Cys^{78}) in Atg4B was identified as critical for redox regulation of the protein. Mutation of this residue abolished regulation of autophagy by exogenous H_2O_2 (141). Other potential targets for redox regulation include the E3 ubiquitin protein ligase activity of Parkin, which may be deregulated by oxidation of cysteine residues (108). The regulation of the mammalian antioxidant response can overlap that of autophagy (Fig. 5). Nuclear factor erythroid 2-related factor 2 (Nrf2) serves as a transcriptional regulator of cellular antioxidant defenses. Nrf2 dissociates from its cytoplasmic anchor, the Kelch-like ECH-associated protein 1 (Keap1), and interacts with antioxidant response elements in the promoter regions of genes critical for the antioxidant response (60).

Nrf2 can transcriptionally regulate the gene encoding the autophagy cargo adaptor protein p62 (60). p62 binds to and displaces Keap1 from Nrf2, and activates Nrf2 transcriptional activity (75). Keap1 is also constitutively degraded by p62-dependent autophagy (158). *Nrf2*$^{-/-}$ mice display impaired cardiac antioxidant responses and increased oxidative stress in these mice after high intensity exercise, which was accompanied by evidence of impaired cardiac autophagy (77).

Hypoxic regulation of autophagy

Hypoxia can cause mitochondrial dysfunction associated with impaired mitochondrial respiration and increased mtROS production. Hypoxia induces autophagy in mammalian cells, which is regulated by the hypoxia-inducible factor-1 (Hif-1), a master regulator of the hypoxic response (196). Hif-1α-deficient mouse embryonic fibroblast displayed inhibition of hypoxia-regulated autophagy. The BH3-containing Bcl-2 family member BNIP3 (Bcl-2/adenovirus E1B 19 kDa-interacting protein-3) and its homologue BNIP3L were identified as proteins encoded by Hif-1 target genes crucial for the hypoxic regulation of autophagy (8, 196). BNIP3/BNIP3L may activate autophagy through the displacement of inhibitory Bcl-2 family proteins (*i.e.*, Bcl-2 and Bcl-X_L) from complexes with BECN1 (8, 196).

Deletion of *BECN1* or *BNIP3/BNIP3L* promoted hypoxia-induced cell death (8). In primary human lung vascular endothelial and smooth muscle cells (SMCs), hypoxia induced the expression of BECN1, LC3B activation, and increased autophagosome formation and autophagic flux (83). Increased activation of LC3B and autophagosome formation in the lung protected against pulmonary vascular disease in mice exposed to chronic hypoxia (83). Genetic interference of LC3B increased intracellular ROS production, stabilized HIF-1α, and increased endothelial and SMC proliferation in response to hypoxia (83). Conversely, overexpression of LC3B in vascular cells suppressed mitogen- and hypoxia-dependent proliferation in cultured vascular cells (83). *Becn1*$^{+/-}$ endothelial cells displayed enhanced proliferation *in vitro* in response to hypoxia relative to wild-type cells (82). These studies suggest that autophagy regulates vascular cell responses to hypoxia.

Autophagy in Hepatic and Metabolic Diseases

Autophagy, as a component of cellular metabolism linked to both catabolic and anabolic pathways, plays a complex role in metabolic disorders (Fig. 6). Recent research has uncovered diverse functions of autophagy in the pathogenesis of various hepatic diseases, including α1-antitrypsin deficiency, alcoholic steatosis, nonalcoholic fatty liver

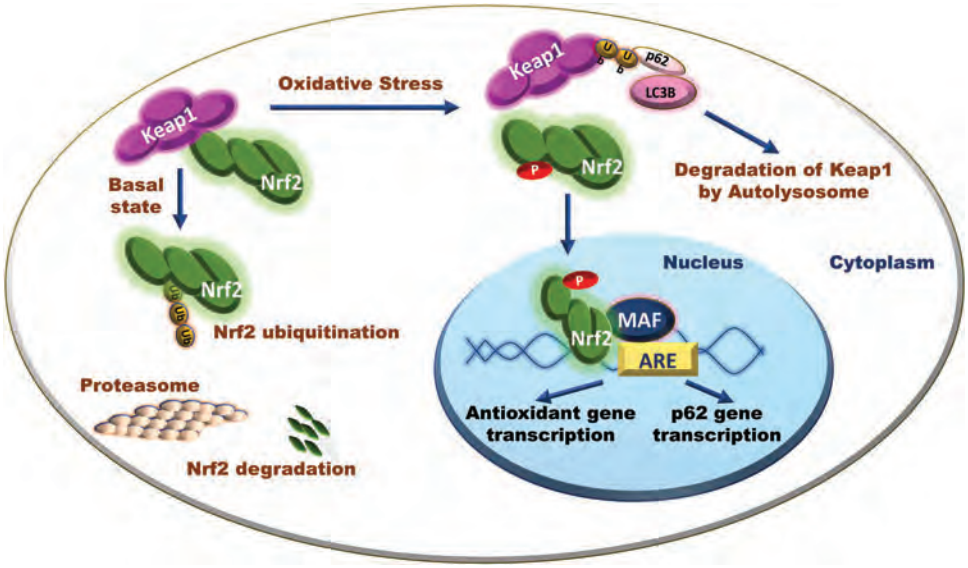

FIG. 5. Interaction of autophagy with the Nrf2-mediated antioxidant response. Under basal conditions, Nrf2 is bound to its repressor, the E3 ubiquitin ligase adaptor protein, Keap1. Keap1 promotes Nrf2 ubiquitylation and proteasomal-mediated degradation. During oxidative stress, increases in autophagic flux promote p62-mediated sequestration and degradation of Keap1. Keap1 can also be degraded by oxidation of its thiol group. Nrf2 that dissociates from Keap1 remains activated and translocates to the nucleus, where it binds with small MAF (musculoaponeurotic-fibrosarcoma virus) proteins. The heterodimer of Nrf2–MAF binds to the promoter regions of target genes *via* the antioxidant response element and positively regulates gene transcription. In addition to regulation of antioxidant genes, Nrf2 may regulate the transcription of p62, a protein involved in cargo recognition. Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

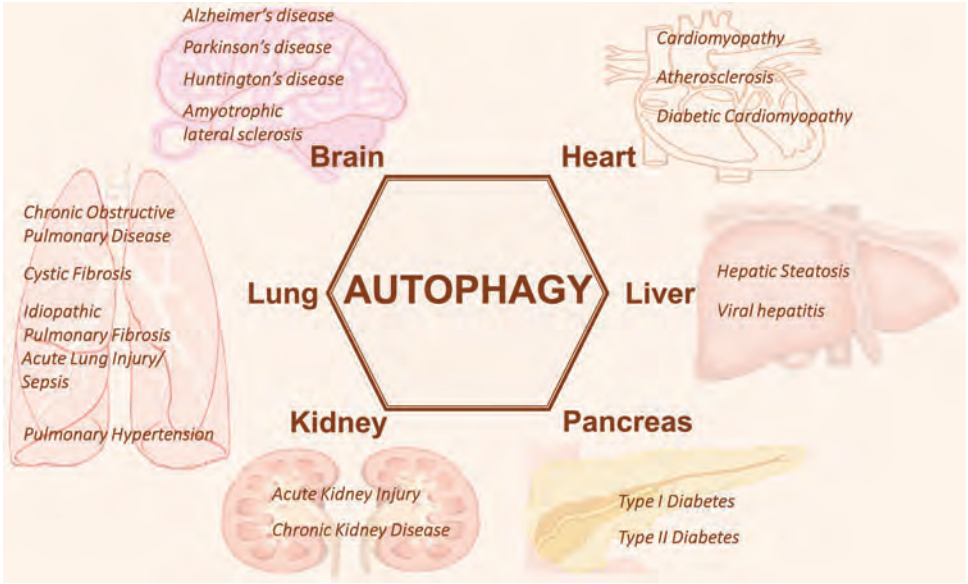

FIG. 6. Autophagy in human diseases. Autophagy plays a complex role in a growing number of human diseases. Scheme of organ-specific pathologies is shown in which alterations in autophagy are discussed in this review, including diseases of the brain, heart, lung, liver, kidney, and pancreas. Both protective and pathogenic roles for autophagy have been proposed in these diseases. Autophagy may modulate disease pathogenesis through selective pathways, which include the preservation of mitochondrial homeostasis through mitophagy, the clearance of aggregated or mutant proteins through aggrephagy, the clearance of cellular substrates such as collagen or glycogen, and the clearance of pathogenic bacteria or viruses through xenophagy. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma, and viral hepatitis (99, 171). Autophagy is predicted to play important roles in the turnover of mitochondria, protein, glycogen, lipids, and other metabolites, and in the regulation of metabolic enzymes, which may be of critical importance in hepatic homeostasis as well as in pathogenesis of hepatic diseases (99, 171).

Hepatic steatosis

Hepatic autophagy is downregulated by chronic alcohol consumption and in obesity or metabolic syndrome, leading to hepatic dysfunction and steatosis. These conditions are characterized by accumulation of fatty deposits and ubiquitinated protein aggregates, and the formation of Mallory–Denk bodies (131). Autophagy has also been identified as a vital regulator of lipid metabolism and storage. Hepatocyte-specific deletion of *Atg7* promoted the storage of triglyerides into lipid droplets in the liver (148). In addition, a role for CMA in the clearance of hepatic lipid droplets has also been identified (68). The capacity of autophagy in the clearance of lipid droplets may be highly relevent to hepatic diseases involving steatosis, although the contribution of other forms of selective autophagy such as mitophagy cannot be excluded (23).

Mice fed a methionine choline-deficient diet, a model of NASH, displayed reduced hepatic autophagic flux (13, 44). Chemical stimulation of autophagy (by rapamycin) or inhibition (by chloroquine), respectively, improved, or aggravated hepatic dysfunction, as marked by evidence of steatosis, fibrosis, ER stress, inflammation, and mitochondrial dysfunction in NASH mice (13, 44). Similarly, hepatocytes from NASH patients displayed increased ER stress and evidence of autophagy impairment, including p62 accumulation (44). Pharmacological induction of autophagy using vitamin D may offer therapeutic potential in reducing steatosis in diseases such as NAFLD and NASH (53).

Viral hepatitis

The autophagy pathway promotes the pathogenesis of viral hepatitis, including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Both HBV and HCV utilize the autophagic pathway for replication. HCV induces the autophagic pathway through stimulation of ER stress, and accumulation of misfolded protein aggregates, yet impairs autophagosomal processing and fusion. HBV and HCV can exploit autophagy proteins to assist in the translation of viral messenger RNA (mRNA). Chloroquine, an inhibitor of lysosomal acidification, may provide a therapeutic option for hepatitis infections (1). Furthermore, microRNA-dependent downregulation of Sirt1 using miR-141 to reduce autophagy, resulted in the inhibition of HBV replication (191).

Diabetes

Type 2 diabetes is characterized by insulin resistance and pancreatic islet β-cell dysfunction, whereas type 1 diabetes is characterized by the autoimmune destruction of pancreatic β-cells, resulting in insulin deficiency. Autophagy plays important roles in the pathogenesis of both type 1 and type 2 diabetes (122). Autophagy can act as mediator of pancreatic β-cell homeostasis (106). Therapies that target β-cell metabolic dysfunction are associated with the upregulation of autophagy (10). Genetic deletion of *Atg7* in β-cells rendered mice hyperglycemic and glucose intolerant and lowered β-cell mass and insulin production in these mice (65, 129). Furthermore, *Atg7*-deficient β-cells displayed accumulation of ubiquitinated proteins, mitochondrial dysfunction, and reduced insulin production (65, 129). Stimulation of autophagy also improved β-cell function and reduced ER stress in a model of diabetes caused by an insulin misfolding mutation (6).

Pathogenic accumulations of glycogen may be important in metabolic diseases, including diabetic cardiomyopathy. A selective autophagy-dependent process termed ''glycophagy'' alleviates glycogen accumulation and has been associated with cardioprotection in diabetes (135). Furthermore, genetic studies implicated mitophagy as a critical protective factor in human type 2 diabetes (143).

Autophagy in Kidney Diseases

The role of autophagy as a cytoprotective mechanism in the kidney has been extensively studied in various renal conditions, including tubular disorders and glomerulopathies (159). Furthermore, genetic studies have revealed important roles for autophagy in kidney function and morphology in both physiological and pathological states. Kidney podocytes, which are postmitotic terminally differentiated cells, exhibit a high basal rate of autophagy relative to kidney tubular cells (48). Podocyte-specific deletion of *Atg5* resulted in glomerulopathy in aged mice, associated with accumulation of oxidized and ubiquitinated proteins, increased ER stress, and proteinuria (48). Podocyte-specific *Atg5* deletion also increased basal podocyte apoptosis, as well as increased susceptibilty of podocytes to hyperglycemia-induced apoptosis (85).

Vascular endothelial cell-specific deletion of *Atg5* resulted in structural changes of the glomerular filtration barrier (85). *Atg5* deletion specific for distal tubule cells alone did not impair kidney function, whereas *Atg5* deletion in both proximal and distal tubules resulted in impaired kidney function (92). Recent research strongly suggests renoprotective roles for autophagy in acute kidney injury (AKI) (67), and in chronic kidney diseases (CKDs) (91, 101), as discussed in the following sections.

Acute kidney injury

The injury and death of tubular epithelial cells are key features of AKI. Various insults such as renal ischemia/reperfusion (I/R), sepsis, or exposure to nephrotoxins contribute to nutrient depletion and oxidative stress-induced activation of autophagy (107). In a rat model of renal I/R injury, the expression of autophagy proteins (*i.e.*, Beclin1, LC3) increased in proximal and distal epithelial cells after I/R (19). Ectopic overexpression of the antiapoptotic protein Bcl-X_L reduced the expression of proapoptotic and autophagy markers and ameliorated AKI in this model (19). Increased autophagosome formation was also observed in renal proximal tubular epithelial cells *in vivo*, in response to renal I/R injury in the mouse, and *in vitro,* in response to hypoxia (155).

Inhibitors of autophagy such as chloroquine and 3-methyladenine (3-MA) aggravated renal I/R injury and enhanced tubular apoptosis (51, 61). The kidney tubule-specific targeted genetic deletion of *Atg5* and *Atg7* resulted in increased susceptiblity to I/R-induced renal injury and apoptosis

(62, 92). The chemotherapeutic agent cisplatin, which induces AKI, induced autophagy in renal tubule tissue (126). Earlier studies suggested that cisplastin-induced increases in autophagy contribute to renal damage and apoptosis (56). However, studies using mice with kidney proximal tubule-specific deletion of *Atg5* revealed higher susceptibility to cisplatin-induced AKI, and elevated DNA damage, protein aggregation, apoptosis, and ROS production in the kidney relative to wild-type mice, indicating that autophagy is renoprotective (160).

Autophagy has been shown to be renoprotective in sepsis-induced AKI. In a rat model of cecal ligation and puncture (CLP)-induced sepsis, indicators of autophagy (*i.e.*, LC3B-II accumulation) were transiently increased in proximal tubules at earlier time points after CLP, and subsequently declined during the progression of sepsis-induced AKI (54). Genetic interference of *Atg7* enhanced, whereas chemical induction of autophagy inhibited tumor necrosis factor-alpha (TNF-α)-induced cell death in tubular epithelial cells *in vitro* (54). Taken together, these studies suggest that autophagy provides a renoprotective mechanism in AKI, in part, by limiting apoptosis, inflammation, and oxidative stress.

Chronic kidney disease

Autophagy may play important roles in the pathogenesis of various forms of CKD, including diabetic nephropathy (DN), and other nephropathies such as obstructive nephropathy and IgA nephropathy (91). CKD is characterized by progressive loss of kidney function. Development of renal fibrosis is a hallmark of CKD, and represents the final common response to injury (84). Targeting fibrogenic components in tubular epithelial cells and fibroblasts or myofibroblasts may represent a therapeutic approach. Transforming growth factor-beta 1 (TGF-β1) has been implicated as a key profibrogenic factor for the development of renal fibrosis (84). In these contexts, autophagy may serve as an endogenous protective mechanism in renal tubular epithelial cells and podocytes (28). Our studies have described a novel antifibrotic role of autophagy in the degradation of collagen (72).

We and others have described enhanced autophagy in renal tubular epithelial cells of obstructed kidneys after unilateral ureteral obstruction (UUO), an experimental model of renal fibrosis (29, 73). Mice genetically deficient in LC3B (*Map1lc3b*$^{-/-}$) or BECN1 (*Becn1*$^{+/-}$) displayed increased collagen deposition and increased mature TGF-β1 levels in obstructed kidneys after UUO surgery. These studies suggest that, in renal proximal tubular epithelial cells, the levels of mature TGF-β1 are regulated by autophagic degradation to suppress kidney fibrosis induced by UUO (29). Targeted deletion of the autophagy proteins *Atg5* or *Atg7* in kidney epithelium resulted in CKD in mice, associated with podocyte and tubular dysfunction, and progressive organ failure (70). Kidney tissue from these mice also exhibited enhanced ER stress, mitochondrial dysfunction, and mtROS production (70).

Similar morphological changes in mitochondria were observed in renal biopsies from patients with idiopathic focal segmental glomerular sclerosis (FSGS) (70). FSGS patients display decreased Beclin1 expression and reduced autophagosome numbers in podocytes compared with patients with minimal change disease (194). In puromycin aminonucleoside (PAN) treated rats, a model of nephrosis and proteinuria, application of chloroquine or 3-MA increased podocyte injury, foot process effacement, and proteinuria, and reduced the expression of podocyte markers (194). Genetic interference of *BECN1* or treatment with the autophagy inhibitors chloroquine or 3-MA enhanced PAN-induced podocyte cell apoptosis *in vitro* (194). Application of the autophagy activator rapamycin protected against these changes *in vitro* and *in vivo* (194).

In DN, a type of podocytopathy, the association of mTOR activation with increased glomerular injury in patients suggests the involvement of autophagy (42). Downregulation of mTORC1 conferred protection in streptozotocin-induced experimental DN in mice (42). In a mouse model of high-fat diet-induced DN, podocyte-specific conditional *Atg5* deletion resulted in podocyte damage, glomerulosclerosis, proteinuria, and increased sensitivity to high glucose-induced apoptosis (157). Endothelial-specific *Atg5* deletion resulted in capillary rarefactions, and glomerular endothelial lesions with loss of fenestrations, and accelerated progression of DN (85). Although autophagy can be induced in podocytes by high concentrations of glucose *via* enhanced oxidative stress (98), the chronic hyperglycemic condition in diabetes is associated with autophagy impairment *via* upregulation of mTORC1 (55).

In diabetic mice, the impaired autophagic flux in podocytes was partially restored by chemical chaperones such as tauroursodeoxycholic acid (34). A decrease in CMA during DN can contribute to protein aggregation and renal hypertrophy (150). Administration of resveratrol (an autophagy activator) protected against capillary loss and rarefactions by regulating angiogenesis (182). Histone deacetylase 4 (HDAC4) is known to suppress podocyte-specific autophagy (181). HDAC4 expression is negatively correlated with glomerular filtration rate, and is highly expressed in podocytes from patients with DN (181). HDAC inhibitors have been shown to protect against renal injury in a diabetic mouse model (88). Hence, the inhibition of podocyte autophagy may contribute to the pathogenesis of DN.

Autophagy may confer renoprotection during the pathogenesis of various kidney diseases through several mechanisms, including the removal of toxic protein aggregates, the inhibition of inflammation and fibrosis, and the maintainence of podocyte structure and function.

Autophagy in Heart and Cardiovascular Diseases

The role of autophagy in cardiac and cardiovascular disorders has been extensively studied in animal models. These include studies in I/R injury, cardiomyopathies, myocardial infarction, heart failure, and atherosclerosis (25). Autophagy has been proposed to exert both adaptive and maladaptive effects in cardiovascular disease, in a model-specific manner.

Cardiomyopathy, hypertrophy, and heart failure

Genetic deficiency in the autophagy-associated lysosomal protein LAMP-2 results in cardiomyopathy (Danon disease) with evidence of increased autophagosome accumulation in cardiomyocytes (163). The LAMP-2 knockout mice display impaired autophagic flux and aberrant autophagosome accumulation in the heart, and cardiac defects including abnormal cardiomyocyte morphology and reduced contractility (163). Mice genetically deficient in transferrin receptor in the

heart have iron deficiency, decreased cardiac iron uptake, and develop cardiomyopathy associated with mitochondrial dysfunction and impaired mitophagic flux (186). Impaired autophagy is also observed in diabetic cardiomyopathy, a condition associated with ventricular dysfunction and increased cardiomyocyte apoptosis (185).

The induction of autophagy may confer cardioprotection. Autophagy activation by stimulation of the AMPK pathway prevented apoptosis in glucose-stimulated cardiomyocytes (50). Chronic metformin administration conferred cardioprotection in mouse models of type 1 diabetes *via* upregulation of AMPK (185). In contrast, knockout of *BECN1* or *Atg7* conferred cardioprotection in type 1 diabetes (187).

Increased hemodynamic stress in the heart leads to compensatory remodeling processes that result in cardiac hypertrophy. Adult mice with conditional deletion of cardiac *Atg5* developed cardiac hypertrophy with left ventricular dilatation and contractile dysfunction, and increased protein ubiquitination (115). In contrast, *Atg5* deletion did not confer cardiac defects during cardiogenesis, but sensitized mice to pressure overload-induced cardiac hypertrophy and left ventricular dilatation (115). Thus, autophagy in failing hearts may serve as an adaptive response that protects cardiomyocytes from hemodynamic stress (115). *Atg5* deficiency also accelerated age-related cardiomyopathy, associated with increased mitochondrial dysfunction (164). Similarly, genetic deficiency of *PIK3C3/Vps34*, a component of the BECN1 complex, was associated with development of cardiac hypertrophy in mice (59).

Mitophagy dependent on dynamin-related protein-1 (Drp1) was transiently increased and then progressively downregulated in mouse hearts subjected to aortic constriction-induced pressure overload (146). *Drp1* haploinsufficient mice suffered accelerated mitochondrial dysfunction and cardiac failure in this model. Restoration of autophagy using Tat-Beclin peptide ameliorated mitochondrial dysfunction and heart failure as the result of pressure overload (146). Overexpression of Sestrin 1 reduced cardiac hypertrophy in mice in response to pressure overload through upregulation of AMPK-dependent autophagy (188). Similarly, rapamycin treatment reduced phenylephrine-induced cardiac hypertrophy in this model by promoting autophagy (46).

Interestingly, excess autophagy is implicated to have a pathogenic role in a heart failure model of pressure overload induced by aortic banding, in which mice sustained heart failure and elevated cardiac autophagy flux (200). *Becn1*$^{+/-}$ (heterozygous) mice displayed reduced autophagy during pressure overload and were resistant to pressure-induced cardiac remodeling. BECN1 overexpression in this model increased autophagy and promoted pathological cardiac remodeling (200).

Pharmacological application of resveratrol conferred cardioprotection in a model of abdominal aortic constriction by downregulation of AMPK-dependent autophagy (179). The mitochondrial division/mitophagy inhibitor (Mdivi) ameliorated pressure overload-induced heart failure (41). These studies suggest that autophagy is altered in cardiac disease, and can modulate cardiomyopathy, hypertrophy, and transition to heart failure. Although autophagy is generally considered a cardioprotective mechanism, maladaptive roles for autophagy have also been proposed in cardiac disease.

Atherosclerosis

Atherosclerosis is an inflammatory disease of the vasculature characterized by plaque formation. Autophagy has been implicated as a protective mechanism during the development of atherosclerosis, on the basis of several selective autophagy functions, including lipophagy, aggrephagy, and mitophagy, leading to anti-inflammatory effects and stabilization of atherosclerotic plaques (25, 96). In macrophage foam cells, autophagy provides a mechanism for lipid droplet clearance and for mobilization of cholesterol (121). Lipid droplets are taken up by autophagosomes and delivered to lysosomes for processing, where liposomal acid lipase hydrolyzes the lipid droplet-associated cholesterol esters. This process liberates free cholesterol for efflux from the foam cell (121).

Autophagy can be induced in cultured vascular cells by proatherogenic stimuli, (*e.g.*, oxidized low-density lipoprotein, oxidized lipids, and lipid peroxidation end-products, proinflammatory states, ER-stress agents, and hypoxia) and facilitates the turnover of oxidized or aggregated proteins under these conditions (25). Increased autophagy is detected in atherosclerotic plaques and can stabilize plaques by selectively preventing SMC apoptosis (25), or promoting the clearance of plaque macrophages (173). Upregulation of Pink1-dependent mitophagy prevented vascular SMC apoptosis, suggesting that mitophagy also contributes to plaque stabilization (156). Upregulation of autophagy in early stage macrophage foam cells was shown to decrease lipid accumulation and prevent apoptosis (93). Furthermore, induction of autophagy in *ApoE*$^{-/-}$ mice using rapamycin delayed atherosclerotic plaque formation and reduced macrophage apoptosis in this model (93).

Autophagy in Pulmonary Diseases

Autophagy is implicated as a major contributor to pulmonary diseases with both adaptive and maladaptive outcomes in model studies. These include studies in acute lung injury (ALI), sepsis, chronic lung disease, and fibrosis.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD), which manifests as an aberrant inflammatory response to inhalation of cigarette smoke (CS), contributes significantly to the global burden of disease; however, the pathogenesis of this disease remains incompletely understood (174). The increased abundance of autophagosomes and increased expression and activation of LC3B and increased expression of PINK1 were observed in human lung tissues from patients with COPD (17, 18, 110).

Genetic deletion of LC3B (*Map1lc3b*$^{-/-}$) protected against airspace enlargement induced by chronic CS exposure (18). *Becn1*$^{+/-}$or *Map1lc3b*$^{-/-}$ mice also resisted adverse changes in airway cilia length and function in response to CS (78). Genetic interference of autophagy proteins, BECN1 or LC3B, protected against activation of extrinsic apoptosis in cultured epithelial cells exposed to CS (17). CS exposure induced mitophagy *in vitro* through mitochondrial depolarization and stabilization of PINK1 in pulmonary epithelial cells (110). *PINK1*-deficient mice were protected against mitochondrial dysfunction, airspace enlargement, and airways

dysfunction during CS exposure. The Mdivi-1 protected against CS-induced mitochondrial dysfunction and necroptotic cell death (110). These results suggested that CS-induced autophagy, or selective autophagy such as mitophagy, is deleterious in CS-induced emphysema in mice.

Recent studies indicate that CS exposure induces epithelial cell senescence attributed to impaired autophagy (38). Furthermore, CS exposure caused accumulation of ubiquitinated protein substrates and increased formation of perinuclear aggresomes in epithelial cells, associated with alveolar cell senescence (167, 175). These effects were attributed to a defect in autophagy, resulting in impaired aggresome clearance (167). Furthermore, increased p62 accumulation was observed in the lungs of advanced COPD patients (167). Impaired autophagy was also observed in the alveolar macrophages of smokers and in CS-exposed macrophages (112), which may render smokers susceptible to infections.

These studies highlight the complexity of the role of autophagy in CS-induced lung injury models that is dependent on cell type, kinetics in the mouse model, and severity of disease in COPD lung tissues. Further investigation will be required to define the complex roles of autophagy in COPD.

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease that originates from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF is characterized by mucus obstruction of the airways that facilitates secondary infections. Human airway epithelial cells or nasal biopsies derived from CF patients displayed dysfunctional aggrephagy, evidenced by impaired clearance of aggregated protein with accumulation of polyubiquitinated proteins and decreased clearance of aggresomes, leading to accumulation of mutant CFTR (95). These events were also associated with enhanced ROS production and accumulation of tissue transglutaminase-2, which promoted crosslinking of BECN1 and its sequestration in aggresomes, leading to impaired PI3KC3-dependent signaling, and p62 accumulation (95).

Dysfunctional autophagy also contributes to heightened inflammatory responses in CF cells, which was ameliorated by an AMPK activating anti-inflammatory peptide (105). The autophagy-dependent clearance of bacteria by xenophagy may be important in defense against the secondary infections associated with CF. Pharmacological enhancement of autophagy with rapamycin reduced inflammation and promoted bacterial clearance in the lungs of CF mice (66). Recent studies indicate that a cluster of microRNAs (Mirc1/Mir17–92) expressed by CF macrophages downregulates the autophagy response in CF (165). Therefore, autophagy and its selective programs, including aggrephagy, xenophagy, and mitophagy, may be compromised in CF and contribute to the pathogenesis of this disease. Therapeutics designed to reverse impaired autophagy represent an attractive target in the treatment of CF.

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a lethal disease characterized by aberrant proliferation of fibroblasts and excessive deposition of extracellular matrix (ECM) protein, leading to loss of lung function. Insufficient autophagy in fibroblasts has been implicated in the pathogenesis of IPF (124). Lung tissues from IPF patients and human lung fibroblasts treated with TGF-β1 displayed increased cellular senescence and decreased autophagic activity as characterized by decreased LC3B expression, and evidence of mitochondrial dysfuncion (4, 124, 125). Treatment with TGF-β1, a major profibrotic regulator, inhibited autophagy in human lung fibroblasts. Genetic deletion of the autophagy proteins, LC3 or BECN1, potentiated the TGF-β1-induced expression of fibronectin and the myofibroblast marker α-smooth muscle actin in fibroblasts (124). Treatment of mice with the mTOR inhibitor rapamycin protected against lung fibrosis (125). Mice deficient in the mitophagy regulator PINK1 were susceptible to bleomycin-induced pulmonary fibrosis (125). Loss of autophagy in patients with IPF may potentiate the effects of TGF-β1 with respect to ECM production and transformation to a myofibroblast phenotype. Further research will determine the relationships between autophagy and the molecular mechanisms of lung fibrosis.

Acute lung injury and sepsis

ALI and sepsis represent primary causes of morbidity and mortality in the management of critically ill patients. Recent studies have implicated autophagy in the pathogenesis of both ALI and sepsis (81, 161). Hyperoxia (elevated pO_2) causes oxidative stress through the increased production of ROS from cytoplasmic and mitochondrial sources. Hyperoxia exposure (>95% O_2) causes ALI in mice, associated with epithelial cell death. Prolonged hyperoxia exposure caused activation of morphological and biochemical markers of autophagy in the mouse lung (161).

In cultured pulmonary epithelial cells, hyperoxia induced autophagosome formation and increased the expression and activation (lipidation) of LC3B, the latter was inhibited by both cytoplasmic and mitochondria-targeting antioxidants (161). Genetic interference of LC3B promoted extrinsic apoptosis in epithelial cells subjected to hyperoxia. These experiments suggest that LC3B exerts a prosurvival role in oxidative stress, and that the mechanisms regulating autophagy and apoptosis may share common features during oxygen toxicity (161).

In mice subjected to CLP, a model of polymicrobial sepsis, elevated autophagy was observed in the lung tissue, including increased LC3-II expression and accumulation of autophagosomes (81). *Becn1*$^{+/-}$ mice were susceptible to the lethal effects of CLP, and displayed reduced bacterial clearance from the blood and vital organs after CLP (81). Thus, BECN1 may significantly contribute to sepsis survival by enhancing bacterial clearance.

Autophagy in Neurodegenerative Diseases

Autophagy can play crucial roles in neuronal homeostasis and neuroprotection by several mechanisms, including the preservation of mitochondrial homeostasis and the removal of aggregate-prone misfolded proteins (37, 40). Genetic deficiency in the autophagy proteins Atg5, Atg7, or FIP200 results in a neurodegenerative phenotype (47, 89). Highly upregulated autophagy can also contribute to neurodegeneration, suggesting that a balanced regulation of autophagy is required for optimal protection in neurodegenerative disorders (37). Autophagy has been widely studied in various

acute and chronic neurodegenerative diseases, including Alzheimer's disease (AD), PD, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) (37, 97, 102). The role of autophagy in other neurodegenerative diseases has been extensively reviewed (37, 109).

Alzheimer's disease

AD is characterized by accumulation of highly insoluble toxic β-amyloid (Aβ) peptide and hyperphosphorylated tau proteins (37). Decreased BECN1 expression was observed in the brains of AD patients (127). Mutation in the Presenilin-1 gene (encoding for γ-secretase) is associated with impaired lysosome acidification and function in a familial autosomal dominant form of AD (80). In this condition, malfunctioning lysosomes fail to fuse with autophagosomes, resulting in autophagy failure.

Accumulation of lipid-loaded autophagosomes and autolysosomes due to impaired autophagic turnover was observed in transgenic mice expressing amyloid precursor protein (APP), a mouse model of AD (190). Conditional neuron-specific *Atg7* deletion in APP expressing transgenic mice resulted in reduced cellular release of Aβ-peptide and reduced deposition of hyperphosphorylated tau protein (119). APP transgenic mice heterozygous for *BECN1* also displayed enhanced neurodegeneration, increased senile plaque accumulation, and malfunctioning lysosomes (127). These studies suggest that the accumulation of neurofibrillary tangles and plaques during early AD and subsequent neurodegeneration are due to impaired autophagy (37, 189).

Pharmacological application of rapamycin (an autophagy inducer) improved cognitive function in a mouse model of AD (11). Administration of Dimebon (an ATG7-dependent autophagy activator) reduced Aβ plaque formation (153). The AMPK activating compounds RSVA314 and RSVA405 also conferred neuroprotection against AD (176). These studies suggest that upregulation of autophagy may represent a therapeutic strategy in AD.

Parkinson's disease

Loss-of-function mutations in the mitochondrial autophagy (mitophagy) regulatory genes (*PINK1* and *PARK2*) have been associated with familial and sporadic PD (172). Genetic deficiency in *Atg5* results in PD-like features, including motor coordination deficits, neuronal aggregate accumulation, and tremors (47). PD is characterized by degeneration of dopaminergic neurons due to intracytoplasmic inclusions (Lewy bodies) of α-synuclein (SNCA) in the *substantia nigra*. Parkin overexpression in a rat model of PD promoted SNCA clearance (94). Increases in SNCA expression result in impaired autophagy due to mislocalization and diffusion of cytoplasmic Atg9 (183). Furthermore, mutation in the gene encoding sterol regulatory element-binding transcription factor-1 (SREBF1), which recruits Parkin during mitophagy (58), may act as risk factor for the development of PD (30).

Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene have been observed in hereditary as well as sporadic forms of PD (9). Genetic interference of the *LRRK2* gene increased autophagic flux in cultured human embryonic kidney cells, suggesting that LRRK2 acts as an autophagy supressor (2). Mutation in *PARK9* has been reported in autosomal recessive PD. PARK9 regulates lysosomal acidification and facilitates fusion of functional lysosomes to autophagosomes (130). Lentiviral gene transfer of *BECN1* reduced neuropathology and enhanced SNCA clearance in transgenic mice overexpressing SNCA (151). Overall, these studies suggest that impaired autophagy and mitophagy contributes to the pathogenesis of PD.

Huntington's disease

HD is characterized by expansion of the CAG trinucleotide repeats in the gene coding for huntingtin (HTT) protein, leading to pathological accumulations of mutant HTT (mHTT) protein (166). Autophagy provides a mechanism for the turnover of accumulated mHTT (133). The conformationally modified mHTT initiates autophagy activation by sequestering mTOR into aggregates (137). However, mHTT aggregrates can also sequester BECN1, leading to impaired BECN1 function (145). Despite accumulation of autophagosomes in this disease as a compensatory response to accumulation of aggregated mHTT, HD is characterized by defect in autophagy at the level of cargo recognition (103). Wild-type HTT interacts with p62 and promotes autophagy by facilitating p62 binding with LC3 (137), whereas the interaction of mHTT with p62 results in failure of cargo recognition and recruitment by the autophagosome (103).

Autophagy activation has been associated with improved cognitive behavior and overall pathology in transgenic mice expressing mHTT. Trehalose, an mTOR-independent autophagy inducer, ameliorated neuropathology in HD transgenic mice (162). Combined treatment with lithium and rapamycin, or trehalose and rapamycin, promoted HTT clearance in a *Drosophila* model of HD (139, 140). Administration of phenoxazine (an autophagy stimulator) inhibited mHTT aggregate formation in a primary neuron model of HD (170).

Wild-type HTT can influence the regulation of the autophagy program by acting as a scaffold for autophagosome transport and biogenesis (102). HTT shows structural resemblance to autophagy associated proteins (Atg11, Atg23, and Vac8) in yeast (120). The HTT-interacting proteins, Rab5 and Rhes, have been found to positively regulate autophagy (132). Phosphorylation of HTT by I-κB kinase (IKK) promotes its recognition by LAMP-2A and lysosomal clearance. Decline in this mechanism with age may contribute to enhanced accumulation of mHTT in HD patients (166). Thus, mutant protein aggregate accumulation with imbalanced neuronal homeostasis in HD is due to inefficient cargo recruitment, leading to the formation of vacant autophagosomes and impaired autophagy.

Amyotrophic lateral sclerosis

Dysfunctional autophagy and impaired lysosomal function have been implicated in the pathogenesis of ALS (14). Autophagy can provide a protective mechanism in ALS by facilitating the clearance of insoluble mutant superoxide dismutase 1 (SOD1) and TAR-DNA binding protein (TDP)-43 containing neuronal aggregates (21, 169). In an ALS mouse model, X-box binding protein-1 deficiency induced autophagy through activation of the transcription factor FOXO1 (neuronal autophagy regulator). The activation of autophagy in this model was correlated with a decrease in

mutant SOD1-induced toxicity (52). Furthermore, the turnover of TDP-43 may be facilitated to the activation of autophagy (7, 169).

Stimulation of autophagy with novel agonists (*e.g.*, methotrimeprazine) improved the viability of motor neurons overexpressing mutant TDP-43 and enhanced TDP-43 turnover (7). The mutation in sigma 1 receptor (SigmaR1) has been found in hereditary ALS (3). Knockdown of SigmaR1 results in suppression of autophagic flux, mitochondrial membrane depolarization, and apoptosis (178). Trehalose, by promoting autophagic flux, reduced accumulation of mutant SOD1 and p62, prevented apoptosis, and improved motor neurons survival in an SOD1G93A ALS mouse model (12, 197). These studies provide evidence for the neuroprotective roles of authophagy.

Interestingly, other studies show that autophagy could have deleterious effects. For instance, BECN1 heterozygous deletion induced protection against ALS in SOD1 transgenic mice (117). Rapamycin administration that is associated with enhanced survival in a lymphocyte-deficient ALS mouse model (152) has a damaging effect on motor neurons in ALS (198). Lithium, an autophagy activator used to treat neurodegenerative and bipolar disorders, was shown to be neuroprotective in the SOD1G93A ALS mouse model (36) but not in two different strains (C57BL/6J or 12S2/Sv) of SOD1 mutant mice (128). Thus, although studies on the role of autophagy suggest neuroprotective functions, additional studies are warranted to elucidate how autophagy may be deleterious and define the complex roles of autophagy in various neurodegenerative diseases.

Conclusions and Therapeutic Considerations of Autophagy in Disease

Autophagy is a cellular homeostatic program that can be induced by various forms of cellular stress, including those associated with pro-oxidant states or heightened inflammation. In addition, this process has now been recognized to exert key functions in the pathogenesis of various human diseases.

The multiple cellular functions impacted by autophagy and its selective programs suggest that this process provides a protective or adaptive function during the pathogenesis of diseases that involve components of metabolic or mitochondrial dysfunction, protein aggregation, oxidative stress, inflammation, and/or infection. The selective processing of mitochondria, proteins, lipids, and pathogens by autophagy and its potential roles in the regulation of inflammation and immune system functions have been cited as potentially modulating the pathogenesis of many diseases, although the relative importance of each selective program may vary depending on the mechanism of disease. Progressive deficiency of autophagy may contribute to disease pathogenesis through loss of cytoprotection.

In addition to protective roles, autophagy may have possible propathogenic roles due to cross talk to cellular death programs. Furthermore, autophagy may accelerate infectious disease in response to pathogens that selectively exploit this pathway for replication.

Intervention strategies to induce autophagy include the use of mTORC1 inhibitors such as rapamycin and its analogues (rapalogs) for diseases involving autophagy deficiency. Chloroquine or hydroxychloroquine (inhibitors of autophagy) has been explored for use as cancer treatments. Additional small molecules that modulate autophagy for potential therapeutic application include targeting peptides (147), trehalose (139), histone deacetylase inhibitors, and AMPK activators (*e.g.*, metformin and vitamin D analogues) (136). An increased understanding of the complex role of autophagy in the pathogenesis of disease will facilitate targeting this pathway for therapeutic gain in specific diseases.

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References

1. Alavian SM, Ande SR, Coombs KM, Yeganeh B, Davoodpour P, Hashemi M, Los M, and Ghavami S. Virus-triggered autophagy in viral hepatitis—possible novel strategies for drug development. *J Viral Hepat* 18: 821–830, 2011.
2. Alegre-Abarrategui J, Christian H, Lufino MM, Mutihac R, Venda LL, Ansorge O, and Wade-Martins R. LRRK2 regulates autophagic activity and localizes to specific membrane microdomains in a novel human genomic reporter cellular model. *Hum Mol Genet* 18: 4022–4034, 2009.
3. Al-Saif A, Al-Mohanna F, and Bohlega S. A mutation in sigma-1 receptor causes juvenile amyotrophic lateral sclerosis. *Ann Neurol* 70: 913–919, 2011.
4. Araya J, Kojima J, Takasaka N, Ito S, Fujii S, Hara H, Yanagisawa H, Kobayashi K, Tsurushige C, Kawaishi M, Kamiya N, Hirano J, Odaka M, Morikawa T, Nishimura SL, Kawabata Y, Hano H, Nakayama K, and Kuwano K. Insufficient autophagy in idiopathic pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 304: L56–L69, 2013.
5. Azad MB, Chen Y, and Gibson SB. Regulation of autophagy by reactive oxygen species (ROS): implications for cancer progression and treatment. *Antioxid Redox Signal* 11: 777–790, 2009.
6. Bachar-Wikstrom E, Wikstrom JD, Ariav Y, Tirosh B, Kaiser N, Cerasi E, and Leibowitz G. Stimulation of autophagy improves endoplasmic reticulum stress-induced diabetes. *Diabetes* 62: 1227–1237, 2013.
7. Barmada SJ, Serio A, Arjun A, Bilican B, Daub A, Ando DM, Tsvetkov A, Pleiss M, Li X, Peisach D, Shaw C, Chandran S, and Finkbeiner S. Autophagy induction enhances TDP43 turnover and survival in neuronal ALS models. *Nat Chem Biol* 10: 677–685, 2014.
8. Bellot G, Garcia-Medina R, Gounon P, Chiche J, Roux D, Pouysségur J, and Mazure NM. Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains. *Mol Cell Biol* 29: 2570–2581, 2009.
9. Bonifati V. Parkinson's disease: the LRRK2-G2019S mutation: opening a novel era in Parkinson's disease genetics. *Eur J Hum Genet* 14: 1061–1062, 2006.
10. Brereton MF, Rohm M, Shimomura K, Holland C, Tornovsky-Babeay S, Dadon D, Iberl M, Chibalina MV, Lee S, Glaser B, Dor Y, Rorsman P, Clark A, and Ashcroft FM. Hyperglycaemia induces metabolic dysfunction

and glycogen accumulation in pancreatic β-cells. *Nat Commun* 7: 13496, 2016.
11. Caccamo A, Majumder S, Richardson A, Strong R, and Oddo S. Molecular interplay between mammalian target of rapamycin (mTOR), amyloid-β, and Tau: effects on cognitive impairments. *J Biol Chem* 285: 13107–13120, 2010.
12. Castillo K, Nassif M, Valenzuela V, Rojas F, Matus S, Mercado G, Court FA, Zundert BV, and Hetz C. Trehalose delays the progression of amyotrophic lateral sclerosis by enhancing autophagy in motoneurons. *Autophagy* 9: 1308–1320, 2013.
13. Chen R, Wang Q, Song S, Liu F, He B, and Gao X. Protective role of autophagy in methionine-choline deficient diet-induced advanced nonalcoholic steatohepatitis in mice. *Eur J Pharmacol* 770: 126–133, 2016.
14. Chen S, Zhang X, Song L, and Le W. Autophagy dysregulation in amyotrophic lateral sclerosis. *Brain Pathol* 22: 110–116, 2012.
15. Chen Y, McMillan-Ward E, Kong J, Israels SJ, and Gibson SB. Mitochondrial electron-transport-chain inhibitors of complexes I and II induce autophagic cell death mediated by reactive oxygen species. *J Cell Sci* 120: 4155–4166, 2007.
16. Chen Y, McMillan-Ward E, Kong J, Israels SJ, and Gibson SB. Oxidative stress induces autophagic cell death independent of apoptosis in transformed and cancer cells. *Cell Death Differ* 15: 171–182, 2008.
17. Chen ZH, Kim HP, Sciurba FC, Lee SJ, Feghali-Bostwick C, Stolz DB, Dhir R, Landreneau RJ, Schuchert MJ, Yousem SA, Nakahira K, Pilewski JM, Lee JS, Zhang Y, Ryter SW, and Choi AM. Egr-1 regulates autophagy in cigarette smoke-induced chronic obstructive pulmonary disease. *PLoS One* 3: e3316, 2008.
18. Chen ZH, Lam HC, Jin Y, Kim HP, Cao J, Lee SJ, Ifedigbo E, Parameswaran H, Ryter SW, and Choi AM. Autophagy protein microtubule-associated protein 1 light chain-3B (LC3B) activates extrinsic apoptosis during cigarette smoke-induced emphysema. *Proc Natl Acad Sci U S A* 107: 18880–18885, 2010.
19. Chien CT, Shyue SK, and Lai MK. Bcl-xL augmentation potentially reduces ischemia/reperfusion induced proximal and distal tubular apoptosis and autophagy. *Transplantation* 84: 1183–1190, 2007.
20. Clausen TH, Lamark T, Isakson P, Finley K, Larsen KB, Brech A, Øvervatn A, Stenmark H, Bjørkøy G, Simonsen A, and Johansen T. p62/SQSTM1 and ALFY interact to facilitate the formation of p62 bodies/ALIS and their degradation by autophagy. *Autophagy* 6: 330–344, 2010.
21. Crippa V, Sau D, Rusmini P, Boncoraglio A, Onesto E, Bolzoni E, Galbiati M Fontana E, Marino M, Carra S, Bendotti C, De Biasi S, and Poletti A. The small heat shock protein B8 (HspB8) promotes autophagic removal of misfolded proteins involved in amyotrophic lateral sclerosis (ALS). *Hum Mol Genet* 19: 3440–3456, 2010.
22. Cuervo AM and Wong E. Chaperone-mediated autophagy: roles in disease and aging. *Cell Res* 24: 92–104, 2014.
23. Czaja MJ. Function of autophagy in nonalcoholic fatty liver disease. *Dig Dis Sci* 61: 1304–1313, 2016.
24. Dagda RK, Cherra SJ, Kulich SM, Tandon A, Park D and Chu CT. Loss of PINK1 function promotes mitophagy through effects on oxidative stress and mitochondrial fission. *J Biol Chem* 284: 13843–13855, 2009.
25. De Meyer GR, Grootaert MO, Michiels CF, Kurdi A, Schrijvers DM, and Martinet W. Autophagy in vascular disease. *Circ Res* 116: 468–479, 2015.
26. Diao J, Liu R, Rong Y, Zhao M, Zhang J, Lai Y, Zhou Q, Wilz LM, Li J, Vivona S, Pfuetzner RA, Brunger AT, and Zhong Q. ATG14 promotes membrane tethering and fusion of autophagosomes to endolysosomes. *Nature* 520: 563–566, 2015.
27. Ding WX, Ni HM, Li M, Liao Y, Chen X, Stolz DB, Dorn GW, and Yin XM. Nix is critical to two distinct phases of mitophagy, reactive oxygen species-mediated autophagy induction and Parkin-ubiquitin-p62-mediated mitochondrial priming. *J Biol Chem* 285: 27879–27890, 2010.
28. Ding Y and Choi ME. Autophagy in diabetic nephropathy. *J Endocrinol* 224: R15–R30, 2015.
29. Ding Y, Kim SL, Lee SY, Koo JK, Wang Z, and Choi ME. Autophagy regulates TGF-beta expression and suppresses kidney fibrosis induced by unilateral ureteral obstruction. *J Am Soc Nephrol* 25: 2835–2846, 2014.
30. Do CB, Tung JY, Dorfman E, Kiefer AK, Drabant EM, Francke U, Mountain JL, Goldman SM, Tanner CM, Langston JW, Wojcicki A, and Eriksson N. Web-based genome-wide association study identifies two novel loci and a substantial genetic component for Parkinson's disease. *PLoS Genet* 7: e1002141, 2011.
31. Dooley HC, Razi M, Polson HE, Girardin SE, Wilson MI, and Tooze SA. WIPI2 links LC3 conjugation with PI3P, autophagosome formation, and pathogen clearance by recruiting Atg12-5-16L1. *Mol Cell* 55: 238–252, 2014.
32. Dröge W. Free radicals in the physiological control of cell function. *Physiol Rev* 82: 47–95, 2002.
33. Evans TD, Sergin I, Zhang X, and Razani B. Target acquired: selective autophagy in cardiometabolic disease. *Sci Signal* 10: pii: eaag2298, 2017.
34. Fang L, Zhou Y, Cao H, Wen P, Jiang L, He W, Dai C, and Yang J. Autophagy attenuates diabetic glomerular damage through protection of hyperglycemia-induced podocyte injury. *PLoS One* 8: e60546, 2013.
35. Feng Y, He D, Yao Z, and Klionsky DJ. The machinery of macroautophagy. *Cell Res* 24: 24–41, 2014.
36. Fornai F, Cafaro L, Kastsiuchenka O, Ferrucci M, Manca ML, Lazzeri G, Spalloni A, Bellio N, Lenzi P, Modugno N, Siiciliano G, Isidoro C, Murri L, Ruggieri S, and Paparelli A. Lithium delays progression of amyotrophic lateral sclerosis Francesco. *Proc Natl Acad Sci U S A* 105: 16404–16407, 2008.
37. Frake RA, Ricketts T, Menzies FM, and Rubinsztein DC. Autophagy and neurodegeneration. *J Clin Invest* 125: 65–74, 2015.
38. Fujii S, Hara H, Araya J, Takasaka N, Kojima J, Ito S, Minagawa S, Yumino Y, Ishikawa T, Numata T, Kawaishi M, Hirano J, Odaka M, Morikawa T, Nishimura S, Nakayama K, and Kuwano K. Insufficient autophagy promotes bronchial epithelial cell senescence in chronic obstructive pulmonary disease. *Oncoimmunology* 1: 630–641, 2012.
39. Gegg ME, Cooper JM, Chau KY, Rojo M, Schapira AH, and Taanman JW. Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. *Hum Mol Genet* 19: 4861–4870, 2010.
40. Giordano S, Darley-Usmar V, and Zhang J. Autophagy as an essential cellular antioxidant pathway in neurodegenerative disease. *Redox Biol* 2: 82–90, 2013.

41. Givvimani S, Munjal C, Tyagi N, Sen U, Metreveli N, and Tyagi SC. Mitochondrial division/mitophagy inhibitor (Mdivi) ameliorates pressure overload induced heart failure. *PLoS One* 7: e32388, 2012.
42. Godel M, Hartleben B, Herbach N, Shuya L, Zschiedrich S, Lu S, Debreczeni-Mór A, Lindenmeyer MT, Rastaldi MP, Hartleben G, Wiech T, Fornoni A, Nelson RG, Kretzler M, Wanke R, Pavenstädt H, Kerjaschki D, Cohen CD, Hall MN, Rüegg MA, Inoki K, Walz G, and Huber TB. Role of mTOR in podocyte function and diabetic nephropathy in humans and mice. *J Clin Invest* 121: 2197–2209, 2011.
43. Gomes LC and Dikic I. Autophagy in antimicrobial immunity. *Mol Cell* 54: 224–233, 2014.
44. González-Rodríguez A, Mayoral R, Agra N, Valdecantos MP, Pardo V, Miquilena-Colina ME, Vargas-Castrillón J, Lo Iacono O, Corazzari M, Fimia GM, Piacentini M, Muntané J, Boscá L, García-Monzón C, Martín-Sanz P, and Valverde ÁM. Impaired autophagic flux is associated with increased endoplasmic reticulum stress during the development of NAFLD. *Cell Death Dis* 5: e1179, 2014.
45. Green DR and Llambi F. Cell death signaling. *Cold Spring Harb Perspect Biol* 7: pii: a006080, 2015.
46. Gu J, Hu W, Song ZP, Chen YG, Zhang DD, and Wang CQ. Rapamycin inhibits cardiac hypertrophy by promoting autophagy via the MEK/ERK/Beclin-1 pathway. *Front Physiol* 7: 104, 2016.
47. Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H, and Mizushima N. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. *Nature* 441: 885–889, 2006.
48. Hartleben B, Godel M, Meyer-Schwesinger C, Liu S, Ulrich T, Köbler S, Wiech T, Grahammer F, Arnold SJ, Lindenmeyer MT, Cohen CD, Pavenstädt H, Kerjaschki D, Mizushima N, Shaw AS, Walz G, and Huber TB. Autophagy influences glomerular disease susceptibility and maintains podocyte homeostasis in aging mice. *J Clin Invest* 120: 1084–1096, 2010.
49. He C and Levine B. The Beclin 1 interactome. *Curr Opin Cell Biol* 22: 140–149, 2010.
50. He C, Zhu H, Li H, Zou MH, and Xie Z. Dissociation of Bcl-2-Beclin1 complex by activated AMPK enhances cardiac autophagy and protects against cardiomyocyte apoptosis in diabetes. *Diabetes* 62: 1270–1281, 2013.
51. He L, Livingston MJ, and Dong Z. Autophagy in acute kidney injury and repair. *Nephron Clin Pract* 127: 56–60, 2014.
52. Hetz C, Thielen P, Matus S, Nassif M, Court F, Kiffin R, Martinez G, Cuervo AM, Brown RH, and Glimcher LH. XBP-1 deficiency in the nervous system protects against amyotrophic lateral sclerosis by increasing autophagy. *Genes Dev* 23: 2294–2306, 2009.
53. Holmes D. NAFLD: vitamin D-induced autophagy prevents steatosis. *Nat Rev Endocrinol* 13: 190, 2017.
54. Hsiao HW, Tsai KL, Wang LF, Chen YH, Chiang PC, Chuang SM, and Hsu C. The decline of autophagy contributes to proximal tubular dysfunction during sepsis. *Shock* 37: 289–296, 2012.
55. Inoki K, Mori H, Wang J, Tsukasa S, Hong SK, Yoshida S, Blattner SM, Ikenoue T, Rüegg MA, Hall MN, Kwiatkowski DJ, Rastaldi MP, Huber TB, Kretzler M, Holzman LB, Wiggins RC, and Guan KL. mTORC1 activation in podocytes is a critical step in the development of diabetic nephropathy in mice. *J Clin Invest* 121: 2181–2196, 2011.
56. Inoue K, Kuwana H, Shimamura Y, Ogata K, Taniguchi Y, Kagawa T, Horino T, Takao T, Morita T, Sasaki S, Mizushima N, and Terada Y. Cisplatin-induced macroautophagy occurs prior to apoptosis in proximal tubules in vivo. *Clin Exp Nephrol* 14: 112–122, 2010.
57. Itakura E, Kishi-Itakura C, and Mizushima N. The hairpin-type tail-anchored SNARE syntaxin 17 targets to autophagosomes for fusion with endosomes/lysosomes. *Cell* 151: 1256–1269, 2012.
58. Ivatt RM, Martinez AS, Godena VK, Brown S, Ziviani E, and Whitworth AJ. Genome-wide RNAi screen identifies the Parkinson disease GWAS risk locus SREBF1 as a regulator of mitophagy. *Proc Natl Acad Sci U S A* 111: 8494–8499, 2014.
59. Jaber N, Dou Z, Chen JS, Catanzaro J, Jiang YP, Ballou LM, Selinger E, Ouyang X, Lin RZ, Zhang J, and Zong WX. Class III PI3K Vps34 plays an essential role in autophagy and in heart and liver function. *Proc Natl Acad Sci U S A* 109: 2003–2008, 2012.
60. Jain A, Lamark T, Sjøttem E, Larsen KB, Awuh JA, Øvervatn A, McMahon M, Hayes JD, and Johansen T. p62/SQSTM1 is a target gene for transcription factor NRF2 and creates a positive feedback loop by inducing antioxidant response element-driven gene transcription. *J Biol Chem* 285: 22576–22591, 2010.
61. Jiang M, Liu K, Luo J, and Dong Z. Autophagy is a renoprotective mechanism during in vitro hypoxia and in vivo ischemia-reperfusion injury. *Am J Pathol* 176: 1181–1192, 2010.
62. Jiang M, Wei Q, Dong G, Komatsu M, Su Y, and Dong Z. Autophagy in proximal tubules protects against acute kidney injury. *Kidney Int* 82: 1271–1283, 2012.
63. Jiang P, Nishimura T, Sakamaki Y, Itakura E, Hatta T, Natsume T, and Mizushima N. The HOPS complex mediates autophagosome-lysosome fusion through interaction with syntaxin 17. *Mol Biol Cell* 25: 1327–1337, 2014.
64. Jung CH, Ro SH, Cao J, Otto NM, and Kim DH. mTOR regulation of autophagy. *FEBS Lett* 584: 1287–1295, 2010.
65. Jung HS, Chung KW, Won Kim J, Kim J, Komatsu M, Tanaka K, Nguyen YH, Kang TM, Yoon KH, Kim JW, Jeong YT, Han MS, Lee MK, Kim KW, Shin J, and Lee MS. Loss of autophagy diminishes pancreatic beta cell mass and function with resultant hyperglycemia. *Cell Metab* 8: 318–324, 2008.
66. Junkins RD, Shen A, Rosen K, McCormick C, and Lin TJ. Autophagy enhances bacterial clearance during P. aeruginosa lung infection. *PLoS One* 8: e72263, 2013.
67. Kaushal GP and Shah SV. Autophagy in acute kidney injury. *Kidney Int* 89: 779–791, 2016.
68. Kaushik S and Cuervo AM. Degradation of lipid droplet-associated proteins by chaperone-mediated autophagy facilitates lipolysis. *Nat Cell Biol* 17: 759–770, 2015.
69. Kawaguchi Y, Kovacs JJ, McLaurin A, Vance JM, Ito A, and Yao TP. The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. *Cell* 115: 727–738, 2003.
70. Kawakami T, Gomez IG, Ren S, Hudkins K, Roach A, Alpers CE, Shankland SJ, D'Agati VD, and Duffield JS. Deficient autophagy results in mitochondrial dysfunction and FSGS. *J Am Soc Nephrol* 26: 1040–1052, 2015.

71. Kim J, Kundu M, Viollet B, and Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol* 13: 132–141, 2011.
72. Kim SI, Na HJ, Ding Y, Wang Z, Lee SJ, and Choi ME. Autophagy promotes intracellular degradation of type I collagen induced by transforming growth factor (TGF)-β1. *J Biol Chem* 287: 11677–11688, 2012.
73. Kim WY, Nam SA, Song HC, Ko JS, Park SH, Kim HL, Choi EJ, Kim YS, Kim J, and Kim YK. The role of autophagy in unilateral ureteral obstruction rat model. *Nephrology (Carlton)* 17: 148–159, 2012.
74. Kim YM, Jung CH, Seo M, Kim EK, Park JM, Bae SS, and Kim DH. mTORC1 phosphorylates UVRAG to negatively regulate autophagosome and endosome maturation. *Mol Cell* 57: 207–218, 2015.
75. Komatsu M, Kurokawa H, Waguri S, Taguchi K, Kobayashi A, Ichimura Y, Sou YS, Ueno I, Sakamoto A, Tong KI, Kim M, Nishito Y, Iemura S, Natsume T, Ueno T, Kominami E, Motohashi H, Tanaka K, and Yamamoto M. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. *Nat Cell Biol* 12: 213–223, 2010.
76. Koyano F, Okatsu K, Kosako H, Tamura Y, Go E, Kimura M, Kimura Y, Tsuchiya H, Yoshihara H, Hirokawa T, Endo T, Fon EA, Trempe JF, Saeki Y, Tanaka K, and Matsuda N. Ubiquitin is phosphorylated by PINK1 to activate parkin. *Nature* 510: 162–166, 2014.
77. Kumar RR, Narasimhan M, Shanmugam G, Hong J, Devarajan A, Palaniappan S, Zhang J, Halade GV, Darley-Usmar VM, Hoidal JR, and Rajasekaran NS. Abrogation of Nrf2 impairs antioxidant signaling and promotes atrial hypertrophy in response to high-intensity exercise stress. *J Transl Med* 14: 86, 2016.
78. Lam HC, Cloonan SM, Bhashyam AR, Haspel JA, Singh A, Sathirapongsasuti JF, Cervo M, Yao H, Chung AL, Mizumura K, An CH, Shan B, Franks JM, Haley KJ, Owen CA, Tesfaigzi Y, Washko GR, Quackenbush J, Silverman EK, Rahman I, Kim HP, Mahmood A, Biswal SS, Ryter SW, and Choi AM. Histone deacetylase 6-mediated selective autophagy regulates COPD-associated cilia dysfunction. *J Clin Invest* 123: 5212–5230, 2013.
79. Lee IH, Cao L, Mostoslavsky R, Lombard DB, Liu J, Bruns NE, Tsokos M, Alt FW, and Finkel T. A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. *Proc Natl Acad Sci U S A* 105: 3374–3379, 2008.
80. Lee JH, Yu WH, Kumar A, Lee S, Mohan PS, Peterhoff CM, Wolfe DM, Martinez-Vicente M, Massey AC, Sovak G, Uchiyama Y, Westaway D, Cuervo AM, and Nixon RA. Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. *Cell* 141: 1146–1158, 2010.
81. Lee S, Lee SJ, Coronata AA, Fredenburgh LE, Chung SW, Perrella MA, Nakahira K, Ryter SW, and Choi AM. Carbon monoxide confers protection in sepsis by enhancing Beclin 1-dependent autophagy and phagocytosis. *Antioxid Redox Signal* 20: 432–442, 2014.
82. Lee SJ, Kim HP, Jin Y, Choi AM, and Ryter SW. Beclin 1 deficiency is associated with increased hypoxia-induced angiogenesis. *Autophagy* 7:829–839, 2011.
83. Lee SJ, Smith A, Guo L, Alastalo TP, Li M, Sawada H, Liu X, Chen ZH, Ifedigbo E, Jin Y, Feghali-Bostwick C, Ryter SW, Kim HP, Rabinovitch M, and Choi AM. Autophagic protein LC3B confers resistance against hypoxia-induced pulmonary hypertension. *Am J Respir Crit Care Med* 183: 649–658, 2011.
84. Lee SY, Kim SI, and Choi ME. Therapeutic targets for treating fibrotic kidney diseases. *Transl Re*s 165: 512–530, 2015.
85. Lenoir O, Jasiek M, Henique C, Guyonnet L, Hartleben B, Bork T, Chipont A, Flosseau K, Bensaada I, Schmitt A, Massé JM, Souyri M, Huber TB, and Tharaux PL. Endothelial cell and podocyte autophagy synergistically protect from diabetes-induced glomerulosclerosis. *Autophagy* 11: 1130–1145, 2015.
86. Levine B, Mizushima N, and Virgin HW. Autophagy in immunity and inflammation. *Nature* 469: 323–335, 2011.
87. Li WW, Li J, and Bao JK. Microautophagy: lesser-known self-eating. *Cell Mol Life Sci* 69: 1125–1136, 2012.
88. Li X, Li C, and Sun G. Histone acetylation and its modifiers in the pathogenesis of diabetic nephropathy. *J Diabetes Res* 2016: 4065382, 2016.
89. Liang CC, Wang C, Peng X, Gan B, and Guan JL. Neural-specific deletion of FIP200 leads to cerebellar degeneration caused by increased neuronal death and axon degeneration. *J Biol Chem* 285: 3499–3509, 2010.
90. Liang XH, Kleeman LK, Jiang HH, Gordon G, Goldman JE, Berry G, Herman B, and Levine B. Protection against fatal Sindbis virus encephalitis by beclin, a novel Bcl-2-interacting protein. *J Virol* 72: 8586–8596, 1998.
91. Liu N, Shi Y, and Zhuang S. Autophagy in chronic kidney diseases. *Kidney Dis (Basel)* 2: 37–45, 2016.
92. Liu S, Hartleben B, Kretz O, Wiech T, Igarashi P, Mizushima N, Walz G, and Huber TB. Autophagy plays a critical role in kidney tubule maintenance, aging and ischemia-reperfusion injury. *Autophagy* 8: 826–837, 2012.
93. Liu X, Tang Y, Cui Y, Zhang H, and Zhang D. Autophagy is associated with cell fate in the process of macrophage-derived foam cells formation and progress. *J Biomed Sci* 23: 57, 2016.
94. Lonskaya I, Hebron ML, Algarzae NK, Desforges N, and Moussa CE. Decreased parkin solubility is associated with impairment of autophagy in the nigrostriatum of sporadic Parkinson's disease. *Neuroscience* 232: 90–105, 2012.
95. Luciani A, Villella VR, Esposito S, Brunetti-Pierri N, Medina D, Settembre C, Gavina M, Pulze L, Giardino I, Pettoello-Mantovani M, D'Apolito M, Guido S, Masliah E, Spencer B, Quaratino S, Raia V, Ballabio A, and Maiuri L. Defective CFTR induces aggresome formation and lung inflammation in cystic fibrosis through ROS-mediated autophagy inhibition. *Nat Cell Biol* 12: 863–875, 2010.
96. Luo Y, Lu S, Zhou P, Ai QD, Sun GB, and Sun XB. Autophagy: an exposing therapeutic target in atherosclerosis. *J Cardiovasc Pharmacol* 67: 266–274, 2016.
97. Lynch-Day MA, Mao K, Wang K, Zhao M, and Klionsky DJ. The role of autophagy in Parkinson's disease. *Cold Spring Harb Perspect Med* 2: a009357, 2012.
98. Ma T, Zhu J, Chen X, Zha D, Singhai PC, and Ding G. High glucose induces autophagy in podocytes. *Exp Cell Res* 319: 779–789, 2013.
99. Madrigal-Matute J and Cuervo AM. Regulation of liver metabolism by autophagy. *Gastroenterology* 150: 328–339, 2016.
100. Mancias JD, Wang X, Gygi SP, Harper JW, and Kimmelman AC. Quantitative proteomics identifies NCOA4

as the cargo receptor mediating ferritinophagy. *Nature* 509: 105–109, 2014.
101. Mao S and Zhang J. Role of autophagy in chronic kidney diseases. *Int J Clin Exp Med* 8: 22022–22029, 2015.
102. Martin DD, Ladha S, Ehrnhoefer DE, and Hayden MR. Autophagy in Huntington disease and huntingtin in autophagy. *Trends Neurosci* 38: 26–35, 2015.
103. Martinez-Vicente M, Talloczy Z, Wong E, Tang G, Koga H, Kaushik S, de Vries R, Arias E, Harris S, Sulzer D, and Cuervo AM. Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. *Nat Neurosci* 13: 567–576, 2010.
104. Matsuda N, Sato S, Shiba K, Okatsu K, Saisho K, Gautier CA, Sou YS, Saiki S, Kawajiri S, Sato F, Kimura M, Komatsu M, Hattori N, and Tanaka K. PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. *J Cell Biol* 189: 211–221, 2010.
105. Mayer ML, Blohmke CJ, Falsafi R, Fjell CD, Madera L, Turvey SE, and Hancock RE. Rescue of dysfunctional autophagy attenuates hyperinflammatory responses from cystic fibrosis cells. *J Immunol* 190: 1227–1238, 2013.
106. Mazza S and Maffucci T. Autophagy and pancreatic β-cells. *Vitam Horm* 95: 145–164, 2014.
107. Mei S, Livingston M, Hao J, li L, Mei C, and Dong Z. Autophagy is activated to protect against endotoxic acute kidney injury. *Sci Rep* 6: 22171, 2016.
108. Meng F, Yao D, Shi Y, Kabakoff J, Wu W, Reicher J, Ma Y, Moosmann B, Masliah E, Lipton SA, and Gu Z. Oxidation of the cysteine-rich regions of parkin perturbs its E3 ligase activity and contributes to protein aggregation. *Mol Neurodegener* 6: 34, 2011.
109. Menzies FM, Fleming A, and Rubinsztein DC. Compromised autophagy and neurodegenerative diseases. *Nat Rev Neurosci* 16: 345–357, 2015.
110. Mizumura K, Cloonan SM, Nakahira K, Bhashyam AR, Cervo M, Kitada T, Glass K, Owen CA, Mahmood A, Washko GR, Hashimoto S, Ryter SW, and Choi AM. Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD. *J Clin Invest* 124: 3987–4003, 2014.
111. Mizushima N and Komatsu M. Autophagy: renovation of cells and tissues. *Cell* 147: 728–741, 2011.
112. Monick MM, Powers LS, Walters K, Lovan N, Zhang M, Gerke A, Hansdottir S, and Hunninghake GW. Identification of an autophagy defect in smokers' alveolar macrophages. *J Immunol* 185: 5425–5435, 2010.
113. Moreau K, Ravikumar B, Renna M, Puri C, and Rubinsztein DC. Autophagosome precursor maturation requires homotypic fusion. *Cell* 146: 303–317, 2011.
114. Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, Englert JA, Rabinovitch M, Cernadas M, Kim HP, Fitzgerald KA, Ryter SW, and Choi AM. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nat Immunol* 12: 222–230, 2011.
115. Nakai A, Yamaguchi O, Takeda T, Higuchi Y, Hikoso S, Taniike M, Omiya S, Mizote I, Matsumura Y, Asahi M, Nishida K, Hori M, Mizushima N, and Otsu K. The role of autophagy in cardiomyocytes in the basal state and in response to hemodynamic stress. *Nat Med* 13: 619–624, 2007.
116. Narendra DP, Jin SM, Tanaka A, Suen DF, Gautier CA, Shen J, Cookson MR, and Youle RJ. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol* 8: e1000298, 2010.
117. Nassif M, Valenzuela V, Rojas-Rivera D, Vidal R, Matus S, Castillo K, Fuentealba Y, Kroemer G, Levine B, and Hetz C. Pathogenic role of BECN1/Beclin 1 in the development of amyotrophic lateral sclerosis. *Autophagy* 10: 1256–1271, 2014.
118. Nguyen TN, Padman BS, Usher J, Oorschot V, Ramm G, and Lazarou M. Atg8 familyLC3/GABARAP proteins are crucial for autophagosome-lysosome fusion but not autophagosome formation during PINK1/Parkin mitophagy and starvation. *J Cell Biol* 215: 857–874, 2016.
119. Nilsson P, Loganathan K, Sekiguchi M, Matsuba Y, Hui K, Tsubuki S, Tanaka M, Iwata N, Saito T, and Saido TC. Aβ secretion and plaque formation depend on autophagy. *Cell Rep* 5: 61–69, 2013.
120. Ochaba J, Lukacsovich T, Csikos G, Zheng S, Margulis J, Salazar L, Mao K, Lau AL, Yeung SY, Humbert S, Saudou F, Klionsky DJ, Finkbeiner S, Zeitlin SO, Marsh JL, Housman DE, Thompson LM, and Steffan JS. Potential function for the huntingtin protein as a scaffold for selective autophagy. *Proc Natl Acad Sci U S A* 111: 16889–16894, 2014.
121. Ouimet M, Franklin V, Mak E, Liao X, Tabas I, and Marcel YL. Autophagy regulates cholesterol efflux from macrophage foam cells via lysosomal acid lipase. *Cell Metab* 13: 655–667, 2011.
122. Ouyang C, You J, and Xie Z. The interplay between autophagy and apoptosis in the diabetic heart. *J Mol Cell Cardiol* 71: 71–80, 2014.
123. Park JM, Jung CH, Seo M, Otto NM, Grunwald D, Kim KH, Moriarity B, Kim YM, Starker C, Nho RS, Voytas D, and Kim DH. The ULK1 complex mediates MTORC1 signaling to the autophagy initiation machinery via binding and phosphorylating ATG14. *Autophagy* 12: 547–564, 2016.
124. Patel AS, Lin L, Geyer A, Haspel JA, An CH, Cao J, Rosas IO, and Morse D. Autophagy in idiopathic pulmonary fibrosis. *PLoS One* 7: e41394, 2012.
125. Patel AS, Song JW, Chu SG, Mizumura K, Osorio JC, Shi Y, El-Chemaly S, Lee CG, Rosas IO, Elias JA, Choi AM, and Morse D. Epithelial cell mitochondrial dysfunction and PINK1 are induced by transforming growth factor-beta1 in pulmonary fibrosis. *PLoS One* 10: e0121246, 2015.
126. Periyasamy-Thandavan S, Jiang M, Wei Q, Smith R, Yin XM, and Dong Z. Autophagy is cytoprotective during cisplatin injury of renal proximal tubular cells. *Kidney Int* 74: 631–640, 2008.
127. Pickford F, Masliah E, Britschgi M, Lucin K, Narasimhan R, Jaeger PA, Small S, Spencer B, Rockenstein E, Levine B, and Coray TW. The autophagy-related protein Beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid β accumulation in mice. *J Clin Invest* 118: 2190–2199, 2008.
128. Pizzasegola C, Caron I, Daleno C, Ronchi A, Minoia C, Carri MT, and Bendotti C. Treatment with lithium carbonate does not improve disease progression in two different strains of SOD1 mutant mice. *Amyotroph Lateral Scler* 10: 221–228, 2009.
129. Quan W, Lim YM, and Lee MS. Role of autophagy in diabetes and endoplasmic reticulum stress of pancreatic β-cells. *Exp Mol Med* 44: 81–88, 2012.
130. Ramirez A, Heimbach A, Gründemann J, Stiller B, Hampshire D, Cid LP, Goebel I, Mubaidin AF, Wriekat

AL, Roeper J, Al-Din A, Hillmer AM, Karsak M, Liss B, Woods CG, Behrens MI, and Kubisch C. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5P-type ATPase. *Nat Genet* 38: 1184–1191, 2006.
131. Rautou PE, Mansouri A, Lebrec D, Durand F, Valla D, and Moreau R. Autophagy in liver diseases. *J Hepatol* 53: 1123–1134, 2010.
132. Ravikumar B, Imarisio S, Sarkar S, O'Kane CJ, and Rubinsztein DC. Rab5 modulates aggregation and toxicity of mutant huntingtin through macroautophagy in cell and fly models of Huntington disease. *J Cell Sci* 121: 1649–1660, 2008.
133. Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O'Kane CJ, and Rubinsztein DC. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat Genet* 36: 585–595, 2004.
134. Redmann M, Benavides GA, Berryhill TF, Wani WY, Ouyang X, Johnson MS, Ravi S, Barnes S, Darley-Usmar VM, and Zhang J. Inhibition of autophagy with bafilomycin and chloroquine decreases mitochondrial quality and bioenergetic function in primary neurons. *Redox Biol* 11: 73–81, 2017.
135. Reichelt ME, Mellor KM, Curl CL, Stapleton D, and Delbridge LM. Myocardial glycophagy—a specific glycogen handling response to metabolic stress is accentuated in the female heart. *J Mol Cell Cardiol* 65: 67–75, 2013.
136. Rubinsztein DC, Codogno P, and Levine B. Autophagy modulation as a potential therapeutic target for diverse diseases. *Nat Rev Drug Discov* 11: 709–730, 2012.
137. Rui YN, Xu Z, Patel B, Chen Z, Chen D, Tito A, David G, Sun Y, Stimming EF, Bellen HJ, Cuervo AM, and Zhang S. Huntingtin functions as a scaffold for selective macroautophagy. *Nat Cell Biol* 17: 262–275, 2015.
138. Russell RC, Tian Y, Yuan H, Park HW, Chang YY, Kim J, Kim H, Neufeld TP, Dillin A, and Guan KL. ULK1 induces autophagy by phosphorylating Beclin-1 and activating VPS34 lipid kinase. *Nat Cell Biol* 15: 741–750, 2013.
139. Sarkar S, Davies J, Huang Z, Tunnacliffe A, and Rubinsztein D. Trehalose, a novel mTOR-independent autophagy enhancer, accelerates the clearance of mutant huntingtin and α-synuclein. *J Biol Chem* 282: 5641–5652, 2007.
140. Sarkar S, Krishna G, Imarisio S, Saiki S, O'Kane CJ, and Rubinsztein DC. A rational mechanism for combination treatment of Huntington's disease using lithium and rapamycin. *Hum Mol Genet* 17: 170–178, 2008.
141. Scherz-Shouval R, Shvets E, Fass E, Shorer H, Gil L, and Elazar Z. Reactive oxygen species are essential for autophagy and specifically regulate the activity of Atg4. *EMBO J* 26: 1749–1760, 2007.
142. Schnaith A, Kashkar H, Leggio SA, Addicks K, Kronke M, and Krut O. *Staphylococcus aureus* subvert autophagy for induction of caspase-independent host cell death. *J Biol Chem* 282: 2695–2706, 2007.
143. Seillier M, Pouyet L, N'Guessan P, Nollet M, Capo F, Guillaumond F, Peyta L, Dumas JF, Varrault A, Bertrand G, Bonnafous S, Tran A, Meur G, Marchetti P, Ravier MA, Dalle S, Gual P, Muller D, Rutter GA, Servais S, Iovanna JL, and Carrier A. Defects in mitophagy promote redox-driven metabolic syndrome in the absence of TP53INP1. *EMBO Mol Med* 7: 802–818, 2015.
144. Shen HM and Codogno P. Autophagic cell death: loch Ness monster or endangered species? *Autophagy* 7: 457–465, 2011.
145. Shibata M, Lu T, Furuya T, Degterev A, Mizushima N, Yoshimori T, MacDonald M, Yankner B, and Yuan J. Regulation of intracellular accumulation of mutant huntingtin by Beclin 1. *J Biol Chem* 281: 14474–14485, 2006.
146. Shirakabe A, Zhai P, Ikeda Y, Saito T, Maejima Y, Hsu CP, Nomura M, Egashira K, Levine B, and Sadoshima J. Drp1-dependent mitochondrial autophagy plays a protective role against pressure overload-induced mitochondrial dysfunction and heart failure. *Circulation* 133: 1249–1263, 2016.
147. Shoji-Kawata S, Sumpter R, Leveno M, Campbell GR, Zou Z, Kinch L, Wilkins AD, Sun Q, Pallauf K, MacDuff D, Huerta C, Virgin HW, Helms JB, Eerland R, Tooze SA, Xavier R, Lenschow DJ, Yamamoto A, King D, Lichtarge O, Grishin NV, Spector SA, Kaloyanova DV, and Levine B. Identification of a candidate therapeutic autophagy-inducing peptide. *Nature* 494: 201–206, 2013.
148. Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM, and Czaja MJ. Autophagy regulates lipid metabolism. *Nature* 458: 1131–1135, 2009.
149. Song X, Narzt MS, Nagelreiter IM, Hohensinner P, Terlecki-Zaniewicz L, Tschachler E, Grillari J, and Gruber F. Autophagy deficient keratinocytes display increased DNA damage, senescence and aberrant lipid composition after oxidative stress in vitro and in vivo. *Redox Biol* 11: 219–230, 2017.
150. Sooparb S, Price SR, Shaoguang J, and Franch HA. Suppression of chaperone mediated autophagy in the renal cortex during acute diabetes mellitus. *Kidney Int* 65: 2135–2144, 2004.
151. Spencer B, Potkar R, Trejo M, Rockenstein E, Patrick C, Gindi R, Adame A, Wyss-Coray T, and Masliah E. 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, 2009.
152. Staats KA, Hernandez S, Schönefeldt S, Bento-Abreu A, Dooley J, Van Damme P, Liston A, Robberecht W, and Van Den Bosch L. Rapamycin increases survival in ALS mice lacking mature lymphocytes. *Mol Neurodegener* 8: 31–35, 2013.
153. Steele JW, Lachenmayer ML, Ju S, Stock A, Liken J, Kim SH, Delgado LM, Alfaro IE, Bernales S, Verdile G, Bharadwaj P, Gupta V, Barr R, Friss A, Dolios G, Wang R, Ringe D, Fraser P, Westaway D, St George-Hyslop PH, Szabo P, Relkin NR, Buxbaum JD, Glabe CG, Protter AA, Martins RN, Ehrlich ME, Petsko GA, Yue Z, and Gandy S. Latrepirdine improves cognition and arrests progression of neuropathology in an Alzheimer's mouse model. *Mol Psychiatry* 18: 889–897, 2013.
154. Stolz A, Ernst A, and Dikic I. Cargo recognition and trafficking in selective autophagy. *Nat Cell Biol* 16: 495–501, 2014.
155. Suzuki C, Isaka Y, Takabatake Y, Tanaka H, Koike M, Shibata M, Uchiyama Y, Takahara S, and Imai E. Participation of autophagy in renal ischemia/reperfusion injury. *Biochem Biophys Res Commun* 368: 100–106, 2008.
156. Swiader A, Nahapetyan H, Faccini J, D'Angelo R, Mucher E, Elbaz M, Boya P, and Vindis C. Mitophagy acts as

a safeguard mechanism against human vascular smooth muscle cell apoptosis induced by atherogenic lipids. *Oncotarget* 7: 28821–28835, 2016.
157. Tagawa A, Yasuda M, Kume S, Yamahara K, Nakazawa J, Chin-Kanasaki M, Araki H, Araki S, Koya D, Asanuma K, Kim EH, Haneda M, Kajiwara N, Hayashi K, Ohashi H, Ugi S, Maegawa H, and Uzu T. Impaired podocyte autophagy exacerbates proteinuria in diabetic nephropathy. *Diabetes* 65: 755–767, 2016.
158. Taguchi K, Fujikawa N, Komatsu M, Ishii T, Unno M, Akaike T, Motohashi H and Yamamoto M. Keap1 degradation by autophagy for the maintenance of redox homeostasis. *Proc Natl Acad Sci U S A* 109: 13561–13566, 2012.
159. Takabatake Y, Kimura T, Takahashi A, and Isaka Y. Autophagy and the kidney: health and disease. *Nephrol Dial Transplant* 29: 1639–1647, 2014.
160. Takahashi A, Kimura T, Takabatake Y, Namba T, Kaimori J, Kitamura H, Matsui I, Niimura F, Matsusaka T, Fujita N, Yoshimori T, Isaka Y, and Rakugi H. Autophagy guards against cisplatin-induced acute kidney injury. *Am J Pathol* 180: 517–525, 2012.
161. Tanaka A, Jin Y, Lee SJ, Zhang M, Kim HP, Stolz DB, Ryter SW and Choi AM. Hyperoxia-induced LC3B interacts with the Fas apoptotic pathway in epithelial cell death. *Am J Respir Cell Mol Biol* 46: 507–514, 2012.
162. Tanaka M, Machida Y, Niu S, Ikeda T, Jana NR, Doi H, Kurosawa M, Nekooki M, and Nukina N. Trehalose alleviates polyglutamine-mediated pathology in a mouse model of Huntington disease. *Nat Med* 10: 148–154, 2004.
163. Tanaka, Y, Guhde G, Suter A, Eskelinen EL, Hartmann D, Lüllmann-Rauch R, Janssen PM, Blanz J, von Figura K, and Saftig P. Accumulation of autophagic vacuoles and cardiomyopathy in LAMP-2-deficient mice. *Nature* 406, 902–906, 2000.
164. Taneike M, Yamaguchi O, Nakai A, Hikoso S, Takeda T, Mizote I, Oka T, Tamai T, Oyabu J, Murakawa T, Nishida K, Shimizu T, Hori M, Komuro I, Takuji Shirasawa TS, Mizushima N, and Otsu K. Inhibition of autophagy in the heart induces age-related cardiomyopathy. *Autophagy* 6: 600–606, 2010.
165. Tazi MF, Dakhlallah DA, Caution K, Gerber MM, Chang SW, Khalil H, Kopp BT, Ahmed AE, Krause K, Davis I, Marsh C, Lovett-Racke AE, Schlesinger LS, Cormet-Boyaka E, and Amer AO. Elevated Mirc1/Mir17-92 cluster expression negatively regulates autophagy and CFTR (cystic fibrosis transmembrane conductance regulator) function in CF macrophages. *Autophagy* 12: 2026–2037, 2016.
166. Thompson LM, Aiken CT, Kaltenbach LS, Agrawal N, Illes K, Khoshnan A, Martinez-Vincente M, Arrasate M, O'Rourke JG, Khashwji H, Lukacsovich T, Zhu YZ, Lau AL, Massey A, Hayden MR, Zeitlin SO, Finkbeiner S, Green KN, LaFerla FM, Bates G, Huang L, Patterson PH, Lo DC, Cuervo AM, Marsh JL, and Steffan JS. IKK phosphorylates huntingtin and targets it for degradation by the proteasome and lysosome. *J Cell Biol* 187: 1083–1099, 2009.
167. Tran I, Ji C, Ni I, Min T, Tang D, and Vij N. Role of cigarette smoke-induced aggresome formation in chronic obstructive pulmonary disease-emphysema pathogenesis. *Am J Respir Cell Mol Biol* 53: 159–173, 2015.
168. Trancikova A, Tsika E, and Moore DJ. Mitochondrial dysfunction in genetic animal models of Parkinson's disease. *Antioxid Redox Signal* 216: 896–919, 2012.
169. Tremblay C, St-Amour I, Schneider J, Bennett DA, and Calon F. Accumulation of TAR DNA binding protein-43 (TDP-43) in mild cognitive impairment and Alzheimer disease. *J Neuropathol Exp Neurol* 70: 788–798, 2011.
170. Tsvetkov AS, Miller J, Arrasate M, Wong JS, Pleiss MA, and Finkbeiner S. A small-molecule scaffold induces autophagy in primary neurons and protects against toxicity in a Huntington disease model. *Proc Natl Acad Sci U S A* 107: 16982–16987, 2010.
171. Ueno T and Komatsu M. Autophagy in the liver: functions in health and disease. *Nat Rev Gastroenterol Hepatol* 14: 170–184, 2017.
172. Valente EM, Abou-Sleiman PM, Caputo V, Muqit MM, Harvey K, Gispert S, Ali Z, Del Turco D, Bentivoglio AR, Healy DG, Albanese A, Nussbaum R, González-Maldonado R, Deller T, Salvi S, Cortelli P, Gilks WP, Latchman DS, Harvey RJ, Dallapiccola B, Auburger G, and Wood NW. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science* 304: 1158–1160, 2004.
173. Verheye S, Martinet W, Kockx MM, Knaapen MW, Salu K, Timmermans JP, Ellis JT, Kilpatrick DL, and De Meyer GR. Selective clearance of macrophages in atherosclerotic plaques by autophagy. *J Am Coll Cardiol* 49: 706–715, 2007.
174. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, and Rodriguez-Roisin R. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 187: 347–365, 2013.
175. Vij N, Chandramani P, Westphal CV, Hole R, and Bodas M. Cigarette smoke induced autophagy-impairment accelerates lung aging, COPD-emphysema exacerbations and pathogenesis. *Am J Physiol Cell Physiol* 314: C73–C87, 2016.
176. Vingtdeux V, Chandakkar P, Zhao H, d'Abramo C, Davies P, and Marambaud P. Novel synthetic small-molecule activators of AMPK as enhancers of autophagy and amyloid-β peptide degradation. *FASEB J* 25: 219–231, 2011.
177. Vives-Bauza C, Zhou C, Huang Y, Cui M, de Vries RL, Kim J, May J, Tocilescu MA, Liu W, Ko HS, Magrané J, Moore DJ, Dawson VL, Grailhe R, Dawson TM, Li C, Tieu K, and Przedborski S. PINK1-dependent recruitment of Parkin to mitochondria in mitophagy. *Proc Natl Acad Sci U S A* 107: 378–383, 2010.
178. Vollrath JT, Sechi A, Dreser A, Katona I, Wiemuth D, Vervoorts, J, Dohmen M, Chandrasekar A, Prause J, Brauers E, Jesse CM, Weis J, and Goswami A. Loss of function of the ALS protein SigR1 leads to ER pathology associated with defective autophagy and lipid raft disturbances. *Cell Death Dis* 5: e1290, 2014.
179. Wang L, Gao M, Chen J, Yang Z, Sun J, Wang Z, Huang X, Yuan T, Shen X, and Xian S. Resveratrol ameliorates pressure overload-induced cardiac dysfunction and attenuates autophagy in rats. *J Cardiovasc Pharmacol* 66: 376–382, 2015.
180. Wang RC, Wei Y, An Z, Zou Z, Xiao G, Bhagat G, White M, Reichelt J, and Levine B. Akt-mediated regulation of

autophagy and tumorigenesis through Beclin 1 phosphorylation. *Science* 338: 956–959, 2012.
181. Wei Q and Dong Z. HDAC4 blocks autophagy to trigger podocyte injury: non-epigenetic action in diabetic nephropathy. *Kidney Int* 86: 666–668, 2014.
182. Wen D, Huang X, Zhang M, Zhang L, Chen J, Gu Y, and Hao CM. Resveratrol attenuates diabetic nephropathy via modulating angiogenesis. *PloS One* 8: e82336, 2013.
183. Winslow AR, Chen CW, Corrochano S, Acevedo-Arozena A, Gordon DE, Peden AA, Lichtenberg M, Menzies FM, Ravikumar B, Imarisio S, Brown S, O'Kane CJ, and Rubinsztein DC. α-Synuclein impairs macroautophagy: implications for Parkinson's disease. *J Cell Biol* 190: 1023–1037, 2010.
184. Wong PM, Puente C, Ganley IG, and Jiang X. The ULK1 complex: sensing nutrient signals for autophagy activation. *Autophagy* 9: 124–137, 2013.
185. Xie Z, Lau K, Eby B, Lozano P, He C, Pennington B, Li H, Rathi S, Dong Y, Tian R, Kem D, and Zou MH. Improvement of cardiac functions by chronic metformin treatment is associated with enhanced cardiac autophagy in diabetic OVE26 mice. *Diabetes* 60: 1770–1778, 2011.
186. Xu W, Barrientos T, Mao L, Rockman HA, Sauve AA, and Andrews NC. Lethal cardiomyopathy in mice lacking transferrin receptor in the heart. *Cell Rep* 13: 533–545, 2015.
187. Xu X, Kobayashi S, Chen K, Timm D, Volden P, Huang Y, Gulick J, Yue Z, Robbins J, Epstein PN, and Liang Q. Diminished autophagy limits cardiac injury in mouse models of type 1 diabetes. *J Biol Chem* 288: 18077–18092, 2013.
188. Xue R, Zeng J, Chen Y, Chen C, Tan W, Zhao J, Dong B, Sun Y, Dong Y, and Liu C. Sestrin 1 ameliorates cardiac hypertrophy via autophagy activation. *J Cell Mol Med* 21: 1193–1205, 2017.
189. Yamamoto A and Simonsen A. The elimination of accumulated and aggregated proteins: a role for aggrephagy in neurodegeneration. *Neurobiol Dis* 43: 17–28, 2011.
190. Yang DS, Stavrides P, Saito P, Kumar A, and Jose A. Rodriguez-Navarro JA, Pawlik M, Huo C, Walkley SU, Saito M, Cuervo AM, and Nixon RA. Defective macroautophagic turnover of brain lipids in the TgCRND8 Alzheimer mouse model: prevention by correcting lysosomal proteolytic deficits. *Brain* 137: 3300–3318, 2014.
191. Yang Y, Liu Y, Xue J, Yang Z, Shi Y, Shi Y, Lou G, Wu S, Qi J, Liu W, Wang J, and Chen Z. MicroRNA-141 targets Sirt1 and inhibits autophagy to reduce HBV replication. *Cell Physiol Biochem* 41: 310–322, 2017.
192. Youle RJ and Narendra DP. Mechanisms of mitophagy. *Nat Rev Mol Cell Biol* 12: 9–14, 2011.
193. Yuan HX, Russell RC, and Guan KL. Regulation of PIK3C3/VPS34 complexes by MTOR in nutrient stress-induced autophagy. *Autophagy* 9: 1983–1995, 2013.
194. Zeng C, Fan Y, Wu J, Shi S, Chen Z, Zhong Y, Zhang C, Zen K, and Liu Z. Podocyte autophagic activity plays a protective role in renal injury and delays the progression of podocytopathies. *J Pathol* 234: 203–213, 2014.
195. Zhang D, Wang W, Sun X, Xu D, Wang C, Zhang Q, Wang H, Luo W, Chen Y, Chen H, and Liu Z. AMPK regulates autophagy by phosphorylating BECN1 at threonine 388. *Autophagy* 12: 1447–1459, 2016.
196. Zhang H, Bosch-Marce M, Shimoda LA, Tan YS, Baek JH, Wesley JB, Gonzalez FJ, and Semenza GL. Mitochondrial autophagy is an HIF-1-dependent adaptive metabolic response to hypoxia. *J Biol Chem* 283: 10892–10903, 2008.
197. Zhang X, Chen S, Song L, Tang Y, Shen Y, Jia L, and Le W. MTOR-independent, autophagic enhancer trehalose prolongs motor neuron survival and ameliorates the autophagic flux defect in a mouse model of amyotrophic lateral sclerosis. *Autophagy* 10: 588–602, 2014.
198. Zhang X, Li L, Chen S, Yang D, Wang Y, Zhang X, Wang Z, and Le W. Rapamycin treatment augments motor neuron degeneration in SOD1(G93A) mouse model of amyotrophic lateral sclerosis. *Autophagy* 7: 412–425, 2011.
199. Zhao Y, Zhang CF, Rossiter H, Eckhart L, König U, Karner S, Mildner M, Bochkov VN, Tschachler E, and Gruber F. Autophagy is induced by UVA and promotes removal of oxidized phospholipids and protein aggregates in epidermal keratinocytes. *J Invest Dermatol* 133: 1629–1637, 2013.
200. Zhu H, Tannous P, Johnstone JL, Kong Y, Shelton JM, Richardson JA, Le V, Levine B, Rothermel BA, and Hill JA. Cardiac autophagy is a maladaptive response to hemodynamic stress. *J Clin Invest* 117: 1782–1793, 2007.

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Abbreviations Used

3-MA = 3-methyladenine
Aβ = β-amyloid
AD = Alzheimer's disease
AKI = acute kidney injury
AKT1S1 = AKT1 substrate 1
ALI = acute lung injury
ALS = amyotrophic lateral sclerosis
AMBRA-1 = autophagy/Beclin 1 regulator
AMPK = 5′-AMP activated protein kinase
APP = amyloid precursor protein
ATG = autophagy-related
BECN1 = Beclin 1
Bif-1 = Bax-interacting factor-1
BNIP3 = Bcl-2/adenovirus E1B 19kDa-interacting protein-3
CF = cystic fibrosis
CFTR = cystic fibrosis transmembrane conductance regulator
CKD = chronic kidney disease
CLP = cecal ligation and puncture
CMA = chaperone-mediated autophagy
COPD = chronic obstructive pulmonary disease
CS = cigarette smoke
DN = diabetic nephropathy

Abbreviations Used (Cont)

Drp1 = dynamin-related protein-1
ECM = extracellular matrix
ER = endoplasmic reticulum
FIP200 = focal adhesion kinase family interacting protein of 200kDa
FSGS = focal segmental glomerular sclerosis
H_2O_2 = hydrogen peroxide
HBV = hepatitis B virus
HCV = hepatitis C virus
HD = Huntington's disease
HDAC4 = histone deacetylase 4
HDAC6 = histone deacetylase 6
Hif-1 = hypoxia-inducible factor-1
HOPS = homotypic fusion and protein sorting
HTT = huntingtin
IL = interleukin
IPF = idiopathic pulmonary fibrosis
I/R = ischemia/reperfusion
Keap1 = Kelch-like ECH-associated protein 1
LAMP-2A = lysosome-associated membrane protein-2A
LC3B = microtubule-associated protein-1 light chain 3B
LIR = LC3-interacting region
LRRK2 = leucine-rich repeat kinase 2
Mdivi = mitochondrial division/mitophagy inhibitor
mHTT = mutant huntingtin
mTOR = mechanistic/mammalian target of rapamycin
mTORC1 = mTOR complex 1
mtROS = mitochondria-derived reactive oxygen species
NAFLD = nonalcoholic fatty liver disease
NASH = nonalcoholic steatohepatitis
NBR1 = neighbor of *BRCA1* gene 1
NLRP = Nod like receptor protein
Nrf2 = nuclear factor erythroid 2-related factor 2
$O_2^{\bullet-}$ = superoxide anion radical
p62 = sequestosome
PAN = puromycin aminonucleoside
PARK2 = Parkin, Parkinson protein-2
PD = Parkinson's disease
PE = phosphatidylethanolamine
PI3K = phosphatidylinositol 3-kinase
PI3P = phosphatidylinositol-3-phosphate
PIK3C3 = phosphatidylinositol 3-kinase Class III
PINK1 = phosphatase and tensin homologue deleted in chromosome 10 (PTEN)-induced putative kinase 1
ROS = reactive oxygen species
Rubicon = run-domain Beclin-1 interacting and cysteine-rich containing protein
SigmaR1 = sigma 1 receptor
SIRT1 = NAD^+-dependent class III histone deactylase sirtuin 1
SMCs = smooth muscle cells
SNARE = soluble *N*-ethylmaleimide-sensitive factor attachment receptor
SNCA = α-synuclein
SOD1 = superoxide dismutase 1
TDP = TAR-DNA binding protein
TGF-β1 = transforming growth factor-beta 1
TNF-α = tumor necrosis factor-alpha
ULK1 = unc-51-like autophagy activating kinase-1
UUO = unilateral ureteral obstruction
UVRAG = ultraviolet radiation resistance-associated gene protein
VPS = vacuolar protein sorting
WIPI = WD-repeat protein interacting with phosphoinositides