



Review

Roles of Autophagy in Oxidative Stress

Hyeong Rok Yun ^{1,2}, Yong Hwa Jo ^{2,3}, Jieun Kim ^{2,3}, Yoonhwa Shin ^{1,2}, Sung Soo Kim ^{1,2,3,*}
and Tae Gyu Choi ^{2,3,*}

¹ Department of Biomedical Science, Graduate School, Kyung Hee University, Seoul 02447, Korea; foryou018@khu.ac.kr (H.R.Y.); jac03032@khu.ac.kr (Y.S.)

² Biomedical Science Institute, Kyung Hee University, Seoul 02447, Korea; yonghwa.jo@khu.ac.kr (Y.H.J.); popje124@khu.ac.kr (J.K.)

³ Department of Biochemistry and Molecular Biology, School of Medicine, Kyung Hee University, Seoul 02447, Korea

* Correspondence: sgskim@khu.ac.kr (S.S.K.); chtag@khu.ac.kr (T.G.C.); Tel.: +82-2-961-0524 (S.S.K.); +82-2-961-0287 (T.G.C.)

Received: 30 March 2020; Accepted: 4 May 2020; Published: 6 May 2020



Abstract: Autophagy is a catabolic process for unnecessary or dysfunctional cytoplasmic contents by lysosomal degradation pathways. Autophagy is implicated in various biological processes such as programmed cell death, stress responses, elimination of damaged organelles and development. The role of autophagy as a crucial mediator has been clarified and expanded in the pathological response to redox signalling. Autophagy is a major sensor of the redox signalling. Reactive oxygen species (ROS) are highly reactive molecules that are generated as by-products of cellular metabolism, principally by mitochondria. Mitochondrial ROS (mROS) are beneficial or detrimental to cells depending on their concentration and location. mROS function as redox messengers in intracellular signalling at physiologically low level, whereas excessive production of mROS causes oxidative damage to cellular constituents and thus incurs cell death. Hence, the balance of autophagy-related stress adaptation and cell death is important to comprehend redox signalling-related pathogenesis. In this review, we attempt to provide an overview the basic mechanism and function of autophagy in the context of response to oxidative stress and redox signalling in pathology.

Keywords: autophagy; reactive oxygen species; oxidative stress

1. Introduction

Autophagy (self-eating) was first introduced by Christian de Duve in 1963 as a lysosome-mediated disposal process [1]. Autophagy is a catabolic process that is essential for cellular homeostasis through the removal of cellular molecules, such as protein aggregates and damaged organelles, via lysosomal digestion [2,3]. Principally, it regulates the balance between organelle biogenesis, protein synthesis and the clearance of cells [4], which is involved in cellular remodelling during development and differentiation [5]. Autophagy occurs under conditions of glucose or amino acid deprivation, oxidative stress, hypoxia and exposure to xenobiotics [6]. Autophagy has emerged as a critical mediator of pathological responses is associated with reactive oxygen species (ROS) in both cellular signalling and damage [7]. The autophagy has also been implicated in the progression of diabetes, cancer, cardiovascular, neurodegeneration, immune diseases and ageing [8–13].

Mitochondria are the major source of ROS within cells [14,15] and mitochondrial ROS (mROS) are generally produced as by-products of the bioenergetics during oxidative phosphorylation (OXPHOS) [16]. The ROS are highly reactive metabolites of molecular oxygen (O₂), including superoxide anion (O₂^{•−}) and hydrogen peroxide (H₂O₂), which are formed by electron reductions of O₂ [17]. In the presence of transition metal ions, the more reactive hydroxyl radical (OH·) is produced [18].

ROS can act as signalling molecules at the physiological level, which contribute to various cellular processes, including proliferation, differentiation, programmed cell death, innate immunity, autophagy, redox signalling, calcium homeostasis, hypoxic stress responses and stem cell reprogramming [19–25]. Conversely, excess oxidative stress causes damages to proteins and cellular components, which is implicated in various pathologies [26].

Physiological ROS induce autophagy to maintain the cellular homeostasis in different types of cells, whereas dysregulation of redox signalling can demoralise the autophagic activity, which results in a variety of diseases [27,28]. However, the underlying mechanism between autophagy and redox signalling remains to be further elucidated. In this review, we introduce recent studies on redox signalling in autophagy regulation. Furthermore, we discuss the effect of autophagy on mitochondrial function and relevance to chronic pathologies.

2. Molecular Mechanisms of Autophagy

2.1. Autophagic Machinery

There are three major types of autophagy: (1) macro-autophagy, (2) micro-autophagy, and (3) chaperone-mediated autophagy (CMA) (Figure 1). Macro-autophagy is the most well-known form of autophagy. All types of autophagy promote degradation of damaged or functionally expired proteins and organelles in the cell.

(1) Macro-autophagy has been considered as a non-selective cellular process; however, this autophagy controls the quality of cellular contents via selective execution (e.g., long-lived proteins, aggregated proteins, damaged organelles, and intracellular pathogens) [29]. The autophagic pathway is initiated with the nucleation of a double-membraned structure, the phagophore (also known as isolation membranes), which is elongated to sequester the materials and to form a vesicle, autophagosome. The autophagosome is fused with lysosome to degrade the contents in the acidic environment. Then, the degraded molecules are recycled to the materials for rebuilding new cellular components [30].

(2) Micro-autophagy is a process that the cytoplasmic substances are directly engulfed into the lysosomes for degradation via entailing invagination, protrusion, or septation of the lysosomal or endosomal membrane [31,32]. Invagination of the endosomal membrane formed by endosomal sorting complexes required for transport (ESCRT) machinery incorporates the sequestered materials into the lysosome [33].

(3) Chaperone-mediated autophagy (CMA) is a form of autophagy present in various types of eukaryotic cell and tissue, but not in yeast [34]. A cytosolic chaperone, heat shock cognate protein of 70 kDa (HSC70), recognises that CMA-target proteins contain a pentapeptide motif biochemically related to KFERQ. The HSC70-target protein complex binds the lysosome-associated membrane protein-2A (LAMP-2A) on the lysosomal membrane, and then the target protein is translocated into the lysosomes to be degraded [35].

The present review focuses on the molecular and cellular mechanism, regulation, and selectivity of mammalian macro-autophagy (hereafter referred to as autophagy).

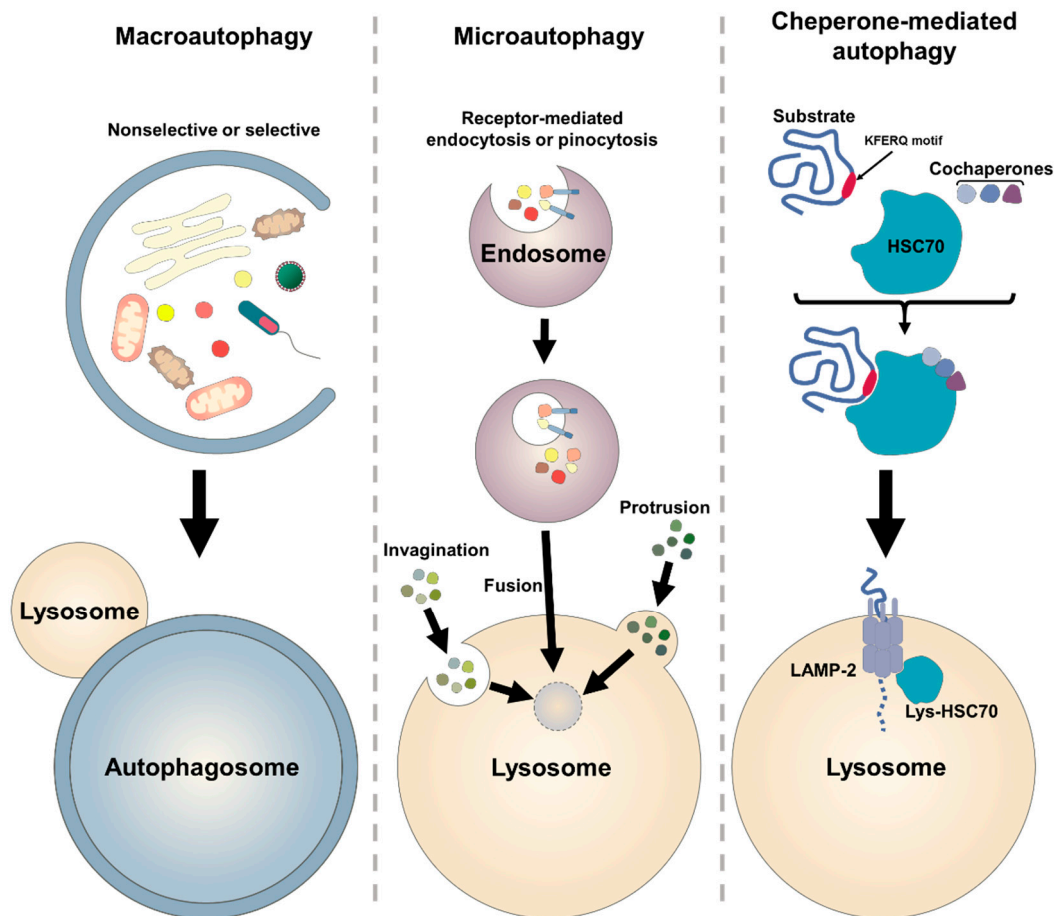


Figure 1. Overview of the mammalian autophagy pathway. Macro-autophagy encapsulates the cytoplasmic cargo by a delimiting membrane, which forms an autophagosome, which finally fuses with lysosome for degradation of the substrates. Micro-autophagy involves invagination or protrusion of the vacuole, which is formed by a lysosomal membrane. It also degrades extracellular molecules encapsulated by endocytosis (receptor-mediated pathway) or pinocytosis, following fusion with lysosome. The pinocytotic vesicles fuse with endosomes to hydrolyse the substrates. Chaperone-mediated autophagy is a selective degradation pathway, in which the protein substrates containing KFERQ-like motifs are recognised by chaperone HSC70 and cochaperones, such as carboxyl terminus of HSC70-interacting protein (CHIP), heat shock protein 40 (HSP40) and HSP70-HSP90 organizing protein (HOP), and are transferred into the lysosome via a lysosomal receptor complex, LAMP-2.

2.2. Molecular Biology of Autophagy

Autophagy induction is stimulated by diverse cellular events, including nutrient starvation, hypoxia, oxidative stress, pathogen infection and endoplasmic reticulum (ER) stress [36]. Autophagic multiprotein complexes are required for autophagic induction, which are hierarchically assembled and operated in the sites of the autophagosome formation termed pre-autophagosomal structure or phagophore assembly site (PAS) [37]. In mammalian cells, the autophagic process is initiated by inactivation of mechanistic/mammalian target of rapamycin (mTOR), which then requires the orchestration of several multiprotein complexes [38,39]. mTOR is a serine/threonine kinase that participates in a wide spectrum of biological processes [40]. It forms two functionally different complexes: mTOR complex 1 (mTORC1) and mTORC2, which are structurally regulated by their modulators such as regulatory-associated protein of mTOR (Raptor), rapamycin-insensitive companion of mTOR (Rictor) and lethal with Sec13 protein 8 (LST8) via inter-complex and intra-complex loops [41]. However, mTORC2 is not responsible for controlling autophagy. Under normal condition,

mTORC1 directly phosphorylates uncoordinated-51-like kinase 1 (ULK1), ULK2 and autophagy-related protein 13 (Atg13), of which both constitute an autophagy initiation complex via interaction with focal adhesion kinase family-interacting protein of 200 kDa (FIP200) and Atg101 [42,43]. ULK1 interacts with Atg13 and FIP200 at its C-terminal region [44] and binds to Atg101 through the N-terminus of Atg13 [45]. In response to starvation or stress conditions, the mTORC1 is dissociated from the ULKs complex via phosphorylations of Rheb and Raptor by AMP-activated protein kinase (AMPK) [46]. Subsequently Ulk1/2 are rapidly dephosphorylated and autophosphorylated, and Atg13 and FIP200 are phosphorylated [47]. The autophagic activation of ULKs complex contributes to phagophore nucleation [48].

The phagophore is a small cup-shape membrane structure, which elongates to form a complete autophagosomal structure, although its origin has still been debated [49,50]. In higher eukaryotic cells, it is accepted that at least under starvation conditions, phagophore nucleation occurs at the omegasome, morphologically resembling Greek capital letter omega (Ω), which is the region of endoplasmic reticulum (ER) enriched for phosphatidylinositol 3-phosphate (PI3) [51,52]. The formation of an omegasome requires Class III PI3 kinase (PI3KC3), which forms a complex with Beclin1, Beclin1-regulated autophagy protein 1 (AMBRA1), general vesicular transport factor (p115), p150 and ATG14L [42,53,54]. The ULKs complex leads to activation of the PI3KC3 complex via phosphorylations of Beclin1 and AMBRA1 [54–56]. The active PI3KC3 generates PIP3 via phosphorylation of PI on the surface of the phagophore, which recruits double FYVE domain-containing protein 1 (DFCP1) [57–59] and WD repeat domain phosphoinositide-interacting protein 2 (WIPI2) to mediate the nucleation and growth of the phagophore [60,61]. The activity PI3KC3 complex is also controlled via interacting with cofactors such as UV radiation resistance-associated gene (UVRAG), Bax-interacting factor 1 (Bif1) and RUN domain- and cysteine-rich domain-containing beclin-1-interacting protein (Rubicon) [30].

The phagophore is elongated to develop into an autophagosome, which is regulated by two ubiquitination-like conjugation systems: Atg5-Atg12 conjugation and microtubule-associated protein light chain 3 (LC3B) processing [62]. The Atg12 is activated by Atg7 (E1-like activating enzyme), and is then conjugated to Atg5 by Atg10 (E2-like conjugating enzyme) [63,64]. The Atg5-Atg12 complex interacts non-covalently with Atg16L1 (E3-like ligase enzyme), which results in the Atg5-Atg12-Atg16L1 multimeric complex [65]. Atg16L1 is recruited to the phagophore by physical binding with WIPI2 [66]. The Atg5-Atg12-Atg16L1 complex is associated with induction of curvature into the extending phagophore via asymmetric insertion of processed LC3B [67,68]. The Atg5-Atg12-Atg16L1 complex is recruited to the outer membrane of the phagophore, essentially avoiding premature fusion with the lysosome [69]. The C-terminal flanking region of nascent LC3B (proLC3B) is converted to LC3B-I via cleavage by Atg4 a cysteine protease. The exposed C-terminal glycine residue of LC3B-I is then activated by Atg7, and the LC3B-I is modified to LC3B-II through phosphatidylethanolamine (PE) conjugation by Atg3 [70,71]. The LC3B-II contributes to the autophagosomes closure [72], and the Atg5-Atg12-Atg16L1 complex is dissociated from completed autophagosomes [73]. The LC3B-II is anchored to the autophagosomal membrane until their fusion with lysosome. Then, the LC3B-II at the outer surface of the membrane is dissociated by Atg4 and recycled [74], whilst that remains associated with the membrane at the inner surface to degrade the substrates in the cargo [75]. An LC3-related protein, gamma-aminobutyric acid receptor-associated protein (GABARAP) has similar roles in the autophagosomal expansion process: autophagosome formation and substrate sequestration into double-membrane vesicles [76].

The phagophore extension is also supported by a transmembrane protein ATG9, which aids to supply lipid bilayers to the nascent phagophore, enabling further elongation of the autophagosome prior to closure of the fully formed autophagosome [50,77].

Tethering of the targeted cellular contents for degradation to an engulfing autophagosome is expedited by autophagy adaptor proteins such as sequestosome 1 (SQSTM1/p62) [78], optineurin [79,80], nuclear dot protein 52 kDa (NDP52) [81], neighbour of BRCA1 gene 1 (NBR1) [82] and autophagy-linked FYVE protein (ALFY) [83]. The completed autophagosome fuses to a lysosome to form autophagolysosome

around centrosome via multiple proteins [84], including: syntaxin 17 (STX17) and synaptosomal-associated protein 29 (SNAP29) on the autophagosome; vesicle-associated membrane protein 8 (VAMP8) and vesicle transport through interaction with t-SNAREs 1B (VTI1B) on the lysosome [85–89]; and UVRAG [90]. The autophagolysosomal contents are finally degraded by lysosomal acidic hydrolases and released from the vesicle to cytoplasm, which produces building blocks and energy for cellular reorganisation and homeostasis [91,92].

3. Redox Signalling in Autophagy

3.1. Mitochondrial ROS and Redox Signalling

Reactive oxygen species (ROS) are small, short-lived and highly reactive molecules that are normally formed as by-products of oxygen metabolism in the mitochondrial electron transport chain (mETC) [93]. In the process of OXPHOS, electron leaks at complex I and III from mETC lead to the formation of partially reduced and highly reactive metabolites of molecular oxygen (O_2), including $O_2^{\cdot-}$ and H_2O_2 , which are most important molecules in cellular signalling [94]. The mitochondrial $O_2^{\cdot-}$ is catalysed to H_2O_2 by two dismutases including Cu/Zn-superoxide dismutase (Cu/ZnSOD) in mitochondrial intermembrane space (IMS) and cytosol, and manganese-dependent superoxide dismutase (MnSOD) in mitochondrial matrix [95]. The H_2O_2 can be converted to hydroxyl radical ($OH\cdot$) by Fenton reaction [96]. Mitochondrial $O_2^{\cdot-}$ also binds with hydrogen protons to form uncharged hydroperoxyl radical ($HOO\cdot$) which react with unsaturated fatty acid of mitochondrial membrane lipids to generate lipid radicals [97]. Mitochondrial NO interacts with $O_2^{\cdot-}$ to form RNS such as $ONOO^-$, which causes cellular dysfunction by S-nitrosylating proteins [98]. Mammalian cells have numerous enzymes to degrade H_2O_2 , including peroxiredoxins (Prxs), glutathione peroxidases (Gpxs), thioredoxins (Trxs) and catalase. Mitochondrial H_2O_2 is primarily eradicated by the action of Gpx1, Gpx2 and Gpx4, Prx3 and Prx5, Trx2 system, in which glutathione (GSH) is necessary [99–101]. Oxidized GSH (GSSG) is reduced to GSH by glutathione reductase (GR) [102]. Oxidized Trx2 is also recycled by Trx reductase (TrxR). The systems of H_2O_2 scavenging depend on nicotinamide adenine dinucleotide phosphate (NADPH) which is regenerated by three mitochondrial matrix enzymes: NADP⁺-linked isocitrate dehydrogenase (IDH), malate dehydrogenase (MDH) and nicotinamide nucleotide transhydrogenase (NNT) [94]. Catalase catalyses the breakdown of hydrogen peroxide to water and oxygen [103].

It has thus far been reported that the ROS are associated with autophagy induction upon deprivation of nutrients such as glucose, amino acids or serum [104–107]. Autophagy is activated in response to oxidative stress to protect the cells from apoptosis [108], whereas impairment of autophagy causes accumulation of oxidative stress [109]. Furthermore, antioxidant molecules moderately or completely suppress autophagic implementation [110]. Thus, mitochondrial ROS not only activate autophagic signalling but also inhibit it. In turn, the mROS and autophagy are mutually influenced. mROS generation and autophagic activation are summarized in Figure 2.

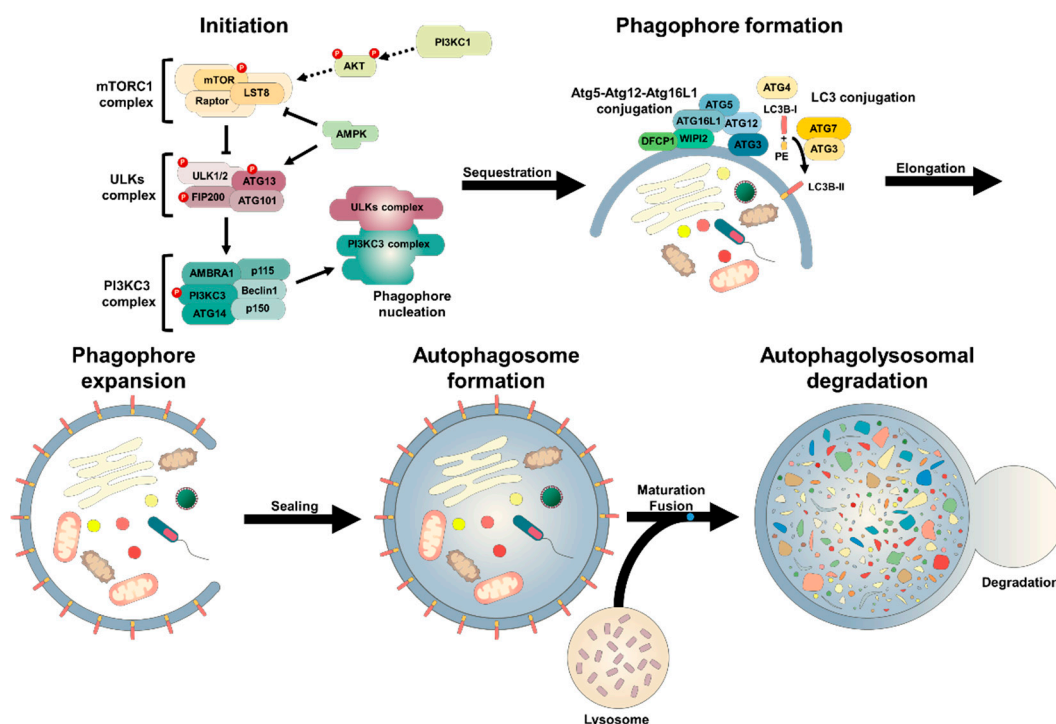


Figure 2. The general autophagy process. The autophagic process is divided into five distinct stages: Initiation, phagophore nucleation, autophagosomal formation (elongation), autophagosome-lysosome fusion (autophagolysosome) and cargo degradation. Autophagy is stimulated by various cellular stress conditions such as nutrient starvation and oxidative stress. Under stress conditions, mTORC1 is inhibited to activate the ULKs complex that encompasses ULK1/2, FIP200, ATG101 and Atg13. Subsequently, phagophore nucleation is induced by the activated ULKs complex, which is then mediated by the PI3KC3 complex that consists of multiple proteins, including Beclin1, AMBRA1, p115, p150 and ATG14L. The ULKs complex provokes activation of the PI3KC3 complex via phosphorylations of Beclin1 and AMBRA1. The active PI3KC3 produces PIP3 via phosphorylation of PI on the surface of the phagophore, which recruits DFCP1 and WIPI2 for phagophore nucleation and expansion. The phagophore is elongated to form the autophagosome, which is regulated by two ubiquitination-like conjugation systems: Atg5-Atg12 conjugation and LC3B-II conjugation. Atg12 is activated by Atg7, which is conjugated to Atg5 by Atg10. The Atg5-Atg12 complex interacts with Atg16L1. Atg16L1 is recruited to the phagophore via binding with WIPI2. The Atg5-Atg12-Atg16L1 complex is involved in the curvature of the elongating phagophore via asymmetric insertion of processed LC3B. The Atg5-Atg12-Atg16L1 complex is recruited to the outer membrane of the phagophore to avoid premature fusion of the autophagosome and lysosome. Nascent LC3B (proLC3B) is converted to LC3B-I via cleavage by Atg4, the exposed C-terminal glycine residue of LC3B-I is then activated by Atg7, and the LC3B-I is converted to LC3B-II via PE conjugation by Atg3. The LC3B-II is anchored to the autophagosomal membrane until the forming of autophagolysosome. Finally, the autophagolysosomal contents are degraded by lysosomal enzymes.

3.2. Autophagy Regulation by Redox Signalling

Mitochondria are generators and targets of ROS, which are inseparable from oxidative stress [109]. Accumulation of oxidative stress causes oxidation and damage of cellular constituents, including proteins, DNA and lipids, which are oxidized and damaged which turn on the autophagic process [111]. Mitochondrial H_2O_2 has important roles in cellular signalling, which is rather stable than the other ROS molecules, and can easily diffuse to cytosol [112,113]. In response to nutrient starvation, the energetic stress possibly increases the demand of ATP production from mitochondria, which subsequently cause an increase of electron leaks, and thus relatively excess ROS are produced [114]. Indeed, mitochondrial H_2O_2 has long been implicated in the autophagic signalling pathway.

In response to nutrient starvation, H₂O₂ enables the reduced form of Atg4 to convert LC3B-I to LC3B-II through thiol modification of the Cys81 of Atg4, thus leading to increased autophagosome formation. However, the reduced form of Atg4 protease delipidates LC3 and inhibits autophagosomal membrane elongation, thereby suppressing autophagy [115]. Exogenous H₂O₂ also leads to oxidative stress and mitochondrial dysfunction, thereby inducing autophagy [116]. Treatment of H₂O₂ stimulated both autophagy and apoptosis in malignant glioma cells [117]. TNF α treatment increased ROS levels, and thus induced autophagy and cell death in Ewing sarcoma, which was also simulated by exogenous H₂O₂ treatment. These effects were reverted by chemical lipid radical scavengers or NF- κ B activation [118,119]. Similarly, lipopolysaccharides (LPS) induce autophagy via H₂O₂ treatment [120]. O₂^{•-} is also closely involved in autophagy induction under starvation conditions of glucose and amino acids [106]. Endogenous O₂^{•-} levels were declined in a mETC-deficient (ρ^0) cervical cancer cell line even under starvation conditions without endogenous levels of H₂O₂. Starvation-induced autophagy was considerably weakened in the ρ^0 cells [121]. Nutrient starvation also activated AMP activated protein kinase (AMPK), which inhibits mTORC1 activity and directly phosphorylates ULK1 at serine 317 (S317) and serine 777 (S777), thereby promoting autophagosome formation and autophagic flux [122,123]. AMPK also phosphorylated ATG13 at Ser224 to inhibition of autophagy, which elicits the intensity and duration of autophagy [124]. Starvation-induced AMPK activation was diminished in both ρ^0 or MnSOD overexpressed cells [121]. AMPK inhibitor compound C treatment or knockdown of AMPK catalytic subunit α 1 also impeded starvation-induced autophagy [121]. AMPK-activated autophagy is modulated by ROS [125], in which upstream kinases of the AMPK are involved, leading to the induction of autophagy [126]. H₂O₂ directly activates AMPK by oxidizing cysteine residues of α and β subunits [127], or oxidation of ataxia-telangiectasia mutated (ATM) protein kinase [128]. Oxidative stress-activated ATM persuades its downstream signalling AMPK-Tuberous Sclerosis Complex 2 (TSC2) to suppress mTORC1, and thus induces autophagy [129,130]. Furthermore, in response to H₂O₂, AMPK is activated via phosphorylation at threonine 172 (T172) by liver kinase B1 (LKB1) kinase, which represses mTORC1, and thus induces autophagy [129].

NO is enzymatically synthesized from L-arginine by NO synthases (NOS) in oxidation processes [131]. In autophagic signalling, NO has different effects depending on the cell types. NO inhibits autophagosomal formation by attenuating the activity of S-nitrosylation substrates such as c-Jun N-terminal kinase 1 (JNK1) and inhibitor of nuclear factor κ B (I κ B) kinase subunit β (IKK β). Starvation-derived autophagy is activated by JNK1 in mTOR-independent. JNK1 can phosphorylate B-cell lymphoma 2 (Bcl-2) to disrupt its interaction with Beclin1 for inducing autophagy [132,133]. IKK β also induces autophagy by enhancing AMPK phosphorylation-dependent mTOR inhibition and JNK1-mediated Bcl-2 phosphorylation [134]. However, in glioma cells, inhibitory effects on the autophagic process were elicited by treatment of NO donors, such as sodium nitroprusside (SNP) and S-nitrosoglutathione (GSNO), following accumulation of LC3B-II [135].

It has increasingly been reported that the cross-talk between mROS and Ca²⁺ signalling has important roles in regulating autophagy. In response to hypoxia, mROS contribute to the transport of the stromal interaction molecule 1 (STIM1) to the plasma membrane, which activates Ca²⁺ release-activated Ca²⁺ (CRAC) channels, thereby inducing a Ca²⁺ influx increase and calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2) activation. Resultantly, AMPK and autophagy were activated [136,137]. Furthermore, mROS activate lysosomal Ca²⁺ channel mucolipin-1 (MCOLN1), which results in Ca²⁺ release and calcineurin-dependent nuclear translocation of transcription factor EB (TFEB), inducing Atgs and lysosomal proteins [138].

Nuclear factor erythroid 2-related factor 2 (NRF2) is a prominent transcription factor that regulates the gene expression of several genes encoding antioxidant and detoxifying enzymes, which maintain cellular redox homeostasis [139,140]. Kelch like ECH associated protein 1 (KEAP1) is a substrate adaptor protein within a larger E3 ubiquitin ligase complex containing cullin 3 (CUL3) and ring-box 1 (RBX1). It enables the ubiquitination and proteasomal degradation of the substrates, including NRF2 [141]. In response to oxidative stress, NRF2 is dissociated from KEAP1 and binds to an antioxidant-response

element (ARE) sequence in the nucleus to activate its target genes [140]. In autophagic signalling, NRF2 induces p62 gene expression in response to oxidative stress, from which the protein further activates NRF2, forming a positive feedback loop [142–144]. Similarly, Sestrin2 leads to further activation of NRF2 [145]. Ubiquitinated p62 is phosphorylated, which enhances its affinity for KEAP1 to facilitate the autophagic degradation of KEAP1, thereby resulting in the stabilization of Nrf2 [146–148].

Tumour protein 53 (TP53 or p53)-induced glycolysis and apoptosis regulator (TIGAR) as a TP53 target interacts with hexokinase2 (HK2), which modulates the glycolysis pathway, thus upregulating NADPH production and reducing mROS levels [149,150]. Inhibition of TIGAR provokes mROS production and autophagy, whilst overexpression of TIGAR alleviates autophagy stimulated by nutrient deprivation or hypoxia in p53-independent [105]. Inhibition of TIGAR also induces mitophagy during ischemic injury, which is restored by antioxidant treatment [151]. Damage-regulated autophagy modulator (DRAM), a p53-regulated gene, also arouses autophagy [152]. Moreover, p53-induced Sestrin1 and Sestrin2 persuade autophagy via the activation of AMPK, thereby inhibiting mTORC1 [153].

3.3. Mitophagy

mROS are spontaneously generated during Mitochondrial ATP production by OXPHOS, which result in a certain degree of mitochondrial damage. The damaged mitochondria lead to ATP depletion and cytoplasmic cytochrome c (Cyt c) release, which ultimately triggers activation of caspases and then apoptosis occurs [154,155]. To prevent cell death, the dysfunctional mitochondria are consequently removed from the mitochondrial network via selective autophagy, mitophagy [2]. Mitophagy can limit further production of mROS, which endorses mitochondria turnover and avoids dysfunctional mitochondria accumulation. Mitophagy is mainly regulated by the PTEN-induced kinase 1 (PINK1)-Parkin pathway, which is stimulated by MMP depolarization. PINK1 is a Ser/Thr kinase that translocates on the outer mitochondrial membrane (OMM), which is stabilized by low MMP, thereby causing mitochondrial depolarization [156–158]. PINK1 then recruits Parkin, which ubiquitylates OMM-located proteins, such as VDAC1, resulting in autophagic machinery recruitment and the selective sequestration of ubiquitylated mitochondria within autophagosomes [2]. Furthermore, the mitochondrial proteins, BCL2/adenovirus E1B 19-kDa interacting protein 3 (BNIP3) and NIX (Bcl-2/adenovirus E1B 19-kDa-interacting protein 3, long form, BNIP3L), contribute to mitophagy [159]. In response to oxidative stress after ischemia/reperfusion (I/R), BNIP3 is activated via homodimerisation, which induces mitophagy [160]. NIX, an atypical BH3 protein, is required for mitophagy in erythrocyte development. It directly recognizes autophagosome-sited GABARAP, and subsequently induces mitophagy [114,161]. ULK1 also regulates mitophagy via translocation to mitochondria to phosphorylate FUN14 domain containing 1 (FUNDC1) protein, an OMM protein, which is a receptor for hypoxia-mediated mitophagy [162]. Relationship between mROS and autophagy is schematized in Figure 3.

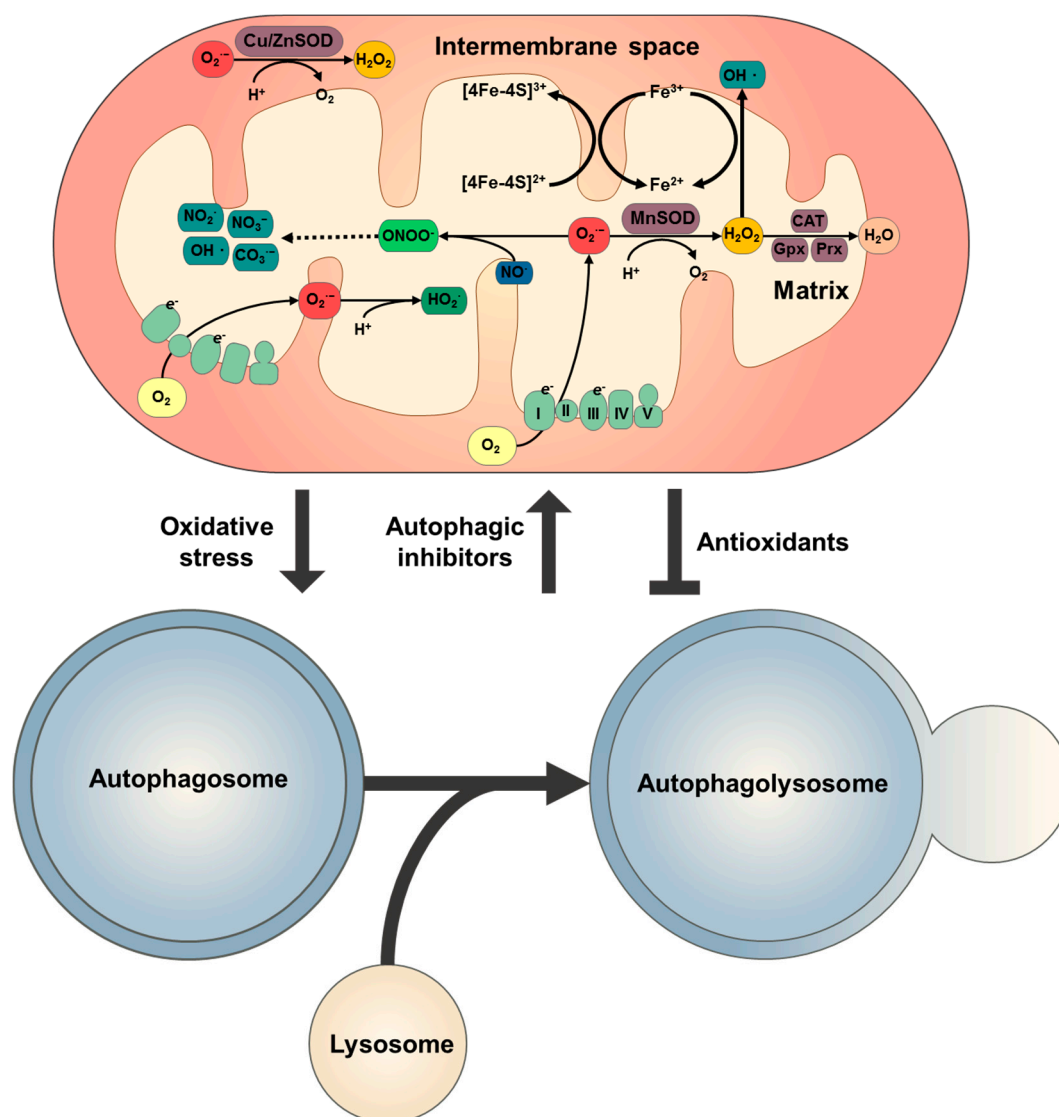


Figure 3. Interaction between mROS production and autophagy activation. Cu/ZnSOD and MnSOD catalyse the dismutation (or partitioning) of superoxide ($O_2^{\cdot-}$) radical into hydrogen peroxide (H_2O_2) in the mitochondrial intermembrane space (IMS) and matrix, respectively. H_2O_2 is converted into water by catalase (CAT) and a group of glutathione peroxidases (Gpxs) and peroxirredoxins (Prxs). H_2O_2 react with redox-active ferrous ions (Fe^{2+}) to generate the hydroxy radical ($OH\cdot$) via the Fenton reaction. The H_2O_2 can easily be diffused to the other parts of the mitochondria or cytosol. The reaction between $O_2^{\cdot-}$ and nitric oxide ($NO\cdot$) produces peroxynitrite ($ONOO^-$), which is decomposed to some highly oxidising intermediates including $NO_2\cdot$, $OH\cdot$, and $CO_3^{\cdot-}$, and finally, to stable NO_3^- . $O_2^{\cdot-}$ by itself can also reduce ferric iron (Fe^{3+}) to Fe^{2+} in iron–sulphur centres of proteins, leading to enzyme inactivation and the concomitant loss of Fe^{2+} from the enzymes. Moreover, $O_2^{\cdot-}$ can form the more reactive hydroperoxyl radical ($HO_2\cdot$) via protonation. The mROS-induced oxidative stress provokes autophagy, and autophagy inhibitors such as chloroquine (CQ) and bafilomycin A1 (BafA1) can further induce mROS production. Furthermore, antioxidants attenuate autophagic activation.

4. Pathological Implications

4.1. Cancer

Cancer cells exhibit continuous proliferation as a common trait, evading the suppression of growth and resisting cell death, during which metabolic activity increases via anaerobic metabolism, known as

the Warburg effect [163]. This effect results in ROS production through incomplete OXPHOS. Moreover, cancer cells are exposed to the microenvironment of relatively low nutrients, oxygen (hypoxia) and pH, which lead to further ROS generation [164]. Thus, the mROS level is frequently increased in cancer cells, compared to normal cells [165]. In addition, treatment of chemotherapeutic agents or radiation induces mROS generation in cancer cells [166]. It is undoubted that autophagy is one of the defence mechanisms against oxidative stress. However, the autophagy regulated by mROS has distinctive beneficial and detrimental functions in cancer biology [167,168].

First, it is considered to have a tumour-suppressive effect during tumour initiation and malignancy progression, which contributes to removing damaged organelles and cells, thereby preventing cell proliferation and genomic instability [169]. Mutant p53 blocks the autophagic process by transcriptional inhibition of Sestrin1 and Sestrin2, which are activators of AMPK [170]. Likewise, mTOR as a nutrient sensor is involved in suppression of autophagy and promotion of proliferation in cancer cells, which is activated by glucose, amino acid, nucleotide, fatty acid, lipid, growth factors and hypoxia [171]. One of those, phosphatidic acid (PA), which is produced by catalysed hydrolysis of phosphatidylcholine via phospholipase D (PLD), can stimulate mTORC1 activation, thereby inhibiting AMPK in cancer cells [172,173]. Thus, controlling of PLD could be important to the efficacy of chemotherapeutic agents via facilitating autophagic pathways. Depletion of Beclin1 is frequently detected in various human cancers such as breast, prostate and ovarian cancers [174–176]. The loss of Beclin1 weakens autophagy induction, enhancing cancer cell proliferation. The attenuation of UVRAG or Bif1 also increases cancer cell proliferation via the impairment of autophagosome formation [177]. Epidermal growth factor receptor (EGFR) impedes autophagy by interacting with Beclin1, while the administration of the cetuximab drug inhibits EGFR via suppression of micro RNA 216b (miR-216b), which can prevent Beclin1 translation [178].

In contrast, autophagy plays roles in tumour progression, participating in the survival of cancer cells and the expression of oncogenes [179,180]. Although autophagy is inactivated during the initiation of tumorigenesis, it inclines to be restored tumour progression by allowing the cancer cells to achieve chemotherapeutic resistance [181,182]. Furthermore, autophagy enables cellular components to be recycled to supply metabolic substrates and removes damaged mitochondria in cancer cells [183,184]. Especially, transcription factor NRF2 is the major regulator of the antioxidant response in cancer cells [185]. The activation of NRF2 is associated to the poor prognosis of cancer patients by chemotherapeutic resistance via reducing the oxidative stress [185,186]. In cancer metabolism, NRF2 contributes to degradation of glutamine into glutamate, which provides cancer cells with nitrogen source to synthesize nucleotides and nonessential amino acids [186–188]. Furthermore, in response to oxidative stress, NRF2 induces autophagy via its noncanonical signalling pathway, transactivation of p62 gene, by which cancer cells avoid the apoptosis [142,143,189]. Activation of NRF2 undermines autophagy-targeted cancer therapy. Thus, a combination therapy to simultaneously targeting autophagy and NRF2 could be a good strategy in cancer treatment.

Cancer stem cells (CSCc) are a subtype of cancer cells, which have the abilities of self-renewal, and are directly associated with tumour initiation, chemoresistance, and metastasis [190]. Autophagy (mitophagy) is also closely involved in cancer stem cell survival via redox balance [191]. Autophagy is required for CD44⁺/CD24^{low} phenotype in breast CSCs, which is attenuated by LC3 or ATG12 knockdown or chloroquine treatment [192]. Autophagy has critical roles in transforming pancreatic cancer cells into CD133⁺ CSC-like cells under hypoxia [193]. Similarly, autophagy proteins, such as Beclin 1, ATG5 and ATG7, are increased in liver CSC CD133⁺ cells under hypoxic condition [194].

4.2. Diabetes

Diabetes mellitus, especially type 2 diabetes mellitus (T2DM), is one of the most common metabolic diseases, which is primarily involved in hyperglycaemia mitochondrial dysfunction, insulin resistance, lipid accumulation and abnormal regulation of autophagy [195–198]. ROS and oxidative stress are closely associated with the onset of diabetes and the development of complications [199].

Hyperglycaemia stimulates diacylglycerol (DAG)-protein kinase C-(PKC)-NADPH oxidase (NOXs) axis to accumulate ROS, which has been suggested to cause the progression of diabetes [200]. However, mitochondria have also been postulated as the main source of ROS in diabetes at the point that glucose is the main source of energy to operate the ETC during OXPHOS [14,201]. Furthermore, antioxidant enzymes are altered in two diabetic patients [202] with increased oxidative stress levels [203, 204]. Autophagy (mitophagy) has cellular protective roles against the development of insulin resistance and increase in adiposity via alleviating mROS-induced oxidative stress [205].

Autophagy is repressed by chronic hyperglycaemia and subsequent insulin resistance. Pancreatic β cell line, Ins-1 cells exhibit apoptotic cell death via autophagy impairment by treatment of cathepsin inhibitors under high glucose conditions [206]. Autophagy is closely involved in the cellular architecture and function: Atg7 genetic ablation in pancreatic β cells causes islet degeneration and impairs insulin secretion, and Atg7 mutant mice exhibit glucose tolerance impairment and hypoinsulinaemia [207]. Moreover, autophagy is inhibited in streptozotocin-induced diabetic mice under high glucose conditions [208]. In diabetic hearts, autophagy is downregulated via inactivation of AMPK and subsequent JNK1-Bcl2, which fails to inhibit mTORC1 [209,210]. Downregulation of autophagic proteins has been observed in skeletal muscle from insulin resistance T2DM patients [211]. In adipose tissue, autophagy is also increased via attenuated mTORC1 activity [212]. In the liver, autophagy is inhibited in the presence of insulin resistance and hyperinsulinemia [213]. Although autophagy evidently has a beneficial role in insulin resistance and T2DM, the exact underlying mechanism of T2DM still remains to be elucidated.

Autophagy is also implicated in lipotoxic conditions. Cholesterol-induced ER stress exhibits increased autophagic flux in pancreatic β cells, facilitating LC3B-I conversion to LC3B-II. Cholesterol-induced autophagy was attenuated by treatment of chemical chaperone 4-phenylbutyrate (4-PBA) [214]. ER-stress induced autophagy can be regulated in mTORC1 independent [215]. In addition, glucolipotoxicity induces autophagy via TFEB in primary pancreatic β cells [216].

4.3. Neurodegeneration

Neurodegenerative diseases are closely associated with certain protein aggregates and abnormal autophagic process. Thus, autophagy plays important roles in the neurodegenerative pathology and therapeutics [217,218]. Autophagy is related to the maintenance and integrity of neuronal cells for the postmitotic nature of neurons [115,219]. It also reduces oxidative stress by removing unnecessary or damaged organelles and abnormal protein aggregates in injured neurons, which is helpful for cell survival [220]. Emerging roles of autophagy have been proposed involving antioxidant defence mechanisms for neuronal homeostasis [221]. Excessive oxidative stress-induced autophagy impairment has been proven to be implicated in the development of neurodegenerative diseases and their aggravation [222,223].

Alzheimer's disease (AD) is one of the most common types of dementia; it is characterized by extracellular amyloid β ($A\beta$) plaques and intracellular tau (τ) protein tangles. $A\beta$ is generated by the enzymatic cleavage of the amyloid precursor protein (APP) [224]. Oxidative stress is prominent in the pathogenesis of AD, related to the formation of $A\beta$ plaque, phosphorylation of τ protein and the formation of neurofibrillary tangles [225]. Autophagy participates in the degradation of $A\beta$ [226]. The accumulation of $A\beta$ results in an impaired fusion of autophagosomes with lysosomes [227]. Autophagy is involved in $A\beta$ secretion into the extracellular space where it forms plaques. The deletion of ATG7 in APP transgenic mice results in downregulated $A\beta$ secretion and plaque formation [228]. A mutation in Presenilin1 (PSEN1), which is involved in APP cleavage, illustrates one of the major characteristics of AD [229,230], and results in the impairment of lysosome function and the accumulation of $A\beta$ [231]. PSEN1 also functions as an ER chaperone for the V0a1 subunit of lysosomal v-ATPase, of which the mutation impairs lysosomal v-ATPase maturation, and thus increases lysosomal pH [232]. Accumulation of τ protein into intracellular tangles is also a hallmark pathology of AD. Hyperphosphorylated τ protein co-localises with LC3B-II and p62 in

patients with AD, as well as other neuronal disorders such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [233]. Moreover, aberrant τ proteins disrupt axonal vesicle transport via the inhibition of complex, thereby increasing the number of autophagosomes in AD [234]. Furthermore, chronic or environmental stress, and increased glucocorticoid levels can induce AD and other pathologies [235,236]. Elevation of glucocorticoid levels could facilitate the formation of A β plaque and phosphorylation of τ protein [235,237], which is mediated by mTOR-dependent inhibition of autophagy [238,239]. It is either associated with glucocorticoid-induced oxidative stress [240]. Recently, it has been reported that autophagy flux and stress granules could be monitored by RNA binding proteins (RBPs) such as T-cell intracellular antigen 1 (TIA-1), poly(A)-binding protein (PABP), Ras GTPase-activating protein-binding protein 1 (G3BP1), fused in sarcoma (FUS), and DEAD box 5 (DDX5) [241]. The level of these proteins is elevated in chronic stress and glucocorticoid responses. In addition, these RBPs are seemed to be related to oxidative stress responses and might be therapeutic targets for prevention of stress granule formation in AD and other τ pathologies.

As a movement disorder, Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra [242], which is pathologically related to oxidative stress, mitochondrial dysfunction and protein aggregation [243]. In PD, the autophagy pathway is impaired, leading to the accumulation of abnormal proteins [217]. Several genes are related to the initial pathology of PD, including PINK1, Parkin, α -synuclein and glucocerebrosidase (GBA) [244]. Autosomal recessive PD is associated with mutations in PINK1 and Parkin [245,246], which impair the degradation of damaged mitochondria via mitophagic activation [247]. Genetic ablation of Pink1 resulted in impairment of striatal mitochondria respiration and vulnerability to oxidative stress in the neuronal cells [248]. Similarly, deletion of parkin causes the dysfunctions of striatal mitochondria and synaptic plasticity [249,250]. PD is also characterised by intracytoplasmic bodies (Lewy bodies) that exist in the neuronal nucleus, which consist of an insoluble protein aggregate of α -synuclein that is degraded by CMA [251]. However, mutant α -synuclein has a high affinity with LAMP-2A, which impedes lysosomal uptake of the substrates, thus preventing CMA-dependent degradation [252]. Independent of the protein inclusions, an increased α -synuclein level impairs autophagy, which leads to the mislocalisation of ATG9 [253]. Moreover, GBA is one of the genetic risk factors of PD, of which homozygotic mutations cause the lysosomal disorder Gaucher disease [254]. A loss of GBA induces the accumulation of its substrate glucosylceramide within lysosomes, leading to autophagy impairment by lysosomal dysfunction [226].

Huntington's disease (HD) is a neuronal disorder caused by mutant proteins with expanded glutamine repeats (polyQ) [255]. HD pathogenesis is strongly affected by neuronal autophagy dysfunction. Huntingtin (HTT) is the most studied polyQ protein, of which the mutation is observed in HD; it impairs cargo recognition by autophagosomes [256]. The wild type of HTT serves as a scaffold protein involved in recruiting several autophagy proteins to autophagosome in the selective autophagic process [257,258]. A loss of huntingtin decreases autophagosome transport and subsequently leads to the degradation of substrates [259]. Mutant HTT also inhibits a striatum specific protein, Rhes, which interacts with Beclin1 to process autophagy [260].

4.4. Cardiovascular Diseases

Autophagy at basal levels is necessary to maintain cellular homeostasis in cardiomyocytes [261]. The cardiomyocytes depend on the elimination of damaged proteins and dysfunctional organelles for their maintenance and survival [262,263]. In particular, cardiomyocytes are highly enriched in mitochondria; once damaged or exhausted, these organelles are rapidly removed by autophagy (mitophagy) degradation. Impairment of the degradation pathway induces high levels of mROS accumulation, leading to accumulation of protein aggregates, dysfunctional mitochondria and pathological cardiac remodelling [263,264]. Autophagy is associated with the development and progression of diverse cardiovascular diseases such as atrial fibrillation, cardiac hypertrophy, heart failure and ischemic/reperfusion (I/R) [197].

Danon disease (or glycogen storage disease Type IIb) is an X-linked lysosomal and glycogen storage disorder, which is associated with cardiac hypertrophy. In Danon disease, LAMP-2, which is required for autophagosome-lysosome fusion, is genetically deficient [265–267]. In transverse aortic constriction (TAC) models, myocardial deletion of Atg5 provokes cardiac hypertrophy, left ventricular dilatation and contractile dysfunction [268]. Moreover, Beclin 1 knockdown inhibits autophagosomal formation, and thus increased cell death in an I/R mouse model [269]. In chronic ischemia, autophagy and mitophagy are required for cardiomyocyte survival, evading tissue damages [270]. Vacuolar ATPase assembly of the integral membrane protein VMA21, a chaperone of V-ATPase, facilitates the proton pump and acidifies the organelles, of which mutation elevates lysosomal pH, thereby interrupting the autophagolysosomal degradation in X-linked myopathy with excessive autophagy [271]. The role of small RNAs has also been investigated in cardiovascular diseases related to autophagy. miR-199a induces cardiac hypertrophy by attenuating the autophagy via activation of mTOR, of which the overexpression results in the accumulation of p62 and inhibition of LC3B-II lipidation [272].

On the contrary, autophagy might play detrimental roles in the cardiovascular disease. Beclin1 haploinsufficient dampens cardiac pathological remodelling, counteracting TAC-induced overload stress. Conversely, cardiomyocyte-specific Beclin1 overexpression magnified the pathological remodelling response [273]. Moreover, inhibition of Beclin1 by cardiac peptide urocortin attenuates cardiomyocyte cell death by excessive autophagic induction in I/R injury [274].

4.5. Immunity

Autophagy has important roles in immunity, which consequently influences inflammatory pathogenesis [12]. Autophagy eliminates invading pathogens via a selective pathway xenophagy in response to various types of infections [275]. The adapter proteins such as NDP52, optineurin and p62 are involved in xenophagy, which bind to the ubiquitinated proteins and further guide the autophagic proteins [276]. It is connected to various aspects of adaptive and innate immunities, including antigen presentation, cytokine and interferon production, and lymphocyte development [276].

Microbial infection activates the host immune system, in which autophagy can serve as a part of innate immunity, thereby eliminating the invading pathogens [12]. Inflammasomes are a cytosolic protein complex formed in response to the invading pathogens, which leads to processing and subsequent release of IL-1 α , IL-1 β , and IL-18. The inflammasome comprises an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), the pro-Caspase1, and proteins for sensing microbial products including the nucleotide oligomerization domain (NOD)-like receptor (NLR) family of proteins, which includes NLRP1, NLRP3 and NLRC4 [277]. mROS and lysosomal damage can induce inflammasome activation, which is inhibited by clearance of the damaged organelles via autophagy [277].

The anti-microbial role of autophagy is also controlled by Type 1 helper T cell (Th1)/Th2 polarization. The Th1 cytokines provoke autophagy, while Th2 cytokines prevent it [278]. The pathogen-associated molecular patterns (PAMPS) on the surfaces of microbial pathogens activate autophagy via sensing by toll-like receptors (TLRs), by which the invading pathogens are destroyed [276].

Crohn's disease is a type of inflammatory bowel disease (IBD), which is closely related to dysregulation of autophagy [279]. It is characterised by a single nucleotide polymorphism (SNP) in *ULK1*. Thus, the autophagic process is impaired during the disease. The mutations in the leucine-rich domain of nucleotide oligomerizing domain-containing protein2 (*NOD2*) are also associated with Crohn's disease. *NOD2* recruits ATG16L in the plasma membrane during bacterial invasion. The mutation in *NOD2* persist the inflammation via impairment of autophagy induction and antigen presentation [280,281]. The SNP in Atg161L also attenuates autophagosomal formation in the disease [282,283]. An autophagy-related protein, microtubule-associated protein 1S (MAP1S), interacts with LC3B, and is involved in autophagosomal formation, which enhances the survival of intestinal epithelial cells via Wnt/ β -catenin signalling in Crohn's disease [284].

5. Concluding Remarks

In the current review, we have provided an overview of the general functions of mROS in autophagy and further introduced the pathological context. mROS are inevitably generated as the by-products of bioenergetics, which in turn forms part of the cellular nature. Further, they are directly or indirectly responsible as messengers for various cellular signalling pathways. Autophagy is a vital integrated biological process for cellular and organismic homeostasis. It allows spatial reorganisation and energy supply to cells via the orderly degradation machinery of unnecessary or dysfunctional components. Mounting evidence indicates that mROS represent the upstream modulators of autophagy. Thus, the interplay between mROS and autophagy is highly important to cellular homeostasis and survival. Autophagy basically has beneficial effects on mROS, which sense oxidative stress, and thus eliminate damaged or expired cellular constituents.

In pathology, a number of studies have also revealed the cross-talk between redox signalling and autophagy in the progression of diverse diseases. Excessive ROS production incurs the accumulation of oxidative stress, which is certainly implicated in chronic pathologies such as metabolic, neurodegenerative, cardiovascular, and immune diseases as well as cancers. Impairment or dysregulation of autophagic process causes mitochondrial dysfunction, thereby increasing mROS production. Of a certainty, autophagy has been inclined to decrease oxidative stress. In this aspect, autophagy restoration might be a therapeutic strategy for oxidative stress-related diseases. However, according to the cellular or tissue environments, autophagy rather exacerbates the diseases in response to mROS generation.

In summary, mROS-induced autophagy could be either a cellular protective mechanism that alleviates oxidative stress, or a destructive process. Therefore, it remains to further dissect the regulatory mechanisms of autophagy in redox signalling of diverse cellular physiologies and pathologies. Appropriate adjustment of autophagy would be crucial for the development of future therapeutic strategies for chronic pathologies responding to oxidative stress, based on the pharmacological modulation.

Author Contributions: H.R.Y., Y.H.J., J.K., Y.S. wrote and revised the manuscript. T.G.C. and S.S.K. conceptualized and supervised the study and wrote the manuscript. All authors revised and approved the final version of the manuscript.

Funding: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MEST) (NRF-2018R1A6A1A03025124 to SSK, and NRF-2013R1A1A2061214 and NRF-2018R1D1A1B07048909 to TGC).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. De Duve, C. The lysosome. *Sci. Am.* **1963**, *208*, 64–72. [[CrossRef](#)] [[PubMed](#)]
2. Dikic, I.; Elazar, Z. Mechanism and medical implications of mammalian autophagy. *Nat. Rev. Mol. Cell Biol.* **2018**, *19*, 349–364. [[CrossRef](#)] [[PubMed](#)]
3. Galluzzi, L.; Baehrecke, E.H.; Ballabio, A.; Boya, P.; Bravo-San Pedro, J.M.; Cecconi, F.; Choi, A.M.; Chu, C.T.; Codogno, P.; Colombo, M.I.; et al. Molecular definitions of autophagy and related processes. *EMBO J.* **2017**, *36*, 1811–1836. [[CrossRef](#)] [[PubMed](#)]
4. Levine, B.; Klionsky, D.J. Development by self-digestion: Molecular mechanisms and biological functions of autophagy. *Dev. Cell* **2004**, *6*, 463–477. [[CrossRef](#)]
5. Boya, P.; Codogno, P.; Rodriguez-Muela, N. Autophagy in stem cells: Repair, remodelling and metabolic reprogramming. *Development* **2018**, *145*, dev146506. [[CrossRef](#)] [[PubMed](#)]
6. Sridhar, S.; Botbol, Y.; Macian, F.; Cuervo, A.M. Autophagy and disease: Always two sides to a problem. *J. Pathol.* **2012**, *226*, 255–273. [[CrossRef](#)]
7. Wible, D.J.; Bratton, S.B. Reciprocity in ROS and autophagic signaling. *Curr. Opin. Toxicol.* **2018**, *7*, 28–36. [[CrossRef](#)]
8. Bhattacharya, D.; Mukhopadhyay, M.; Bhattacharyya, M.; Karmakar, P. Is autophagy associated with diabetes mellitus and its complications? A review. *EXCLI J.* **2018**, *17*, 709–720.

9. Santana-Codina, N.; Mancias, J.D.; Kimmelman, A.C. The Role of Autophagy in Cancer. *Annu. Rev. Cancer Biol.* **2017**, *1*, 19–39. [[CrossRef](#)]
10. Hochfeld, W.E.; Lee, S.; Rubinsztein, D.C. Therapeutic induction of autophagy to modulate neurodegenerative disease progression. *Acta Pharmacol. Sin.* **2013**, *34*, 600–604. [[CrossRef](#)]
11. Fujikake, N.; Shin, M.; Shimizu, S. Association Between Autophagy and Neurodegenerative Diseases. *Front. Neurosci.* **2018**, *12*, 255. [[CrossRef](#)] [[PubMed](#)]
12. Deretic, V.; Saitoh, T.; Akira, S. Autophagy in infection, inflammation and immunity. *Nat. Rev. Immunol.* **2013**, *13*, 722–737. [[CrossRef](#)] [[PubMed](#)]
13. Leidal, A.M.; Levine, B.; Debnath, J. Autophagy and the cell biology of age-related disease. *Nat. Cell Biol.* **2018**, *20*, 1338–1348. [[CrossRef](#)] [[PubMed](#)]
14. Balaban, R.S.; Nemoto, S.; Finkel, T. Mitochondria, oxidants, and aging. *Cell* **2005**, *120*, 483–495. [[CrossRef](#)] [[PubMed](#)]
15. Brand, M.D. Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling. *Free Radic. Biol. Med.* **2016**, *100*, 14–31. [[CrossRef](#)]
16. Thannickal, V.J.; Fanburg, B.L. Reactive oxygen species in cell signaling. *Am. J. Physiol Lung Cell Mol. Physiol.* **2000**, *279*, L1005–L1028. [[CrossRef](#)]
17. Li, X.; Fang, P.; Mai, J.; Choi, E.T.; Wang, H.; Yang, X.F. Targeting mitochondrial reactive oxygen species as novel therapy for inflammatory diseases and cancers. *J. Hematol. Oncol.* **2013**, *6*, 19. [[CrossRef](#)]
18. Radi, R. Oxygen radicals, nitric oxide, and peroxynitrite: Redox pathways in molecular medicine. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 5839–5848. [[CrossRef](#)]
19. Finkel, T. Signal transduction by reactive oxygen species. *J. Cell Biol.* **2011**, *194*, 7–15. [[CrossRef](#)]
20. Chandel, N.S. Mitochondrial regulation of oxygen sensing. *Adv. Exp. Med. Biol.* **2010**, *661*, 339–354.
21. Antico Arciuch, V.G.; Elguero, M.E.; Poderoso, J.J.; Carreras, M.C. Mitochondrial regulation of cell cycle and proliferation. *Antioxid Redox Signal.* **2012**, *16*, 1150–1180. [[CrossRef](#)] [[PubMed](#)]
22. Rambold, A.S.; Pearce, E.L. Mitochondrial Dynamics at the Interface of Immune Cell Metabolism and Function. *Trends Immunol.* **2018**, *39*, 6–18. [[CrossRef](#)] [[PubMed](#)]
23. Gunter, T.E.; Yule, D.I.; Gunter, K.K.; Eliseev, R.A.; Salter, J.D. Calcium and mitochondria. *FEBS Lett.* **2004**, *567*, 96–102. [[CrossRef](#)] [[PubMed](#)]
24. Nikolettou, V.; Markaki, M.; Palikaras, K.; Tavernarakis, N. Crosstalk between apoptosis, necrosis and autophagy. *Biochim. Biophys. Acta* **2013**, *1833*, 3448–3459. [[CrossRef](#)] [[PubMed](#)]
25. Kamer, K.J.; Mootha, V.K. The molecular era of the mitochondrial calcium uniporter. *Nat. Rev. Mol. Cell Biol.* **2015**, *16*, 545–553. [[CrossRef](#)]
26. Bhatti, J.S.; Bhatti, G.K.; Reddy, P.H. Mitochondrial dysfunction and oxidative stress in metabolic disorders—A step towards mitochondria based therapeutic strategies. *Biochim. Biophys. Acta Mol. Basis Dis.* **2017**, *1863*, 1066–1077. [[CrossRef](#)]
27. Szumiel, I. Autophagy, reactive oxygen species and the fate of mammalian cells. *Free Radic. Res.* **2011**, *45*, 253–265. [[CrossRef](#)]
28. Petibone, D.M.; Majeed, W.; Casciano, D.A. Autophagy function and its relationship to pathology, clinical applications, drug metabolism and toxicity. *J. Appl. Toxicol.* **2017**, *37*, 23–37. [[CrossRef](#)]
29. Stolz, A.; Ernst, A.; Dikic, I. Cargo recognition and trafficking in selective autophagy. *Nat. Cell Biol.* **2014**, *16*, 495–501. [[CrossRef](#)]
30. Carlsson, S.R.; Simonsen, A. Membrane dynamics in autophagosome biogenesis. *J. Cell Sci.* **2015**, *128*, 193–205. [[CrossRef](#)]
31. Parzych, K.R.; Klionsky, D.J. An overview of autophagy: Morphology, mechanism, and regulation. *Antioxid Redox Signal.* **2014**, *20*, 460–473. [[CrossRef](#)] [[PubMed](#)]
32. Oku, M.; Sakai, Y. Three Distinct Types of Micro-autophagy Based on Membrane Dynamics and Molecular Machineries. *Bioessays* **2018**, *40*, e1800008. [[CrossRef](#)] [[PubMed](#)]
33. Sahu, R.; Kaushik, S.; Clement, C.C.; Cannizzo, E.S.; Scharf, B.; Follenzi, A.; Potolicchio, I.; Nieves, E.; Cuervo, A.M.; Santambrogio, L. Micro-autophagy of cytosolic proteins by late endosomes. *Dev. Cell* **2011**, *20*, 131–139. [[CrossRef](#)] [[PubMed](#)]
34. Patel, B.; Cuervo, A.M. Methods to study chaperone-mediated autophagy. *Methods* **2015**, *75*, 133–140. [[CrossRef](#)] [[PubMed](#)]

35. Kaushik, S.; Cuervo, A.M. Chaperone-mediated autophagy: A unique way to enter the lysosome world. *Trends Cell Biol.* **2012**, *22*, 407–417. [[CrossRef](#)]
36. Khandia, R.; Dadar, M.; Munjal, A.; Dhama, K.; Karthik, K.; Tiwari, R.; Yattoo, M.I.; Iqbal, H.M.N.; Singh, K.P.; Joshi, S.K.; et al. A Comprehensive Review of Autophagy and Its Various Roles in Infectious, Non-Infectious, and Lifestyle Diseases: Current Knowledge and Prospects for Disease Prevention, Novel Drug Design, and Therapy. *Cells* **2019**, *8*, 674. [[CrossRef](#)] [[PubMed](#)]
37. Itakura, E.; Mizushima, N. Characterization of autophagosome formation site by a hierarchical analysis of mammalian Atg proteins. *Autophagy* **2010**, *6*, 764–776. [[CrossRef](#)]
38. Rabanal-Ruiz, Y.; Otten, E.G.; Korolchuk, V.I. mTORC1 as the main gateway to autophagy. *Essays Biochem.* **2017**, *61*, 565–584.
39. Ravanan, P.; Srikumar, I.F.; Talwar, P. Autophagy: The spotlight for cellular stress responses. *Life Sci.* **2017**, *188*, 53–67. [[CrossRef](#)]
40. Laplante, M.; Sabatini, D.M. mTOR signaling in growth control and disease. *Cell* **2012**, *149*, 274–293. [[CrossRef](#)]
41. Ma, X.M.; Blenis, J. Molecular mechanisms of mTOR-mediated translational control. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 307–318. [[CrossRef](#)] [[PubMed](#)]
42. Glick, D.; Barth, S.; Macleod, K.F. Autophagy: Cellular and molecular mechanisms. *J. Pathol.* **2010**, *221*, 3–12. [[CrossRef](#)] [[PubMed](#)]
43. Hung, C.M.; Garcia-Haro, L.; Sparks, C.A.; Guertin, D.A. mTOR-dependent cell survival mechanisms. *Cold Spring Harb Perspect Biol* **2012**, *4*, a008771. [[CrossRef](#)] [[PubMed](#)]
44. Papinski, D.; Kraft, C. Regulation of Autophagy By Signaling Through the Atg1/ULK1 Complex. *J. Mol. Biol.* **2016**, *428*, 1725–1741. [[CrossRef](#)]
45. Hosokawa, N.; Sasaki, T.; Iemura, S.; Natsume, T.; Hara, T.; Mizushima, N. Atg101, a novel mammalian autophagy protein interacting with Atg13. *Autophagy* **2009**, *5*, 973–979. [[CrossRef](#)]
46. Gwinn, D.M.; Shackelford, D.B.; Egan, D.F.; Mihaylova, M.M.; Mery, A.; Vasquez, D.S.; Turk, B.E.; Shaw, R.J. AMPK phosphorylation of raptor mediates a metabolic checkpoint. *Mol. Cell* **2008**, *30*, 214–226. [[CrossRef](#)]
47. Alers, S.; Loffler, A.S.; Wesselborg, S.; Stork, B. Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: Cross talk, shortcuts, and feedbacks. *Mol. Cell Biol.* **2012**, *32*, 2–11. [[CrossRef](#)]
48. Hurley, J.H.; Young, L.N. Mechanisms of Autophagy Initiation. *Annu Rev. Biochem.* **2017**, *86*, 225–244. [[CrossRef](#)]
49. Lamb, C.A.; Yoshimori, T.; Tooze, S.A. The autophagosome: Origins unknown, biogenesis complex. *Nat. Rev. Mol. Cell Biol.* **2013**, *14*, 759–774. [[CrossRef](#)]
50. Bento, C.F.; Renna, M.; Ghislat, G.; Puri, C.; Ashkenazi, A.; Vicinanza, M.; Menzies, F.M.; Rubinsztein, D.C. Mammalian Autophagy: How Does It Work? *Annu Rev. Biochem.* **2016**, *85*, 685–713. [[CrossRef](#)]
51. Axe, E.L.; Walker, S.A.; Manifava, M.; Chandra, P.; Roderick, H.L.; Habermann, A.; Griffiths, G.; Ktistakis, N.T. Autophagosome formation from membrane compartments enriched in phosphatidylinositol 3-phosphate and dynamically connected to the endoplasmic reticulum. *J. Cell Biol.* **2008**, *182*, 685–701. [[CrossRef](#)] [[PubMed](#)]
52. Biazik, J.; Yla-Anttila, P.; Vihinen, H.; Jokitalo, E.; Eskelinen, E.L. Ultrastructural relationship of the phagophore with surrounding organelles. *Autophagy* **2015**, *11*, 439–451. [[CrossRef](#)] [[PubMed](#)]
53. Sun, Q.; Fan, W.; Chen, K.; Ding, X.; Chen, S.; Zhong, Q. Identification of Barkor as a mammalian autophagy-specific factor for Beclin 1 and class III phosphatidylinositol 3-kinase. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 19211–19216. [[CrossRef](#)] [[PubMed](#)]
54. Di Bartolomeo, S.; Corazzari, M.; Nazio, F.; Oliverio, S.; Lisi, G.; Antonioli, M.; Pagliarini, V.; Matteoni, S.; Fuoco, C.; Giunta, L.; et al. The dynamic interaction of AMBRA1 with the dynein motor complex regulates mammalian autophagy. *J. Cell Biol.* **2010**, *191*, 155–168. [[CrossRef](#)] [[PubMed](#)]
55. Russell, R.C.; Tian, Y.; Yuan, H.; Park, H.W.; Chang, Y.Y.; Kim, J.; Kim, H.; Neufeld, T.P.; Dillin, A.; Guan, K.L. ULK1 induces autophagy by phosphorylating Beclin-1 and activating VPS34 lipid kinase. *Nat. Cell Biol.* **2013**, *15*, 741–750. [[CrossRef](#)]
56. Mercer, T.J.; Gubas, A.; Tooze, S.A. A molecular perspective of mammalian autophagosome biogenesis. *J. Biol. Chem.* **2018**, *293*, 5386–5395. [[CrossRef](#)] [[PubMed](#)]

57. Simonsen, A.; Birkeland, H.C.; Gillooly, D.J.; Mizushima, N.; Kuma, A.; Yoshimori, T.; Slagsvold, T.; Brech, A.; Stenmark, H. Alfy, a novel FYVE-domain-containing protein associated with protein granules and autophagic membranes. *J. Cell Sci.* **2004**, *117*, 4239–4251. [[CrossRef](#)]
58. Matsunaga, K.; Morita, E.; Saitoh, T.; Akira, S.; Ktistakis, N.T.; Izumi, T.; Noda, T.; Yoshimori, T. Autophagy requires endoplasmic reticulum targeting of the PI3-kinase complex via Atg14L. *J. Cell Biol.* **2010**, *190*, 511–521. [[CrossRef](#)]
59. Hamasaki, M.; Furuta, N.; Matsuda, A.; Nezu, A.; Yamamoto, A.; Fujita, N.; Oomori, H.; Noda, T.; Haraguchi, T.; Hiraoka, Y.; et al. Autophagosomes form at ER-mitochondria contact sites. *Nature* **2013**, *495*, 389–393. [[CrossRef](#)]
60. Proikas-Cezanne, T.; Waddell, S.; Gaugel, A.; Frickey, T.; Lupas, A.; Nordheim, A. WIPI-1alpha (WIPI49), a member of the novel 7-bladed WIPI protein family, is aberrantly expressed in human cancer and is linked to starvation-induced autophagy. *Oncogene* **2004**, *23*, 9314–9325. [[CrossRef](#)]
61. Polson, H.E.; De Lartigue, J.; Rigden, D.J.; Reedijk, M.; Urbe, S.; Clague, M.J.; Tooze, S.A. Mammalian Atg18 (WIPI2) localizes to omegasome-anchored phagophores and positively regulates LC3 lipidation. *Autophagy* **2010**, *6*, 506–522. [[CrossRef](#)] [[PubMed](#)]
62. Ravikumar, B.; Sarkar, S.; Davies, J.E.; Futter, M.; Garcia-Arencibia, M.; Green-Thompson, Z.W.; Jimenez-Sanchez, M.; Korolchuk, V.I.; Lichtenberg, M.; Luo, S.; et al. Regulation of mammalian autophagy in physiology and pathophysiology. *Physiol. Rev.* **2010**, *90*, 1383–1435. [[CrossRef](#)] [[PubMed](#)]
63. Mizushima, N. Autophagy: Process and function. *Genes Dev.* **2007**, *21*, 2861–2873. [[CrossRef](#)]
64. Kirkin, V.; McEwan, D.G.; Novak, I.; Dikic, I. A role for ubiquitin in selective autophagy. *Mol. Cell* **2009**, *34*, 259–269. [[CrossRef](#)] [[PubMed](#)]
65. Nakatogawa, H. Two ubiquitin-like conjugation systems that mediate membrane formation during autophagy. *Essays Biochem.* **2013**, *55*, 39–50. [[PubMed](#)]
66. Dooley, H.C.; Razi, M.; Polson, H.E.; Girardin, S.E.; Wilson, M.I.; Tooze, S.A. WIPI2 links LC3 conjugation with PI3P, autophagosome formation, and pathogen clearance by recruiting Atg12-5-16L1. *Mol. Cell* **2014**, *55*, 238–252. [[CrossRef](#)]
67. Otomo, C.; Metlagel, Z.; Takaesu, G.; Otomo, T. Structure of the human ATG12~ATG5 conjugate required for LC3 lipidation in autophagy. *Nat. Struct. Mol. Biol.* **2013**, *20*, 59–66. [[CrossRef](#)]
68. Chen, Y.; Klionsky, D.J. The regulation of autophagy - unanswered questions. *J. Cell Sci.* **2011**, *124*, 161–170. [[CrossRef](#)]
69. Kaur, J.; Debnath, J. Autophagy at the crossroads of catabolism and anabolism. *Nat. Rev. Mol. Cell Biol.* **2015**, *16*, 461–472. [[CrossRef](#)]
70. Hamasaki, M.; Shibutani, S.T.; Yoshimori, T. Up-to-date membrane biogenesis in the autophagosome formation. *Curr. Opin. Cell Biol.* **2013**, *25*, 455–460. [[CrossRef](#)]
71. Mizushima, N.; Yoshimori, T.; Ohsumi, Y. The role of Atg proteins in autophagosome formation. *Annu Rev. Cell Dev. Biol.* **2011**, *27*, 107–132. [[CrossRef](#)] [[PubMed](#)]
72. Fujita, N.; Hayashi-Nishino, M.; Fukumoto, H.; Omori, H.; Yamamoto, A.; Noda, T.; Yoshimori, T. An Atg4B mutant hampers the lipidation of LC3 paralogues and causes defects in autophagosome closure. *Mol. Biol. Cell* **2008**, *19*, 4651–4659. [[CrossRef](#)] [[PubMed](#)]
73. Tanida, I. Autophagy basics. *Microbiol. Immunol.* **2011**, *55*, 1–11. [[CrossRef](#)] [[PubMed](#)]
74. Satoo, K.; Noda, N.N.; Kumeta, H.; Fujioka, Y.; Mizushima, N.; Ohsumi, Y.; Inagaki, F. The structure of Atg4B-LC3 complex reveals the mechanism of LC3 processing and delipidation during autophagy. *EMBO J.* **2009**, *28*, 1341–1350. [[CrossRef](#)]
75. Tanida, I.; Ueno, T.; Kominami, E. LC3 and Autophagy. *Methods Mol. Biol.* **2008**, *445*, 77–88. [[PubMed](#)]
76. Szalai, P.; Hagen, L.K.; Saetre, F.; Luhr, M.; Sponheim, M.; Overbye, A.; Mills, I.G.; Seglen, P.O.; Engedal, N. Autophagic bulk sequestration of cytosolic cargo is independent of LC3, but requires GABARAPs. *Exp. Cell Res.* **2015**, *333*, 21–38. [[CrossRef](#)] [[PubMed](#)]
77. Feng, Y.; Klionsky, D.J. Autophagic membrane delivery through ATG9. *Cell Res.* **2017**, *27*, 161–162. [[CrossRef](#)]
78. Lamark, T.; Svenning, S.; Johansen, T. Regulation of selective autophagy: The p62/SQSTM1 paradigm. *Essays Biochem.* **2017**, *61*, 609–624.
79. Wong, Y.C.; Holzbaur, E.L. Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E4439–E4448. [[CrossRef](#)]

80. Wild, P.; Farhan, H.; McEwan, D.G.; Wagner, S.; Rogov, V.V.; Brady, N.R.; Richter, B.; Korac, J.; Waidmann, O.; Choudhary, C.; et al. Phosphorylation of the autophagy receptor optineurin restricts Salmonella growth. *Science* **2011**, *333*, 228–233. [[CrossRef](#)]
81. Viret, C.; Rozieres, A.; Faure, M. Novel Insights into NDP52 Autophagy Receptor Functioning. *Trends Cell Biol.* **2018**, *28*, 255–257. [[CrossRef](#)] [[PubMed](#)]
82. Kirkin, V.; Lamark, T.; Sou, Y.S.; Bjorkoy, G.; Nunn, J.L.; Bruun, J.A.; Shvets, E.; McEwan, D.G.; Clausen, T.H.; Wild, P.; et al. A role for NBR1 in autophagosomal degradation of ubiquitinated substrates. *Mol. Cell* **2009**, *33*, 505–516. [[CrossRef](#)] [[PubMed](#)]
83. Isakson, P.; Holland, P.; Simonsen, A. The role of ALFY in selective autophagy. *Cell Death Differ.* **2013**, *20*, 12–20. [[CrossRef](#)] [[PubMed](#)]
84. Kast, D.J.; Dominguez, R. The Cytoskeleton-Autophagy Connection. *Curr. Biol.* **2017**, *27*, R318–R326. [[CrossRef](#)]
85. Viret, C.; Faure, M. Regulation of Syntaxin 17 during Autophagosome Maturation. *Trends Cell Biol.* **2019**, *29*, 1–3. [[CrossRef](#)]
86. Fader, C.M.; Sanchez, D.G.; Mestre, M.B.; Colombo, M.I. TI-VAMP/VAMP7 and VAMP3/cellubrevin: Two v-SNARE proteins involved in specific steps of the autophagy/multivesicular body pathways. *Biochim. Et Biophys. Acta-Mol. Cell Res.* **2009**, *1793*, 1901–1916. [[CrossRef](#)]
87. Furuta, N.; Fujita, N.; Noda, T.; Yoshimori, T.; Amano, A. Combinational Soluble N-Ethylmaleimide-sensitive Factor Attachment Protein Receptor Proteins VAMP8 and Vti1b Mediate Fusion of Antimicrobial and Canonical Autophagosomes with Lysosomes. *Mol. Biol. Cell* **2010**, *21*, 1001–1010. [[CrossRef](#)]
88. Itakura, E.; Kishi-Itakura, C.; Mizushima, N. The Hairpin-type Tail-Anchored SNARE Syntaxin 17 Targets to Autophagosomes for Fusion with Endosomes/Lysosomes. *Cell* **2012**, *151*, 1256–1269. [[CrossRef](#)]
89. Diao, J.J.; Liu, R.; Rong, Y.G.; Zhao, M.L.; Zhang, J.; Lai, Y.; Zhou, Q.J.; Wilz, L.M.; Li, J.X.; Vivona, S.; et al. ATG14 promotes membrane tethering and fusion of autophagosomes to endolysosomes. *Nature* **2015**, *520*, 563–566. [[CrossRef](#)]
90. Munson, M.J.; Allen, G.F.; Toth, R.; Campbell, D.G.; Lucocq, J.M.; Ganley, I.G. mTOR activates the VPS34-UVRAG complex to regulate autolysosomal tubulation and cell survival. *EMBO J.* **2015**, *34*, 2272–2290. [[CrossRef](#)]
91. Mizushima, N.; Komatsu, M. Autophagy: Renovation of cells and tissues. *Cell* **2011**, *147*, 728–741. [[CrossRef](#)] [[PubMed](#)]
92. Boya, P.; Reggiori, F.; Codogno, P. Emerging regulation and functions of autophagy. *Nat. Cell Biol.* **2013**, *15*, 713–720. [[CrossRef](#)] [[PubMed](#)]
93. Zorov, D.B.; Juhaszova, M.; Sollott, S.J. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. *Physiol. Rev.* **2014**, *94*, 909–950. [[CrossRef](#)] [[PubMed](#)]
94. Starkov, A.A. The role of mitochondria in reactive oxygen species metabolism and signaling. *Ann. N. Y. Acad. Sci.* **2008**, *1147*, 37–52. [[CrossRef](#)]
95. Fukui, T.; Ushio-Fukai, M. Superoxide dismutases: Role in redox signaling, vascular function, and diseases. *Antioxid Redox Signal.* **2011**, *15*, 1583–1606. [[CrossRef](#)]
96. Winterbourn, C.C. Toxicity of iron and hydrogen peroxide: The Fenton reaction. *Toxicol. Lett.* **1995**, *82–83*, 969–974. [[CrossRef](#)]
97. Higdon, A.; Diers, A.R.; Oh, J.Y.; Landar, A.; Darley-Usmar, V.M. Cell signalling by reactive lipid species: New concepts and molecular mechanisms. *Biochem. J.* **2012**, *442*, 453–464. [[CrossRef](#)]
98. Kalogeris, T.; Bao, Y.; Korthuis, R.J. Mitochondrial reactive oxygen species: A double edged sword in ischemia/reperfusion vs preconditioning. *Redox Biol.* **2014**, *2*, 702–714. [[CrossRef](#)]
99. Cox, A.G.; Winterbourn, C.C.; Hampton, M.B. Mitochondrial peroxiredoxin involvement in antioxidant defence and redox signalling. *Biochem. J.* **2009**, *425*, 313–325. [[CrossRef](#)]
100. Andreyev, A.Y.; Kushnareva, Y.E.; Murphy, A.N.; Starkov, A.A. Mitochondrial ROS Metabolism: 10 Years Later. *Biochemistry (Mosc)* **2015**, *80*, 517–531. [[CrossRef](#)]
101. Liemburg-Apers, D.C.; Willems, P.H.; Koopman, W.J.; Grefte, S. Interactions between mitochondrial reactive oxygen species and cellular glucose metabolism. *Arch. Toxicol.* **2015**, *89*, 1209–1226. [[CrossRef](#)] [[PubMed](#)]
102. Birben, E.; Sahiner, U.M.; Sackesen, C.; Erzurum, S.; Kalayci, O. Oxidative stress and antioxidant defense. *World Allergy Organ. J.* **2012**, *5*, 9–19. [[CrossRef](#)] [[PubMed](#)]

103. Kirkman, H.N.; Rolfo, M.; Ferraris, A.M.; Gaetani, G.F. Mechanisms of protection of catalase by NADPH. Kinetics and stoichiometry. *J. Biol. Chem.* **1999**, *274*, 13908–13914. [[CrossRef](#)] [[PubMed](#)]
104. Filomeni, G.; Desideri, E.; Cardaci, S.; Rotilio, G.; Ciriolo, M.R. Under the ROS: Thiol network is the principal suspect for autophagy commitment. *Autophagy* **2010**, *6*, 999–1005. [[CrossRef](#)]
105. Bensaad, K.; Cheung, E.C.; Vousden, K.H. Modulation of intracellular ROS levels by TIGAR controls autophagy. *EMBO J.* **2009**, *28*, 3015–3026. [[CrossRef](#)]
106. Chen, Y.; Azad, M.B.; Gibson, S.B. Superoxide is the major reactive oxygen species regulating autophagy. *Cell Death Differ.* **2009**, *16*, 1040–1052. [[CrossRef](#)]
107. Scherz-Shouval, R.; Shvets, E.; Elazar, Z. Oxidation as a post-translational modification that regulates autophagy. *Autophagy* **2007**, *3*, 371–373. [[CrossRef](#)]
108. Mizushima, N.; Levine, B.; Cuervo, A.M.; Klionsky, D.J. Autophagy fights disease through cellular self-digestion. *Nature* **2008**, *451*, 1069–1075. [[CrossRef](#)]
109. Lee, J.; Giordano, S.; Zhang, J. Autophagy, mitochondria and oxidative stress: Cross-talk and redox signalling. *Biochem. J.* **2012**, *441*, 523–540. [[CrossRef](#)]
110. Levonen, A.L.; Hill, B.G.; Kansanen, E.; Zhang, J.; Darley-USmar, V.M. Redox regulation of antioxidants, autophagy, and the response to stress: Implications for electrophile therapeutics. *Free Radic. Biol. Med.* **2014**, *71*, 196–207. [[CrossRef](#)]
111. Scherz-Shouval, R.; Elazar, Z. Regulation of autophagy by ROS: Physiology and pathology. *Trends Biochem. Sci.* **2011**, *36*, 30–38. [[CrossRef](#)] [[PubMed](#)]
112. Sies, H. Hydrogen peroxide as a central redox signaling molecule in physiological oxidative stress: Oxidative eustress. *Redox Biol.* **2017**, *11*, 613–619. [[CrossRef](#)] [[PubMed](#)]
113. Lennicke, C.; Rahn, J.; Lichtenfels, R.; Wessjohann, L.A.; Seliger, B. Hydrogen peroxide - production, fate and role in redox signaling of tumor cells. *Cell Commun. Signal.* **2015**, *13*, 39. [[CrossRef](#)] [[PubMed](#)]
114. Filomeni, G.; De Zio, D.; Cecconi, F. Oxidative stress and autophagy: The clash between damage and metabolic needs. *Cell Death Differ.* **2015**, *22*, 377–388. [[CrossRef](#)]
115. Scherz-Shouval, R.; Shvets, E.; Fass, E.; Shorer, H.; Gil, L.; Elazar, Z. Reactive oxygen species are essential for autophagy and specifically regulate the activity of Atg4. *EMBO J.* **2007**, *26*, 1749–1760. [[CrossRef](#)]
116. Murphy, M.P. How mitochondria produce reactive oxygen species. *Biochem. J.* **2009**, *417*, 1–13. [[CrossRef](#)]
117. Zhang, H.; Kong, X.; Kang, J.; Su, J.; Li, Y.; Zhong, J.; Sun, L. Oxidative stress induces parallel autophagy and mitochondria dysfunction in human glioma U251 cells. *Toxicol. Sci.* **2009**, *110*, 376–388. [[CrossRef](#)]
118. Djavaheri-Mergny, M.; Amelotti, M.; Mathieu, J.; Besancon, F.; Bauvy, C.; Souquere, S.; Pierron, G.; Codogno, P. NF-kappaB activation represses tumor necrosis factor-alpha-induced autophagy. *J. Biol. Chem.* **2006**, *281*, 30373–30382. [[CrossRef](#)]
119. Djavaheri-Mergny, M.; Javelaud, D.; Wietzerbin, J.; Besancon, F. NF-kappaB activation prevents apoptotic oxidative stress via an increase of both thioredoxin and MnSOD levels in TNFalpha-treated Ewing sarcoma cells. *FEBS Lett.* **2004**, *578*, 111–115. [[CrossRef](#)]
120. Yuan, H.; Perry, C.N.; Huang, C.; Iwai-Kanai, E.; Carreira, R.S.; Glembotski, C.C.; Gottlieb, R.A. LPS-induced autophagy is mediated by oxidative signaling in cardiomyocytes and is associated with cytoprotection. *Am. J. Physiol Heart Circ. Physiol* **2009**, *296*, H470–H479. [[CrossRef](#)]
121. Li, L.; Chen, Y.; Gibson, S.B. Starvation-induced autophagy is regulated by mitochondrial reactive oxygen species leading to AMPK activation. *Cell Signal.* **2013**, *25*, 50–65. [[CrossRef](#)] [[PubMed](#)]
122. Meijer, A.J.; Codogno, P. Autophagy: Regulation by energy sensing. *Curr. Biol.* **2011**, *21*, R227–R229. [[CrossRef](#)] [[PubMed](#)]
123. Corona Velazquez, A.F.; Jackson, W.T. So Many Roads: The Multifaceted Regulation of Autophagy Induction. *Mol. Cell Biol.* **2018**, *38*. [[CrossRef](#)] [[PubMed](#)]
124. Puente, C.; Hendrickson, R.C.; Jiang, X. Nutrient-regulated Phosphorylation of ATG13 Inhibits Starvation-induced Autophagy. *J. Biol. Chem.* **2016**, *291*, 6026–6035. [[CrossRef](#)] [[PubMed](#)]
125. Cardaci, S.; Filomeni, G.; Ciriolo, M.R. Redox implications of AMPK-mediated signal transduction beyond energetic clues. *J. Cell Sci.* **2012**, *125*, 2115–2125. [[CrossRef](#)]
126. Poillet-Perez, L.; Despouy, G.; Delage-Mourroux, R.; Boyer-Guittaut, M. Interplay between ROS and autophagy in cancer cells, from tumor initiation to cancer therapy. *Redox Biol.* **2015**, *4*, 184–192. [[CrossRef](#)]

127. Zmijewski, J.W.; Banerjee, S.; Bae, H.; Friggeri, A.; Lazarowski, E.R.; Abraham, E. Exposure to hydrogen peroxide induces oxidation and activation of AMP-activated protein kinase. *J. Biol. Chem.* **2010**, *285*, 33154–33164. [[CrossRef](#)]
128. Guo, Z.; Kozlov, S.; Lavin, M.F.; Person, M.D.; Paull, T.T. ATM activation by oxidative stress. *Science* **2010**, *330*, 517–521. [[CrossRef](#)]
129. Alexander, A.; Cai, S.L.; Kim, J.; Nanez, A.; Sahin, M.; MacLean, K.H.; Inoki, K.; Guan, K.L.; Shen, J.; Person, M.D.; et al. ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 4153–4158. [[CrossRef](#)]
130. Tripathi, D.N.; Chowdhury, R.; Trudel, L.J.; Tee, A.R.; Slack, R.S.; Walker, C.L.; Wogan, G.N. Reactive nitrogen species regulate autophagy through ATM-AMPK-TSC2-mediated suppression of mTORC1. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, E2950–E2957. [[CrossRef](#)]
131. Knowles, R.G.; Moncada, S. Nitric oxide synthases in mammals. *Biochem. J.* **1994**, *298 Pt 2*, 249–258. [[CrossRef](#)]
132. Pattingre, S.; Tassa, A.; Qu, X.; Garuti, R.; Liang, X.H.; Mizushima, N.; Packer, M.; Schneider, M.D.; Levine, B. Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy. *Cell* **2005**, *122*, 927–939. [[CrossRef](#)] [[PubMed](#)]
133. Wei, Y.; Pattingre, S.; Sinha, S.; Bassik, M.; Levine, B. JNK1-mediated phosphorylation of Bcl-2 regulates starvation-induced autophagy. *Mol. Cell* **2008**, *30*, 678–688. [[CrossRef](#)] [[PubMed](#)]
134. Criollo, A.; Senovilla, L.; Authier, H.; Maiuri, M.C.; Morselli, E.; Vitale, I.; Kepp, O.; Tasdemir, E.; Galluzzi, L.; Shen, S.; et al. The IKK complex contributes to the induction of autophagy. *EMBO J.* **2010**, *29*, 619–631. [[CrossRef](#)] [[PubMed](#)]
135. Janjetovic, K.; Misirkic, M.; Vucicevic, L.; Harhaji, L.; Trajkovic, V. Synergistic antiglioma action of hyperthermia and nitric oxide. *Eur. J. Pharmacol.* **2008**, *583*, 1–10. [[CrossRef](#)]
136. Mungai, P.T.; Waypa, G.B.; Jairaman, A.; Prakriya, M.; Dokic, D.; Ball, M.K.; Schumacker, P.T. Hypoxia triggers AMPK activation through reactive oxygen species-mediated activation of calcium release-activated calcium channels. *Mol. Cell Biol.* **2011**, *31*, 3531–3545. [[CrossRef](#)]
137. Hoyer-Hansen, M.; Bastholm, L.; Szyniarowski, P.; Campanella, M.; Szabadkai, G.; Farkas, T.; Bianchi, K.; Fehrenbacher, N.; Elling, F.; Rizzuto, R.; et al. Control of macro-autophagy by calcium, calmodulin-dependent kinase kinase-beta, and Bcl-2. *Mol. Cell* **2007**, *25*, 193–205. [[CrossRef](#)]
138. Zhang, X.; Cheng, X.; Yu, L.; Yang, J.; Calvo, R.; Patnaik, S.; Hu, X.; Gao, Q.; Yang, M.; Lawas, M.; et al. MCOLN1 is a ROS sensor in lysosomes that regulates autophagy. *Nat. Commun.* **2016**, *7*, 12109. [[CrossRef](#)]
139. Itoh, K.; Chiba, T.; Takahashi, S.; Ishii, T.; Igarashi, K.; Katoh, Y.; Oyake, T.; Hayashi, N.; Satoh, K.; Hatayama, I.; et al. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. *Biochem. Biophys. Res. Commun.* **1997**, *236*, 313–322. [[CrossRef](#)]
140. Tonelli, C.; Chio, I.I.C.; Tuveson, D.A. Transcriptional Regulation by Nrf2. *Antioxid Redox Signal.* **2018**, *29*, 1727–1745. [[CrossRef](#)]
141. Jiang, T.; Harder, B.; Rojo de la Vega, M.; Wong, P.K.; Chapman, E.; Zhang, D.D. p62 links autophagy and Nrf2 signaling. *Free Radic. Biol. Med.* **2015**, *88*, 199–204. [[CrossRef](#)] [[PubMed](#)]
142. Lau, A.; Wang, X.J.; Zhao, F.; Villeneuve, N.F.; Wu, T.; Jiang, T.; Sun, Z.; White, E.; Zhang, D.D. A noncanonical mechanism of Nrf2 activation by autophagy deficiency: Direct interaction between Keap1 and p62. *Mol. Cell Biol.* **2010**, *30*, 3275–3285. [[CrossRef](#)] [[PubMed](#)]
143. Komatsu, M.; Kurokawa, H.; Waguri, S.; Taguchi, K.; Kobayashi, A.; Ichimura, Y.; Sou, Y.S.; Ueno, I.; Sakamoto, A.; Tong, K.I.; et al. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. *Nat. Cell Biol.* **2010**, *12*, 213–223. [[CrossRef](#)] [[PubMed](#)]
144. Jain, A.; Lamark, T.; Sjøttem, E.; Larsen, K.B.; Awuh, J.A.; Overvatn, A.; McMahon, M.; Hayes, J.D.; 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.* **2010**, *285*, 22576–22591. [[CrossRef](#)] [[PubMed](#)]
145. Rhee, S.G.; Bae, S.H. The antioxidant function of sestrins is mediated by promotion of autophagic degradation of Keap1 and Nrf2 activation and by inhibition of mTORC1. *Free Radic. Biol. Med.* **2015**, *88*, 205–211. [[CrossRef](#)]

146. Ichimura, Y.; Waguri, S.; Sou, Y.S.; Kageyama, S.; Hasegawa, J.; Ishimura, R.; Saito, T.; Yang, Y.; Kouno, T.; Fukutomi, T.; et al. Phosphorylation of p62 activates the Keap1-Nrf2 pathway during selective autophagy. *Mol. Cell* **2013**, *51*, 618–631. [[CrossRef](#)]
147. Taguchi, K.; Fujikawa, N.; Komatsu, M.; Ishii, T.; Unno, M.; Akaike, T.; Motohashi, H.; Yamamoto, M. Keap1 degradation by autophagy for the maintenance of redox homeostasis. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 13561–13566. [[CrossRef](#)]
148. Bae, S.H.; Sung, S.H.; Oh, S.Y.; Lim, J.M.; Lee, S.K.; Park, Y.N.; Lee, H.E.; Kang, D.; Rhee, S.G. Sestrins activate Nrf2 by promoting p62-dependent autophagic degradation of Keap1 and prevent oxidative liver damage. *Cell Metab.* **2013**, *17*, 73–84. [[CrossRef](#)]
149. Bensaad, K.; Tsuruta, A.; Selak, M.A.; Vidal, M.N.; Nakano, K.; Bartrons, R.; Gottlieb, E.; Vousden, K.H. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell* **2006**, *126*, 107–120. [[CrossRef](#)]
150. Cheung, E.C.; Ludwig, R.L.; Vousden, K.H. Mitochondrial localization of TIGAR under hypoxia stimulates HK2 and lowers ROS and cell death. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 20491–20496. [[CrossRef](#)]
151. Hoshino, A.; Matoba, S.; Iwai-Kanai, E.; Nakamura, H.; Kimata, M.; Nakaoka, M.; Katamura, M.; Okawa, Y.; Ariyoshi, M.; Mita, Y.; et al. p53-TIGAR axis attenuates mitophagy to exacerbate cardiac damage after ischemia. *J. Mol. Cell Cardiol.* **2012**, *52*, 175–184. [[CrossRef](#)] [[PubMed](#)]
152. Crighton, D.; Wilkinson, S.; O'Prey, J.; Syed, N.; Smith, P.; Harrison, P.R.; Gasco, M.; Garrone, O.; Crook, T.; Ryan, K.M. DRAM, a p53-induced modulator of autophagy, is critical for apoptosis. *Cell* **2006**, *126*, 121–134. [[CrossRef](#)] [[PubMed](#)]
153. Budanov, A.V.; Karin, M. p53 target genes sestrin1 and sestrin2 connect genotoxic stress and mTOR signaling. *Cell* **2008**, *134*, 451–460. [[CrossRef](#)] [[PubMed](#)]
154. Mao, K.; Klionsky, D.J. Participation of mitochondrial fission during mitophagy. *Cell Cycle* **2013**, *12*, 3131–3132. [[CrossRef](#)] [[PubMed](#)]
155. Bolisetty, S.; Jaimes, E.A. Mitochondria and reactive oxygen species: Physiology and pathophysiology. *Int J. Mol. Sci.* **2013**, *14*, 6306–6344. [[CrossRef](#)]
156. Ordureau, A.; Sarraf, S.A.; Duda, D.M.; Heo, J.M.; Jedrychowski, M.P.; Sviderskiy, V.O.; Olszewski, J.L.; Koerber, J.T.; Xie, T.; Beausoleil, S.A.; et al. Quantitative proteomics reveal a feedforward mechanism for mitochondrial PARKIN translocation and ubiquitin chain synthesis. *Mol. Cell* **2014**, *56*, 360–375. [[CrossRef](#)]
157. Shiba-Fukushima, K.; Arano, T.; Matsumoto, G.; Inoshita, T.; Yoshida, S.; Ishihama, Y.; Ryu, K.Y.; Nukina, N.; Hattori, N.; Imai, Y. Phosphorylation of mitochondrial polyubiquitin by PINK1 promotes Parkin mitochondrial tethering. *PLoS Genet.* **2014**, *10*, e1004861. [[CrossRef](#)]
158. Lazarou, M.; Sliter, D.A.; Kane, L.A.; Sarraf, S.A.; Wang, C.; Burman, J.L.; Sideris, D.P.; Fogel, A.I.; Youle, R.J. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature* **2015**, *524*, 309–314. [[CrossRef](#)]
159. Ney, P.A. Mitochondrial autophagy: Origins, significance, and role of BNIP3 and NIX. *Biochim. Biophys. Acta* **2015**, *1853*, 2775–2783. [[CrossRef](#)]
160. Saito, T.; Sadoshima, J. Molecular mechanisms of mitochondrial autophagy/mitophagy in the heart. *Circ. Res.* **2015**, *116*, 1477–1490. [[CrossRef](#)]
161. Novak, I.; Kirkin, V.; McEwan, D.G.; Zhang, J.; Wild, P.; Rozenknop, A.; Rogov, V.; Lohr, F.; Popovic, D.; Occhipinti, A.; et al. Nix is a selective autophagy receptor for mitochondrial clearance. *EMBO Rep.* **2010**, *11*, 45–51. [[CrossRef](#)] [[PubMed](#)]
162. Wu, W.; Tian, W.; Hu, Z.; Chen, G.; Huang, L.; Li, W.; Zhang, X.; Xue, P.; Zhou, C.; Liu, L.; et al. ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. *EMBO Rep.* **2014**, *15*, 566–575. [[CrossRef](#)] [[PubMed](#)]
163. Vander Heiden, M.G.; Cantley, L.C.; Thompson, C.B. Understanding the Warburg effect: The metabolic requirements of cell proliferation. *Science* **2009**, *324*, 1029–1033. [[CrossRef](#)] [[PubMed](#)]
164. Jin, S.; White, E. Role of autophagy in cancer: Management of metabolic stress. *Autophagy* **2007**, *3*, 28–31. [[CrossRef](#)] [[PubMed](#)]
165. Pelicano, H.; Carney, D.; Huang, P. ROS stress in cancer cells and therapeutic implications. *Drug Resist. Updat* **2004**, *7*, 97–110. [[CrossRef](#)] [[PubMed](#)]
166. Wang, J.; Yi, J. Cancer cell killing via ROS: To increase or decrease, that is the question. *Cancer Biol. Ther.* **2008**, *7*, 1875–1884. [[CrossRef](#)]

167. Gibson, S.B. A matter of balance between life and death: Targeting reactive oxygen species (ROS)-induced autophagy for cancer therapy. *Autophagy* **2010**, *6*, 835–837. [[CrossRef](#)]
168. Li, L.; Ishdorj, G.; Gibson, S.B. Reactive oxygen species regulation of autophagy in cancer: Implications for cancer treatment. *Free Radic. Biol. Med.* **2012**, *53*, 1399–1410. [[CrossRef](#)]
169. Levy, J.M.M.; Towers, C.G.; Thorburn, A. Targeting autophagy in cancer. *Nat. Rev. Cancer* **2017**, *17*, 528–542. [[CrossRef](#)]
170. Cordani, M.; Butera, G.; Pacchiana, R.; Donadelli, M. Molecular interplay between mutant p53 proteins and autophagy in cancer cells. *Biochim. Biophys. Acta Rev. Cancer* **2017**, *1867*, 19–28. [[CrossRef](#)]
171. Tian, T.; Li, X.; Zhang, J. mTOR Signaling in Cancer and mTOR Inhibitors in Solid Tumor Targeting Therapy. *Int. J. Mol. Sci.* **2019**. [[CrossRef](#)] [[PubMed](#)]
172. Mukhopadhyay, S.; Saqcena, M.; Chatterjee, A.; Garcia, A.; Frias, M.A.; Foster, D.A. Reciprocal regulation of AMP-activated protein kinase and phospholipase D. *J. Biol. Chem.* **2015**, *290*, 6986–6993. [[CrossRef](#)] [[PubMed](#)]
173. Jang, Y.H.; Choi, K.Y.; Min, D.S. Phospholipase D-mediated autophagic regulation is a potential target for cancer therapy. *Cell Death Differ.* **2014**, *21*, 533–546. [[CrossRef](#)] [[PubMed](#)]
174. Qu, X.; Yu, J.; Bhagat, G.; Furuya, N.; Hibshoosh, H.; Troxel, A.; Rosen, J.; Eskelinen, E.L.; Mizushima, N.; Ohsumi, Y.; et al. Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. *J. Clin. Invest.* **2003**, *112*, 1809–1820. [[CrossRef](#)]
175. Shen, Y.; Li, D.D.; Wang, L.L.; Deng, R.; Zhu, X.F. Decreased expression of autophagy-related proteins in malignant epithelial ovarian cancer. *Autophagy* **2008**, *4*, 1067–1068. [[CrossRef](#)]
176. Yue, Z.; Jin, S.; Yang, C.; Levine, A.J.; Heintz, N. Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 15077–15082. [[CrossRef](#)]
177. Takahashi, Y.; Coppola, D.; Matsushita, N.; Cialing, H.D.; Sun, M.; Sato, Y.; Liang, C.; Jung, J.U.; Cheng, J.Q.; Mule, J.J.; et al. Bif-1 interacts with Beclin 1 through UVRAG and regulates autophagy and tumorigenesis. *Nat. Cell Biol.* **2007**, *9*, 1142–1151. [[CrossRef](#)]
178. Henson, E.; Chen, Y.; Gibson, S. EGFR Family Members' Regulation of Autophagy Is at a Crossroads of Cell Survival and Death in Cancer. *Cancers (Basel)* **2017**, *9*, 27. [[CrossRef](#)]
179. Rosenfeldt, M.T.; Ryan, K.M. The multiple roles of autophagy in cancer. *Carcinogenesis* **2011**, *32*, 955–963. [[CrossRef](#)]
180. Gewirtz, D.A. The four faces of autophagy: Implications for cancer therapy. *Cancer Res.* **2014**, *74*, 647–651. [[CrossRef](#)]
181. White, E. Deconvoluting the context-dependent role for autophagy in cancer. *Nat. Rev. Cancer* **2012**, *12*, 401–410. [[CrossRef](#)] [[PubMed](#)]
182. Liao, J.K.; Zhou, B.; Zhuang, X.M.; Zhuang, P.L.; Zhang, D.M.; Chen, W.L. Cancer-associated fibroblasts confer cisplatin resistance of tongue cancer via autophagy activation. *Biomed. Pharmacother.* **2018**, *97*, 1341–1348. [[CrossRef](#)]
183. Rabinowitz, J.D.; White, E. Autophagy and metabolism. *Science* **2010**, *330*, 1344–1348. [[CrossRef](#)] [[PubMed](#)]
184. Liu, E.Y.; Ryan, K.M. Autophagy and cancer-issues we need to digest. *J. Cell Sci.* **2012**, *125*, 2349–2358. [[CrossRef](#)]
185. Rojo de la Vega, M.; Chapman, E.; Zhang, D.D. NRF2 and the Hallmarks of Cancer. *Cancer Cell* **2018**, *34*, 21–43. [[CrossRef](#)] [[PubMed](#)]
186. Mukhopadhyay, S.; Goswami, D.; Adisheshaiah, P.P.; Burgan, W.; Yi, M.; Guerin, T.M.; Kozlov, S.V.; Nissley, D.V.; McCormick, F. Undermining Glutaminolysis Bolsters Chemotherapy While NRF2 Promotes Chemoresistance in KRAS-Driven Pancreatic Cancers. *Cancer Res.* **2020**, *80*, 1630–1643. [[CrossRef](#)] [[PubMed](#)]
187. Hayes, J.D.; Dinkova-Kostova, A.T. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. *Trends Biochem. Sci.* **2014**, *39*, 199–218. [[CrossRef](#)]
188. Mitsuishi, Y.; Taguchi, K.; Kawatani, Y.; Shibata, T.; Nukiwa, T.; Aburatani, H.; Yamamoto, M.; Motohashi, H. Nrf2 redirects glucose and glutamine into anabolic pathways in metabolic reprogramming. *Cancer Cell* **2012**, *22*, 66–79. [[CrossRef](#)]
189. Lau, A.; Zheng, Y.; Tao, S.; Wang, H.; Whitman, S.A.; White, E.; Zhang, D.D. Arsenic inhibits autophagic flux, activating the Nrf2-Keap1 pathway in a p62-dependent manner. *Mol. Cell Biol.* **2013**, *33*, 2436–2446. [[CrossRef](#)]

190. Nguyen, L.V.; Vanner, R.; Dirks, P.; Eaves, C.J. Cancer stem cells: An evolving concept. *Nat. Rev. Cancer* **2012**, *12*, 133–143. [[CrossRef](#)]
191. Nazio, F.; Bordi, M.; Cianfanelli, V.; Locatelli, F.; Cecconi, F. Autophagy and cancer stem cells: Molecular mechanisms and therapeutic applications. *Cell Death Differ.* **2019**, *26*, 690–702. [[CrossRef](#)]
192. Cufi, S.; Vazquez-Martin, A.; Oliveras-Ferraros, C.; Martin-Castillo, B.; Vellon, L.; Menendez, J.A. Autophagy positively regulates the CD44(+) CD24(-/low) breast cancer stem-like phenotype. *Cell Cycle* **2011**, *10*, 3871–3885. [[CrossRef](#)] [[PubMed](#)]
193. Zhu, H.; Wang, D.; Liu, Y.; Su, Z.; Zhang, L.; Chen, F.; Zhou, Y.; Wu, Y.; Yu, M.; Zhang, Z.; et al. Role of the Hypoxia-inducible factor-1 alpha induced autophagy in the conversion of non-stem pancreatic cancer cells into CD133+ pancreatic cancer stem-like cells. *Cancer Cell Int.* **2013**, *13*, 119. [[CrossRef](#)] [[PubMed](#)]
194. Song, Y.J.; Zhang, S.S.; Guo, X.L.; Sun, K.; Han, Z.P.; Li, R.; Zhao, Q.D.; Deng, W.J.; Xie, X.Q.; Zhang, J.W.; et al. Autophagy contributes to the survival of CD133+ liver cancer stem cells in the hypoxic and nutrient-deprived tumor microenvironment. *Cancer Lett.* **2013**, *339*, 70–81. [[CrossRef](#)] [[PubMed](#)]
195. Abel, E.D.; O’Shea, K.M.; Ramasamy, R. Insulin resistance: Metabolic mechanisms and consequences in the heart. *Arterioscler Thromb. Vasc. Biol.* **2012**, *32*, 2068–2076. [[CrossRef](#)]
196. Higgins, G.C.; Coughlan, M.T. Mitochondrial dysfunction and mitophagy: The beginning and end to diabetic nephropathy? *Br. J. Pharmacol.* **2014**, *171*, 1917–1942. [[CrossRef](#)]
197. Pena-Oyazun, D.; Bravo-Sagua, R.; Diaz-Vega, A.; Aleman, L.; Chiong, M.; Garcia, L.; Bambs, C.; Troncoso, R.; Cifuentes, M.; Morselli, E.; et al. Autophagy and oxidative stress in non-communicable diseases: A matter of the inflammatory state? *Free Radic. Biol. Med.* **2018**, *124*, 61–78. [[CrossRef](#)]
198. Volpe, C.M.O.; Villar-Delfino, P.H.; Dos Anjos, P.M.F.; Nogueira-Machado, J.A. Cellular death, reactive oxygen species (ROS) and diabetic complications. *Cell Death Dis.* **2018**, *9*, 119. [[CrossRef](#)]
199. Giacco, F.; Brownlee, M. Oxidative stress and diabetic complications. *Circ. Res.* **2010**, *107*, 1058–1070. [[CrossRef](#)]
200. Nogueira-Machado, J.A.; Chaves, M.M. From hyperglycemia to AGE-RAGE interaction on the cell surface: A dangerous metabolic route for diabetic patients. *Expert Opin Ther Targets* **2008**, *12*, 871–882. [[CrossRef](#)]
201. Nishikawa, T.; Araki, E. Impact of mitochondrial ROS production in the pathogenesis of diabetes mellitus and its complications. *Antioxid Redox Signal.* **2007**, *9*, 343–353. [[CrossRef](#)] [[PubMed](#)]
202. Ahmed, F.N.; Naqvi, F.N.; Shafiq, F. Lipid peroxidation and serum antioxidant enzymes in patients with type 2 diabetes mellitus. *Ann. N. Y. Acad. Sci.* **2006**, *1084*, 481–489. [[CrossRef](#)]
203. Dandona, P.; Thusu, K.; Cook, S.; Snyder, B.; Makowski, J.; Armstrong, D.; Nicotera, T. Oxidative damage to DNA in diabetes mellitus. *Lancet* **1996**, *347*, 444–445. [[CrossRef](#)]
204. Al-Aubaidy, H.A.; Jelinek, H.F. Oxidative DNA damage and obesity in type 2 diabetes mellitus. *Eur. J. Endocrinol.* **2011**, *164*, 899–904. [[CrossRef](#)] [[PubMed](#)]
205. Karunakaran, U.; Park, K.G. A systematic review of oxidative stress and safety of antioxidants in diabetes: Focus on islets and their defense. *Diabetes Metab. J.* **2013**, *37*, 106–112. [[CrossRef](#)] [[PubMed](#)]
206. Jung, M.; Lee, J.; Seo, H.Y.; Lim, J.S.; Kim, E.K. Cathepsin inhibition-induced lysosomal dysfunction enhances pancreatic beta-cell apoptosis in high glucose. *PLoS ONE* **2015**, *10*, e0116972. [[CrossRef](#)] [[PubMed](#)]
207. Jung, H.S.; Chung, K.W.; Won Kim, J.; Kim, J.; Komatsu, M.; Tanaka, K.; Nguyen, Y.H.; Kang, T.M.; Yoon, K.H.; Kim, J.W.; et al. Loss of autophagy diminishes pancreatic beta cell mass and function with resultant hyperglycemia. *Cell Metab* **2008**, *8*, 318–324. [[CrossRef](#)] [[PubMed](#)]
208. Zhao, Y.; Zhang, L.; Qiao, Y.; Zhou, X.; Wu, G.; Wang, L.; Peng, Y.; Dong, X.; Huang, H.; Si, L.; et al. Heme oxygenase-1 prevents cardiac dysfunction in streptozotocin-diabetic mice by reducing inflammation, oxidative stress, apoptosis and enhancing autophagy. *PLoS ONE* **2013**, *8*, e75927. [[CrossRef](#)]
209. He, C.; Zhu, H.; Li, H.; Zou, M.H.; Xie, Z. Dissociation of Bcl-2-Beclin1 complex by activated AMPK enhances cardiac autophagy and protects against cardiomyocyte apoptosis in diabetes. *Diabetes* **2013**, *62*, 1270–1281. [[CrossRef](#)]
210. Das, A.; Durrant, D.; Koka, S.; Salloum, F.N.; Xi, L.; Kukreja, R.C. Mammalian target of rapamycin (mTOR) inhibition with rapamycin improves cardiac function in type 2 diabetic mice: Potential role of attenuated oxidative stress and altered contractile protein expression. *J. Biol. Chem.* **2014**, *289*, 4145–4160. [[CrossRef](#)]
211. Moller, A.B.; Kampmann, U.; Hedegaard, J.; Thorsen, K.; Nordentoft, I.; Vendelbo, M.H.; Moller, N.; Jessen, N. Altered gene expression and repressed markers of autophagy in skeletal muscle of insulin resistant patients with type 2 diabetes. *Sci. Rep.* **2017**, *7*, 43775. [[CrossRef](#)] [[PubMed](#)]

212. Ost, A.; Svensson, K.; Ruishalme, I.; Brannmark, C.; Franck, N.; Krook, H.; Sandstrom, P.; Kjolhede, P.; Stralfors, P. Attenuated mTOR signaling and enhanced autophagy in adipocytes from obese patients with type 2 diabetes. *Mol. Med.* **2010**, *16*, 235–246. [[CrossRef](#)] [[PubMed](#)]
213. Liu, H.Y.; Han, J.; Cao, S.Y.; Hong, T.; Zhuo, D.; Shi, J.; Liu, Z.; Cao, W. Hepatic autophagy is suppressed in the presence of insulin resistance and hyperinsulinemia: Inhibition of FoxO1-dependent expression of key autophagy genes by insulin. *J. Biol. Chem.* **2009**, *284*, 31484–31492. [[CrossRef](#)] [[PubMed](#)]
214. Kong, F.J.; Wu, J.H.; Sun, S.Y.; Zhou, J.Q. The endoplasmic reticulum stress/autophagy pathway is involved in cholesterol-induced pancreatic beta-cell injury. *Sci. Rep.* **2017**, *7*, 44746. [[CrossRef](#)]
215. Wu, J.; Kong, F.; Pan, Q.; Du, Y.; Ye, J.; Zheng, F.; Li, H.; Zhou, J. Autophagy protects against cholesterol-induced apoptosis in pancreatic beta-cells. *Biochem. Biophys. Res. Commun.* **2017**, *482*, 678–685. [[CrossRef](#)]
216. Zummo, F.P.; Cullen, K.S.; Honkanen-Scott, M.; Shaw, J.A.M.; Lovat, P.E.; Arden, C. Glucagon-Like Peptide 1 Protects Pancreatic beta-Cells From Death by Increasing Autophagic Flux and Restoring Lysosomal Function. *Diabetes* **2017**, *66*, 1272–1285. [[CrossRef](#)]
217. Abdullah, R.; Basak, I.; Patil, K.S.; Alves, G.; Larsen, J.P.; Moller, S.G. Parkinson's disease and age: The obvious but largely unexplored link. *Exp. Gerontol.* **2015**, *68*, 33–38. [[CrossRef](#)]
218. Nikolettou, V.; Papandreou, M.E.; Tavernarakis, N. Autophagy in the physiology and pathology of the central nervous system. *Cell Death Differ.* **2015**, *22*, 398–407. [[CrossRef](#)]
219. Cherra, S.J., 3rd; Chu, C.T. Autophagy in neuroprotection and neurodegeneration: A question of balance. *Future Neurol.* **2008**, *3*, 309–323.
220. Carloni, S.; Buonocore, G.; Balduini, W. Protective role of autophagy in neonatal hypoxia-ischemia induced brain injury. *Neurobiol. Dis.* **2008**, *32*, 329–339. [[CrossRef](#)]
221. Redmann, M.; Darley-Usmar, V.; Zhang, J. The Role of Autophagy, Mitophagy and Lysosomal Functions in Modulating Bioenergetics and Survival in the Context of Redox and Proteotoxic Damage: Implications for Neurodegenerative Diseases. *Aging Dis.* **2016**, *7*, 150–162. [[CrossRef](#)] [[PubMed](#)]
222. Ghavami, S.; Shojaei, S.; Yeganeh, B.; Ande, S.R.; Jangamreddy, J.R.; Mehrpour, M.; Christoffersson, J.; Chaabane, W.; Moghadam, A.R.; Kashani, H.H.; et al. Autophagy and apoptosis dysfunction in neurodegenerative disorders. *Prog. Neurobiol.* **2014**, *112*, 24–49. [[CrossRef](#)] [[PubMed](#)]
223. Kamat, P.K.; Kalani, A.; Kyles, P.; Tyagi, S.C.; Tyagi, N. Autophagy of mitochondria: A promising therapeutic target for neurodegenerative disease. *Cell Biochem. Biophys.* **2014**, *70*, 707–719. [[CrossRef](#)] [[PubMed](#)]
224. Querfurth, H.W.; LaFerla, F.M. Alzheimer's disease. *N. Engl. J. Med.* **2010**, *362*, 329–344. [[CrossRef](#)]
225. Cheignon, C.; Tomas, M.; Bonnefont-Rousselot, D.; Faller, P.; Hureau, C.; Collin, F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. *Redox Biol.* **2018**, *14*, 450–464. [[CrossRef](#)]
226. Menzies, F.M.; Fleming, A.; Caricasole, A.; Bento, C.F.; Andrews, S.P.; Ashkenazi, A.; Fullgrabe, J.; Jackson, A.; Jimenez Sanchez, M.; Karabiyik, C.; et al. Autophagy and Neurodegeneration: Pathogenic Mechanisms and Therapeutic Opportunities. *Neuron* **2017**, *93*, 1015–1034. [[CrossRef](#)]
227. Ulamek-Kozioł, M.; Furmaga-Jablonska, W.; Januszewski, S.; Brzozowska, J.; Scislewska, M.; Jablonski, M.; Pluta, R. Neuronal autophagy: Self-eating or self-cannibalism in Alzheimer's disease. *Neurochem. Res.* **2013**, *38*, 1769–1773. [[CrossRef](#)]
228. Nilsson, P.; Loganathan, K.; Sekiguchi, M.; Matsuba, Y.; Hui, K.; Tsubuki, S.; Tanaka, M.; Iwata, N.; Saito, T.; Saido, T.C. Abeta secretion and plaque formation depend on autophagy. *Cell Rep.* **2013**, *5*, 61–69. [[CrossRef](#)]
229. Yu, W.H.; Cuervo, A.M.; Kumar, A.; Peterhoff, C.M.; Schmidt, S.D.; Lee, J.H.; Mohan, P.S.; Mercken, M.; Farmery, M.R.; Tjernberg, L.O.; et al. Macro-autophagy—a novel Beta-amyloid peptide-generating pathway activated in Alzheimer's disease. *J. Cell Biol.* **2005**, *171*, 87–98. [[CrossRef](#)]
230. Boland, B.; Kumar, A.; Lee, S.; Platt, F.M.; Wegiel, J.; Yu, W.H.; Nixon, R.A. Autophagy induction and autophagosome clearance in neurons: Relationship to autophagic pathology in Alzheimer's disease. *J. Neurosci.* **2008**, *28*, 6926–6937. [[CrossRef](#)]
231. Kesidou, E.; Lagoudaki, R.; Touloumi, O.; Poulatsidou, K.N.; Simeonidou, C. Autophagy and neurodegenerative disorders. *Neural Regen Res.* **2013**, *8*, 2275–2283.
232. Lee, J.H.; Yu, W.H.; Kumar, A.; Lee, S.; Mohan, P.S.; Peterhoff, C.M.; Wolfe, D.M.; Martinez-Vicente, M.; Massey, A.C.; Sovak, G.; et al. Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. *Cell* **2010**, *141*, 1146–1158. [[CrossRef](#)] [[PubMed](#)]

233. Piras, A.; Collin, L.; Gruninger, F.; Graff, C.; Ronnback, A. Autophagic and lysosomal defects in human tauopathies: Analysis of post-mortem brain from patients with familial Alzheimer disease, corticobasal degeneration and progressive supranuclear palsy. *Acta Neuropathol. Commun.* **2016**, *4*, 22. [[CrossRef](#)] [[PubMed](#)]
234. Butzlaff, M.; Hannan, S.B.; Karsten, P.; Lenz, S.; Ng, J.; Vossfeldt, H.; Prussing, K.; Pflanz, R.; Schulz, J.B.; Rasse, T.; et al. Impaired retrograde transport by the Dynein/Dynactin complex contributes to Tau-induced toxicity. *Hum. Mol. Genet.* **2015**, *24*, 3623–3637. [[CrossRef](#)] [[PubMed](#)]
235. Green, K.N.; Billings, L.M.; Roozendaal, B.; McGaugh, J.L.; LaFerla, F.M. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J. Neurosci.* **2006**, *26*, 9047–9056. [[CrossRef](#)] [[PubMed](#)]
236. Sotiropoulos, I.; Catania, C.; Pinto, L.G.; Silva, R.; Pollerberg, G.E.; Takashima, A.; Sousa, N.; Almeida, O.F. Stress acts cumulatively to precipitate Alzheimer's disease-like tau pathology and cognitive deficits. *J. Neurosci.* **2011**, *31*, 7840–7847. [[CrossRef](#)]
237. Dey, A.; Hao, S.; Wosiski-Kuhn, M.; Stranahan, A.M. Glucocorticoid-mediated activation of GSK3beta promotes tau phosphorylation and impairs memory in type 2 diabetes. *Neurobiol. Aging* **2017**, *57*, 75–83. [[CrossRef](#)]
238. Caccamo, A.; Magri, A.; Medina, D.X.; Wisely, E.V.; Lopez-Aranda, M.F.; Silva, A.J.; Oddo, S. mTOR regulates tau phosphorylation and degradation: Implications for Alzheimer's disease and other tauopathies. *Aging Cell* **2013**, *12*, 370–380. [[CrossRef](#)]
239. Vidal, R.L.; Matus, S.; Bargsted, L.; Hetz, C. Targeting autophagy in neurodegenerative diseases. *Trends Pharmacol. Sci.* **2014**, *35*, 583–591. [[CrossRef](#)]
240. Sato, H.; Takahashi, T.; Sumitani, K.; Takatsu, H.; Urano, S. Glucocorticoid Generates ROS to Induce Oxidative Injury in the Hippocampus, Leading to Impairment of Cognitive Function of Rats. *J. Clin. Biochem. Nutr.* **2010**, *47*, 224–232. [[CrossRef](#)]
241. Silva, J.M.; Rodrigues, S.; Sampaio-Marques, B.; Gomes, P.; Neves-Carvalho, A.; Dioli, C.; Soares-Cunha, C.; Mazuik, B.F.; Takashima, A.; Ludovico, P.; et al. Dysregulation of autophagy and stress granule-related proteins in stress-driven Tau pathology. *Cell Death Differ.* **2019**, *26*, 1411–1427. [[CrossRef](#)]
242. Poewe, W.; Seppi, K.; Tanner, C.M.; Halliday, G.M.; Brundin, P.; Volkman, J.; Schrag, A.E.; Lang, A.E. Parkinson disease. *Nat. Rev. Dis Primers* **2017**, *3*, 17013. [[CrossRef](#)] [[PubMed](#)]
243. Lynch-Day, M.A.; Mao, K.; Wang, K.; Zhao, M.; Klionsky, D.J. The role of autophagy in Parkinson's disease. *Cold Spring Harb Perspect Med.* **2012**, *2*, a009357. [[CrossRef](#)] [[PubMed](#)]
244. Alcalay, R.N.; Caccappolo, E.; Mejia-Santana, H.; Tang, M.X.; Rosado, L.; Ross, B.M.; Verbitsky, M.; Kisselev, S.; Louis, E.D.; Comella, C.; et al. Frequency of known mutations in early-onset Parkinson disease: Implication for genetic counseling: The consortium on risk for early onset Parkinson disease study. *Arch. Neurol.* **2010**, *67*, 1116–1122. [[CrossRef](#)] [[PubMed](#)]
245. Kitada, T.; Asakawa, S.; Hattori, N.; Matsumine, H.; Yamamura, Y.; Minoshima, S.; Yokochi, M.; Mizuno, Y.; Shimizu, N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* **1998**, *392*, 605–608. [[CrossRef](#)]
246. Valente, E.M.; Abou-Sleiman, P.M.; Caputo, V.; Muqit, M.M.; Harvey, K.; Gispert, S.; Ali, Z.; Del Turco, D.; Bentivoglio, A.R.; Healy, D.G.; et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science* **2004**, *304*, 1158–1160. [[CrossRef](#)]
247. Nguyen, T.N.; Padman, B.S.; Lazarou, M. Deciphering the Molecular Signals of PINK1/Parkin Mitophagy. *Trends Cell Biol.* **2016**, *26*, 733–744. [[CrossRef](#)]
248. Gautier, C.A.; Kitada, T.; Shen, J. Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 11364–11369. [[CrossRef](#)]
249. Kitada, T.; Pisani, A.; Karouani, M.; Haburcak, M.; Martella, G.; Tschertner, A.; Platania, P.; Wu, B.; Pothos, E.N.; Shen, J. Impaired dopamine release and synaptic plasticity in the striatum of parkin-/- mice. *J. Neurochem.* **2009**, *110*, 613–621. [[CrossRef](#)]
250. Palacino, J.J.; Sagi, D.; Goldberg, M.S.; Krauss, S.; Motz, C.; Wacker, M.; Klose, J.; Shen, J. Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. *J. Biol. Chem.* **2004**, *279*, 18614–18622. [[CrossRef](#)]
251. Cai, Y.; Arikath, J.; Yang, L.; Guo, M.L.; Periyasamy, P.; Buch, S. Interplay of endoplasmic reticulum stress and autophagy in neurodegenerative disorders. *Autophagy* **2016**, *12*, 225–244. [[CrossRef](#)] [[PubMed](#)]

252. Cuervo, A.M.; Stefanis, L.; Fredenburg, R.; Lansbury, P.T.; Sulzer, D. Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy. *Science* **2004**, *305*, 1292–1295. [[CrossRef](#)] [[PubMed](#)]
253. Winslow, A.R.; Chen, C.W.; Corrochano, S.; Acevedo-Arozena, A.; Gordon, D.E.; Peden, A.A.; Lichtenberg, M.; Menzies, F.M.; Ravikumar, B.; Imarisio, S.; et al. alpha-Synuclein impairs macro-autophagy: Implications for Parkinson's disease. *J. Cell Biol.* **2010**, *190*, 1023–1037. [[CrossRef](#)]
254. Michel, P.P.; Hirsch, E.C.; Hunot, S. Understanding Dopaminergic Cell Death Pathways in Parkinson Disease. *Neuron* **2016**, *90*, 675–691. [[CrossRef](#)] [[PubMed](#)]
255. Finkbeiner, S. Huntington's Disease. *Cold Spring Harb. Perspect Biol.* **2011**, *3*, a007476. [[CrossRef](#)] [[PubMed](#)]
256. Martinez-Vicente, M.; Talloczy, Z.; Wong, E.; Tang, G.; Koga, H.; Kaushik, S.; De Vries, R.; Arias, E.; Harris, S.; Sulzer, D.; et al. Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. *Nat. Neurosci.* **2010**, *13*, 567–576. [[CrossRef](#)] [[PubMed](#)]
257. Ochaba, J.; Lukacsovich, T.; Csikos, G.; Zheng, S.; Margulis, J.; Salazar, L.; Mao, K.; Lau, A.L.; Yeung, S.Y.; Humbert, S.; et al. Potential function for the Huntingtin protein as a scaffold for selective autophagy. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 16889–16894. [[CrossRef](#)] [[PubMed](#)]
258. Rui, Y.N.; Xu, Z.; Patel, B.; Chen, Z.; Chen, D.; Tito, A.; David, G.; Sun, Y.; Stimming, E.F.; Bellen, H.J.; et al. Huntingtin functions as a scaffold for selective macro-autophagy. *Nat. Cell Biol.* **2015**, *17*, 262–275. [[CrossRef](#)]
259. Wong, Y.C.; Holzbaur, E.L. The regulation of autophagosome dynamics by huntingtin and HAP1 is disrupted by expression of mutant huntingtin, leading to defective cargo degradation. *J. Neurosci.* **2014**, *34*, 1293–1305. [[CrossRef](#)]
260. Mealer, R.G.; Murray, A.J.; Shahani, N.; Subramaniam, S.; Snyder, S.H. Rhes, a striatal-selective protein implicated in Huntington disease, binds beclin-1 and activates autophagy. *J. Biol. Chem.* **2014**, *289*, 3547–3554. [[CrossRef](#)]
261. Terman, A.; Brunk, U.T. Autophagy in cardiac myocyte homeostasis, aging, and pathology. *Cardiovasc. Res.* **2005**, *68*, 355–365. [[CrossRef](#)] [[PubMed](#)]
262. Cao, D.J.; Gillette, T.G.; Hill, J.A. Cardiomyocyte autophagy: Remodeling, repairing, and reconstructing the heart. *Curr. Hypertens Rep.* **2009**, *11*, 406–411. [[CrossRef](#)] [[PubMed](#)]
263. Morales, C.R.; Pedrozo, Z.; Lavandero, S.; Hill, J.A. Oxidative stress and autophagy in cardiovascular homeostasis. *Antioxid Redox Signal.* **2014**, *20*, 507–518. [[CrossRef](#)] [[PubMed](#)]
264. Luo, C.; Li, Y.; Wang, H.; Feng, Z.; Li, Y.; Long, J.; Liu, J. Mitochondrial accumulation under oxidative stress is due to defects in autophagy. *J. Cell Biochem.* **2013**, *114*, 212–219. [[CrossRef](#)] [[PubMed](#)]
265. Lobrinus, J.A.; Schorderet, D.F.; Payot, M.; Jeanrenaud, X.; Bottani, A.; Superti-Furga, A.; Schlaepfer, J.; Fromer, M.; Jeannet, P.Y. Morphological, clinical and genetic aspects in a family with a novel LAMP-2 gene mutation (Danon disease). *Neuromuscul Disord* **2005**, *15*, 293–298. [[CrossRef](#)]
266. Nishino, I.; Fu, J.; Tanji, K.; Yamada, T.; Shimojo, S.; Koori, T.; Mora, M.; Riggs, J.E.; Oh, S.J.; Koga, Y.; et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature* **2000**, *406*, 906–910. [[CrossRef](#)]
267. Maron, B.J.; Roberts, W.C.; Arad, M.; Haas, T.S.; Spirito, P.; Wright, G.B.; Almquist, A.K.; Baffa, J.M.; Saul, J.P.; Ho, C.Y.; et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. *JAMA* **2009**, *301*, 1253–1259. [[CrossRef](#)]
268. Nakai, A.; Yamaguchi, O.; Takeda, T.; Higuchi, Y.; Hikoso, S.; Taniike, M.; Omiya, S.; Mizote, I.; Matsumura, Y.; Asahi, M.; et al. The role of autophagy in cardiomyocytes in the basal state and in response to hemodynamic stress. *Nat. Med.* **2007**, *13*, 619–624. [[CrossRef](#)]
269. Ma, X.; Liu, H.; Foyil, S.R.; Godar, R.J.; Weinheimer, C.J.; Hill, J.A.; Diwan, A. Impaired autophagosome clearance contributes to cardiomyocyte death in ischemia/reperfusion injury. *Circulation* **2012**, *125*, 3170–3181. [[CrossRef](#)]
270. Yan, L.; Vatner, D.E.; Kim, S.J.; Ge, H.; Masurekar, M.; Massover, W.H.; Yang, G.P.; Matsui, Y.; Sadoshima, J.; Vatner, S.F. Autophagy in chronically ischemic myocardium. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 13807–13812. [[CrossRef](#)]
271. Munteanu, I.; Kalimo, H.; Saraste, A.; Nishino, I.; Minassian, B.A. Cardiac autophagic vacuolation in severe X-linked myopathy with excessive autophagy. *Neuromuscul Disord* **2017**, *27*, 185–187. [[CrossRef](#)]
272. Li, Z.; Song, Y.; Liu, L.; Hou, N.; An, X.; Zhan, D.; Li, Y.; Zhou, L.; Li, P.; Yu, L.; et al. miR-199a impairs autophagy and induces cardiac hypertrophy through mTOR activation. *Cell Death Differ.* **2017**, *24*, 1205–1213. [[CrossRef](#)] [[PubMed](#)]

273. Zhu, H.; Tannous, P.; Johnstone, J.L.; Kong, Y.; Shelton, J.M.; Richardson, J.A.; Le, V.; Levine, B.; Rothermel, B.A.; Hill, J.A. Cardiac autophagy is a maladaptive response to hemodynamic stress. *J. Clin. Invest.* **2007**, *117*, 1782–1793. [[CrossRef](#)] [[PubMed](#)]
274. Valentim, L.; Laurence, K.M.; Townsend, P.A.; Carroll, C.J.; Soond, S.; Scarabelli, T.M.; Knight, R.A.; Latchman, D.S.; Stephanou, A. Urocortin inhibits Beclin1-mediated autophagic cell death in cardiac myocytes exposed to ischaemia/reperfusion injury. *J. Mol. Cell Cardiol.* **2006**, *40*, 846–852. [[CrossRef](#)] [[PubMed](#)]
275. Dupont, N.; Temime-Smaali, N.; Lafont, F. How ubiquitination and autophagy participate in the regulation of the cell response to bacterial infection. *Biol. Cell* **2010**, *102*, 621–634. [[CrossRef](#)] [[PubMed](#)]
276. Takahama, M.; Akira, S.; Saitoh, T. Autophagy limits activation of the inflammasomes. *Immunol. Rev.* **2018**, *281*, 62–73. [[CrossRef](#)]
277. Deretic, V.; Levine, B. Autophagy balances inflammation in innate immunity. *Autophagy* **2018**, *14*, 243–251. [[CrossRef](#)]
278. Harris, J.; De Haro, S.A.; Master, S.S.; Keane, J.; Roberts, E.A.; Delgado, M.; Deretic, V. T helper 2 Cytokines inhibit autophagic control of intracellular Mycobacterium tuberculosis. *Immunity* **2007**, *27*, 505–517. [[CrossRef](#)]
279. Yano, T.; Kurata, S. An unexpected twist for autophagy in Crohn's disease. *Nat. Immunol.* **2009**, *10*, 134–136. [[CrossRef](#)]
280. Henckaerts, L.; Cleyne, I.; Brinar, M.; John, J.M.; Van Steen, K.; Rutgeerts, P.; Vermeire, S. Genetic variation in the autophagy gene ULK1 and risk of Crohn's disease. *Inflamm. Bowel. Dis.* **2011**, *17*, 1392–1397. [[CrossRef](#)]
281. Hoefkens, E.; Nys, K.; John, J.M.; Van Steen, K.; Arijis, I.; Van der Goten, J.; Van Assche, G.; Agostinis, P.; Rutgeerts, P.; Vermeire, S.; et al. Genetic association and functional role of Crohn disease risk alleles involved in microbial sensing, autophagy, and endoplasmic reticulum (ER) stress. *Autophagy* **2013**, *9*, 2046–2055. [[CrossRef](#)] [[PubMed](#)]
282. Rioux, J.D.; Xavier, R.J.; Taylor, K.D.; Silverberg, M.S.; Goyette, P.; Huett, A.; Green, T.; Kuballa, P.; Barmada, M.M.; Datta, L.W.; et al. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat. Genet.* **2007**, *39*, 596–604. [[CrossRef](#)] [[PubMed](#)]
283. Qiao, Y.Q.; Huang, M.L.; Zheng, Q.; Wang, T.R.; Xu, A.T.; Cao, Y.; Zhao, D.; Ran, Z.H.; Shen, J. CNTNAP3 associated ATG16L1 expression and Crohn's disease. *Mediat. Inflamm.* **2015**, *2015*, 404185. [[CrossRef](#)] [[PubMed](#)]
284. Bai, W.; Bai, J.; Li, Y.; Tian, D.; Shi, R. Microtubule-associated protein 1S-related autophagy inhibits apoptosis of intestinal epithelial cells via Wnt/beta-catenin signaling in Crohn's disease. *Biochem. Biophys. Res. Commun.* **2017**, *485*, 635–642. [[CrossRef](#)]

