Journal of the Neurological Sciences 400 (2019) 72–82

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

The progress of neuronal autophagy in cerebral ischemia stroke: Mechanisms, roles and research methods

Kai Hou, Dan Xu, Fengyang Li, Shijie Chen, Yunman Li*

State Key Laboratory of Natural Medicines, Department of Physiology, China Pharmaceutical University, Nanjing 210009, China

ARTICLE INFO

Keywords:
Autophagy
Neurons
Cerebral ischemic injury
Apoptosis
Regulators

ABSTRACT

There is increasing evidence indicating that autophagy may be a new target in the treatment of ischemic stroke. Moderate autophagy can clear damaged organelles, thereby protecting cells against various injuries. However, long-term excessive autophagy brings redundant degradation of cell contents, leading to cell death and eventually serious damage to tissues and organs. A number of different animal models of ischemic brain injury shows that autophagy is activated and involved in the regulation of neuronal death during ischemic brain injury. This article summarizes the role of autophagy, its underlying regulators and mechanisms in ischemic neuronal injury. We briefly introduce the relationship between apoptosis and autophagy and give a summary of research methods and modulators of autophagy.

1. Introduction

Autophagy is a process in which a cell fuses with its own substance surrounded by a lysosome and a bilayer membrane, thereby degrading the cell's own substance. Autophagy process is crucial in pathogenesis, progression and treatment of many diseases [1]. However, its role in these diseases remains controversial. In the central nervous system (CNS), it has been reported that mice lacking autophagy-related genes 5 or 7 (*Atg5 or Atg7*) exhibit motor dysfunction and accumulation of neuronal inclusion bodies [2,3], indicating that reduced autophagy affects motor functions. However, studies on the effects of autophagy on spinal cord ischemia-reperfusion injury (SCIR) are inconsistent. Some studies showed that the activation of autophagy can reduce nerve damage, while others reported that the inhibition of autophagy can provide protection to neurons [4,5]. In the cardiovascular system, autophagy is considered to have a dual role in ischemia-reperfusion (I/R) injury. Autophagy has played a protective role in improving energy metabolism and maintaining cell homeostasis during I/R [6]. However, the study found that the use of autophagy inhibitors 3-methyladenine (3-MA) and LY294002 can reduce the death of cardiomyocytes in glucose-free culture, suggesting that autophagy can lead to cell death [7].

Stroke is an acute cerebrovascular disease mainly manifested by the damage of brain tissue caused by cerebrovascular lesion and relevant neurological deficits. It is reported that stroke is the primary cause of disability and affects approximately 795,000 people annually [8]. Ischemic stroke is considered as one of the major fatal diseases in the world with high incidence, mortality, disability and recurrence rates. At present, clinical treatment strategies for acute ischemic stroke,

Abbreviations: CNS, Central nervous system; SCIR, Spinal cord ischemia-reperfusion injury; I/R, Ischemia and reperfusion; 3-MA, 3-methyladenine; HI, Hypoxia-ischemia; GF, Growth factors; AMPK, Adenosine monophosphate activated protein kinase; mTOR, Mammalian target of rapamycin; WM, Wortmannin; CREB, cAMP response element binding protein; TIA, Transient ischemic attack; OGD, oxygen-glucose deprivation; IPC, Ischemic preconditioning; ATV, Atorvastatin; MCAO, Middle cerebral artery model; ROS, Reactive oxygen species; JNK, c-Jun N-terminal kinase; LC3-II, type II microtubule-associated protein 1 light chain 3; mTORC1, mammalian target of rapamycin complex 1; AMP, Adenosine monophosphate; ATP, adenosine triphosphate; ERS, Endoplasmic reticulum stress; PERK, Protein kinase R (PKR)-like endoplasmic reticulum kinase; eIF2a, Eukaryotic initiation factor 2a; IRE1, Inositol-requiring enzyme-1; TRAF2, Tumor necrosis factor receptor associated factor 2; CaMKK, Calcium/calmodulin-dependent protein kinase kinase; NMDA, *N*-methyl-D-aspartic acid receptors; TSC1/2, Tuberous sclerosis complex 1/2; Rheb, Ras homolog enriched in brain; PI3K, Phosphatidylinositol 3-kinases; PIP3, phosphatidylinositol(3,4,5)-trisphosphate; PPAR-γ, peroxisome proliferator-activated receptor-γ; BCL-2, B-cell lymphoma-2; BCL-XL, B-cell lymphoma extra large; HIF-1α, Hypoxia-inducible factor 1α; ULK1, Unc-51 like autophagy activating kinase; NF-κB, Nuclear factor kappa B; HIF-1α, Hypoxia-inducible factor 1α; VEGF, Vascular endothelial growth factor; EPO, Erythropoietin; GLUT1, Glucose transporter 1; BNIP3, Bcl-2 and adenovirus E1B 19 kDa interacting protein 3; BH3, Bcl-2 homology domain 3; LC3, Microtubule associated protein 1 light chain 3; LAMP, Lysosome Associated Membrane Protein; HCQ, HCQ: hydroxychloroquine

* Corresponding author.
E-mail addresses: 1721091056@stu.cpu.edu.cn (K. Hou), 1621090709@stu.cpu.edu.cn (D. Xu), 17768126930@163.com (F. Li), 17351014665@163.com (S. Chen), yunmanlicpu@163.com (Y. Li).

https://doi.org/10.1016/j.jns.2019.03.015
Received 24 November 2018; Received in revised form 25 February 2019; Accepted 15 March 2019
Available online 16 March 2019
0022-510X/

thrombolytic [9] and thrombectomy therapy are limited by their narrow therapeutic window [10]. Neuronal damage and death in infarct areas are the direct consequence of acute cerebral ischemia [11]. Previous studies showed that both autophagy and apoptosis of neurons are activated during stroke, suggesting that there may be a common pathway of autophagy and apoptosis, and its conversion and regulation determine the fate of neurons [12], with the underlying mechanisms not yet clear. In this review, we will introduce in detail the concept of autophagy, its relationship with apoptosis in neuronal death during cerebral ischemia, and potential research methods and modulators targeting neuronal autophagy after cerebral ischemia.

2. Autophagy

In some cases, autophagy could be involved in cell death but in most cases autophagy is a normal and important process of degradation, a process where cellular components are engulfed by autophagosome and fuse with lysosome for degradation [13,14]. Autophagosomes are vesicular structures surrounded by a bilayer membrane in cells. The main site of autophagosome biosynthesis in neurons is the axon terminals. Proper basal autophagy can be transported retrogradely to the cell body by autophagosomes, and fuse with lysosomes to become mature autophagosomes during transportation, which plays an important role in maintaining axis homeostasis [15].

Inadequate autophagy or transport in axons may lead to the accumulation of proteins, organelles, and abnormal membrane structures in axons, causing pathological changes. Pathological conditions may induce autophagy, local biosynthesis of autophagosomes increases and axons accumulate, resulting in cell death [16]. Autophagy is a highly conserved degradation pathway of cells under the control of *Atg* to maintain cell survival, differentiation, growth, and stability [17,18].

2.1. Neuronal autophagy

Since neurons are the most sensitive cells in ischemic injury, neuronal autophagy can be observed early in an ischemic stroke. Neuronal autophagy is increased in neonatal cerebral hypoxia-ischemia (HI) [19]. In the 1990s, Nitatori et al. discovered membrane-bound vacuoles containing an unordered intracellular component in CA1 neurons after an ischemic injury [20]. The same group found that autophagy occurs before cells undergo typical nuclear contraction in the early stages of apoptosis when they observed morphological features of PC12 neuronal cells after serum deprivation in vitro. In addition, cortical neurons in the ischemic region show multiple cytoplasmic vacuoles in ischemic brain tissue, and many follow-up studies have confirmed this phenomenon [21] (Fig. 1). Neuronal autophagy can be divided into basal inducible autophagy in different states.

2.1.1. Neuronal basal autophagy

In neurons, basal autophagy is thought to have a role of “housekeeper” [22]. It is generally believed that the level of neuronal autophagy and autophagosome biosynthesis rate are low under normal condition [15] which may be related to its ability to use both glucose and ketone bodies for energy supply [23]. Glycogen is little in the brain, almost all of which is stored in astrocytes. Under the condition of low blood glucose, glycogen in adjacent astrocytes can be degraded into lactic acid, ketone bodies and glucose, released through gap junctions to neighboring neurons. Then neurons use glucose, lactic acid or ketone bodies to supply energy in a short period of time. Astrocytes also secrete growth factors (GF) and neuropeptides that also contribute to neuronal protection [24]. Many existing data indicate that the basal autophagy have protective effects on neurons. Basal autophagy prevents the accumulation of damaged organelles and the accumulation of abnormal proteins, thereby maintaining the axon's homeostasis and effectively eliminating dead cells. However, with the progress of autophagy, when neurons receive more stimulation, the control of autophagy is relieved, causing the conversion of basic autophagy to inducible autophagy [15].

2.1.2. Neuronal inducible autophagy

Compared with basal autophagy, the degree of inducible autophagy is significantly stronger and it is a protective response of cells to external stimuli. Activation of autophagy in the CNS is not only associated with cerebral I/R but also with nutritional deficiencies, neurotoxins, excitotoxic stimuli, closed craniocerebral trauma, and neuropathic pathways [15,25,26]. Current data indicate that autophagy is controlled by multiple regulators and its activation depends on nutrient availability, such as insulin, amino acids and adenosine monophosphate activated protein kinase (AMPK), which act through mammalian target of rapamycin (mTOR) [27]. It is generally believed that mTOR is involved in the negative regulation of autophagy, involving the regulation of cell survival, differentiation, transcription, translation, protein degradation, actin cytoskeleton organization, which has multifunctional biological properties. However, the negative regulation mechanism of mTOR on autophagy is still not clear [28].Current findings suggest that inhibition of neuronal basal autophagy prior to ischemic injury can worsen subsequent ischemic injury [66,84]. Conversely, after the onset of ischemic injury, autophagy in neurons has been activated, at which point inhibition of autophagy level provides neuroprotection, whereas excessive activation of autophagy levels worsens the injury.

3. The role of autophagy during cerebral ischemia

Current evidence suggests that autophagy plays a dual role in the determination of neuronal fate after cerebral ischemic injury [30]. On the one hand, the activation of autophagy pathways is inhibited by 3-methyladenine (3-MA) and wortmannin (WM), which promotes neuronal apoptosis and necrosis, and increases the infarct volume and neurological deficit caused by ischemia and hypoxia in neonatal rats. Conversely, the use of rapamycin to activate the autophagy pathway before ischemia and hypoxia can increase phosphorylation of protein kinase B(Akt) and cAMP response element binding protein (CREB), which in turn significantly reduces neuronal death and brain injury [31]. A variety of neuroprotective strategies have been demonstrated to be associated with increased autophagy in neurons, such as endogenous neuroprotective mechanism induced by ischemic preconditioning and hypoxia preconditioning [32,33] and the neuroprotection activated by neuroprotective drugs [34,35]. On the other hand, in vitro and in vivo studies have also shown that excessive cell autophagy also leads to neuronal death (autophagic cell death) [36,37]. Inhibition of autophagy and mitochondrial autophagy is also implicated in neuroprotection triggered by some exercise training [38,39], ischemic postconditioning [40] and neuroprotective drugs [41,42]. Therefore, the role of autophagy in cerebral ischemia may be determined by the time of its action or the degree of activation/inhibition.

More in-depth mechanism research is still needed about autophagy pathway and it has great potential to be a new therapeutic target for stroke. There are two contradictory views about the potential impact of autophagy on ischemic neurons based on existing experimental data as follows.

3.1. Autophagy plays a protective role in ischemia-induced neuronal death

After focal cerebral ischemia, Beclin-1 in brain tissue is overexpressed, and 3-MA can significantly reduce Beclin-1 expression and transfer cell death patterns from apoptosis to necrosis. Beclin-1 is a key regulator of the autophagic initiation phase and its expression is significantly up-regulated after cerebral ischemia, and consistent with the time course of neuronal autophagy [43]. Beclin-1 induces the formation of autophagosomes and initiates autophagy by accumulating key autophagy proteins on the precursor structures of autophagosomes, including Beclin1, Vps34, and Vps15 complexes [38]. On the contrary,

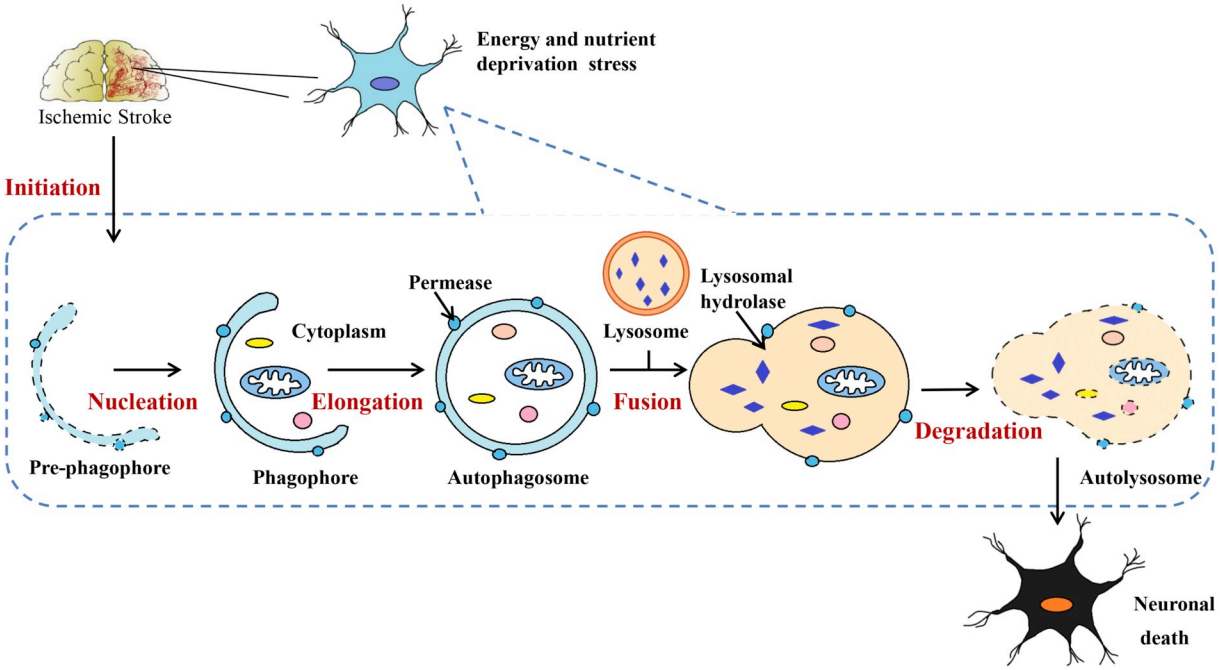

Fig. 1. The complete autophagy cycle is a highly regulated multi-step process, which can be divided into four stages: (1) Under the regulation of autophagy initiation signal, phagocytic vacuole in the cytoplasm is formed. (2) The phagocytic vacuole is continuously extended to form a cup-shaped bilayer membrane structure, which encapsulates the part of the cytoplasm that needs to be degraded, and finally becomes a closed "O"-shaped bilayer membrane structure autophagosome. (3) The formed autophagosome reaches the lysosome through the intracellular transport system and fuses with the lysosome. (4) The membrane of the autophagosome and its encapsulated cytosolic components are degraded by lysosomal enzymes while the useful substances are transported to the cytosol for reuse [23,29].

rapamycin can induce autophagy, upregulate the expression of Beclin-1 to reduce cell death and reduce the degree of brain tissue damage [44]. Carloni et al. used a neonatal mouse model of hypoxic-ischemic brain damage. After administration of rapamycin [45], it was found that the expression of Beclin-1 was significantly up-regulated, and the death of hippocampus and cortical neurons was significantly reduced. For patients with large-area cerebral infarction or transient ischemic attack (TIA), drugs with appropriate up-regulation of autophagy may have some neuroprotective effects [46].

Autophagy inhibitors 3-MA and wortmannin inhibited autophagy and reduced neuronal damage in rats 24 h after OGD(oxygen-glucose deprivation) [12]. Conversely, in models of brain injury induced by I/R in neonatal rats. The use of Rapamycin (mTOR specific inhibitor) induces autophagy, leading to increased expression of Beclin-1 in the cerebral cortex and hippocampus, which can reduce necrotizing cell death and brain injury [45]. Zhou et al. reported that Oxymatrine treatment alleviated histological injury in I/R rats, inhibiting apoptosis, promoting autophagy and accompanied by upregulated expression of silent mating type information regulation 2 homolog-1 (SIRT1) proteins [47]. Autophagic activation may also be associated with neuroprotection of ischemic preconditioning (IPC), as the previous brief exposure to the ischemic site increased neuronal tolerance to ischemia and reduced neuronal damage in cerebral cortex [48]. In addition, autophagy plays a protective role in cerebral I/R injury of brain microvascular endothelial cells, and increasing autophagy helps maintain the integrity of the blood-brain barrier [49]. Zhang et al. reported the neuroprotective function of Atorvastatin (ATV) depended on autophagic activity to diminish ER stress-related cell apoptosis in rats with the middle cerebral artery model (MCAO) and suggested that compounds that inhibit autophagic activity might reduce the neuroprotective effect of ATV after brain ischemia [50–52].

3.2. Excessive autophagy activation exacerbates neuronal death

Adhami et al. observed rapid massive degeneration of axons 24 h after ischemia/hypoxia in cerebral cortical neurons [51]. It has also been found that AMPK-mediated autophagy can expand the ischemic volume and aggravate the pathological changes [53,54]. In contrast, in *Atg7*-deficient ($Atg^{flox/flox}$, nestin-cre) mouse neurons, the loss of hippocampal pyramidal cells was observed after ischemia stroke. Drug-inhibited autophagy also reduced neuronal damage caused by focal cerebral ischemia in rats. Intraventricular infusion of the autophagy inhibitor 3-MA after a permanent MCAO in rats has a significant reduction in infarct volume [55]. Recent studies have shown that inhibition of autophagy with 3-MA in rats with severe global cerebral ischemia can prevent the occurrence of programmed necrosis in hippocampal CA1 neurons, indicating that autophagy has a damaging effect in cerebral ischemia [56]. Wang et al. Suggested intermedin has a similar effect as 3-MA, can reduce pathological neuronal injury and protect the brain against cerebral ischemia injury in rats by attenuating the effects of autophagy [57].

If I/R injury cannot be promptly corrected, ischemia cells in an "autophagic stress state" will result in activation of a large number of lysosomes, eventually leading to cell death [58]. The neurotoxic effect of autophagy is also reflected by excessive self-feeding of the necessary intracellular components, or interaction with the apoptotic pathway [55]. Koike et al. found that *Atg7* knockout neonatal mice had almost no neurological deficits after I/R injury [59]. Zheng et al. used a ribonucleic acid RNA interference technique to down-regulate the expression of Beclin-1 in a rat model of cerebral ischemia to reduce infarct volume and improve symptoms of neurological deficits [60]. Xing et al. used a BECN1 knockout mouse to obtain similar conclusions [50].

The role of autophagy activation after ischemic stroke remains controversial. Autophagy observed in dying cells at different stages of ischemic injury is responsible for cell death, or as a cell endogenous neuroprotection process? The reaction needs more experiments and research to confirm.

4. Interplay between neuronal autophagy and apoptosis in the ischemic penumbra after stroke

The clinical manifestations of ischemic strokes are cerebral tissue ischemia, hypoxia, edema, brain metabolism disorders and neurological deficit resulting from cerebral blood flow supply disorders [61]. Existing studies have shown that a few minutes of cerebral ischemia can trigger a series of cascade reactions, such as nutrient and energy depletion, release of toxic amino acids, and reactive oxygen species (ROS) [62], leading to irreversible necrotic death of neurons in the ischemic core region [63,64]. However, there is an ischemic penumbra in the peripheral region around the ischemic core region due to collateral circulation and other reasons, the neurons in this region are affected by ischemia to varying degrees, thereby presenting different fates aside from autophagy—necrosis, apoptosis, pyroptosis (a form of inflammatory programmed cell death [65]), among which the relationship between apoptosis and autophagy has drawn the biggest interest in researchers.

4.1. Autophagy and apoptosis after cerebral ischemia

Although autophagy and apoptosis are two different responses of cells to environmental stress and energy depletion, existing research results suggest that stroke induces autophagy and apoptosis in the penumbra area at the same time, and two pathways coexist in the same cell. Significant up-regulation of apoptosis and autophagy can be detected within hours of cerebral hypoxia-ischemia [66]. After 6 to 24 h after cerebral ischemia in rats, elevated caspase-3/Beclin1 double-labeled positive cells were observed [67]. Previous studies have also shown that permanent ischemia in rats induced both neuronal apoptosis and autophagy. In addition, after 6 h of ischemia and hypoxia, a large amount of autophagosome was detected in the cytoplasm of partially dead neurons [38]. Rami et al. also observed that when the neurons in ischemic penumbra show strong autophagy but do not exhibit apoptosis by means of TUNEL. These neurons show a certain degree of nuclear condensation [68]. This phenomenon suggests that the autophagic pathway may be earlier than the apoptotic pathway, it is even possible that autophagy triggered apoptosis. These phenomena all indicated that stroke also activates neuronal apoptosis and autophagy pathways in the ischemic penumbra [69], which play a distinct role in determining the fate of damaged neurons: apoptosis represents death, whereas autophagy may indicate possible survival [41].

4.2. Mechanisms of the relationship between autophagy and apoptosis after cerebral ischemia

Although it is now clear that there are common regulatory pathways for autophagy and apoptosis, we still lack in-depth studies of the mechanisms for the conversion and regulation of autophagy or apoptosis in injured neurons after stroke. Beclin-1 interacts with the important anti-apoptotic protein Bcl2 through its unique BH3 pattern to form the Bcl2-Beclin-1 complex, which blocks the autophagic effects [39,70]. Pattingre et al. demonstrated that cells were more likely to undergo apoptosis by knocking out Beclin-1 or over expressing Bcl2 when nutrient was depleted [71]. Therefore, stabilization of this complex inhibits autophagy and promotes apoptosis, and cells enter the apoptotic pathway while dissociation of the complex promotes autophagy and inhibits apoptosis, leading cells into the autophagy pathway [38].

The c-Jun N-terminal kinase (JNK) is a key neuronal death-modulating kinase. However, JNK may also be associated with neuroprotection [46]. Using MCAO, Murata revealed a novel role for JNK, which suppresses the JNK pathway in the acute phase to reduce neurological deficits and cerebral infarct volume, whereas inhibition of the JNK pathway after 7 days shows the opposite effect. An important target of JNK is the phosphorylation of multiple sites of interaction between Bcl2 and Beclin-1 (Ser87, Ser70, Thr69), which ultimately leads to the dissociation of the Bcl2-Beclin-1 complex and promotes the entry of autophagy into the cell [72]. Mutation of these phosphorylation sites of Bcl2 or knockdown of JNK1 can block autophagy. Moderately phosphorylated Bcl2 inhibits apoptosis, whereas hyperphosphorylation causes the promotion of apoptosis [73]. Therefore, JNK1-mediated Bcl2 phosphorylation may be responsible for the regulation of the stability of the Bcl2-Beclin-1 complex, which determines the important regulation and conversion factors for neuronal autophagy or apoptotic after cerebral ischemia.

In summary, the neurons are confronted with both two fates after cerebral ischemia, fatal apoptotic and possibly surviving autophagy. Proper promotion of autophagy by inhibiting apoptosis can rescue damaged neurons within the penumbra.

5. Autophagy-inducing factors and signaling pathways in cerebral ischemia

5.1. Inducing factors of autophagy during cerebral ischemia

Ischemia and hypoxia in brain are strong stimulating factors for inducing autophagy in neurons, which is achieved in a number of ways. Adhami et al. [51] and Koike et al. [59] used neonatal and adult rat respectively to found that a large number of autophagosomes were formed in brain tissue within a short period of time after ischemia-anoxia induction accompanied by a rapid increase in the level of type II microtubule-associated protein 1 light chain 3 (LC3-II). The supply of insulin and amino acids is reduced when the brain tissue is hypoxic, and their activation effect on the main inhibitor of autophagy, mammalian target of rapamycin complex 1(mTORC1), is diminished; At the same time, the energy supply is reduced, increasing the ratio of adenosine monophosphate (AMP) and adenosine triphosphate (ATP), activating AMPK, which induces an enhancement in autophagy. Secondly, ischemia and hypoxia in brain tissue can directly induce endoplasmic reticulum stress (ERS), to produce a large number of unfolded proteins and enhance autophagy through protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK)/ eukaryotic initiation factor 2a (eIF2a) [74] and inositol-requiring enzyme-1 (IRE1)/tumor necrosis factor receptor associated factor 2 (TRAF2)/JNK [75] pathways. Increased intracellular Ca^{2+} concentration can also be involved in ERS-induced autophagy through the calcium/calmodulin-dependent protein kinase kinase (CaMKK)/AMPK/mTORC1 pathway. Finally, cerebral ischemia and hypoxia lead to mitochondrial dysfunction, producing excess ROS, leading to DNA damage, lipid peroxidation, and increased or ruptured lysosomal membrane permeability [76], inducing autophagy activation. In addition, H_2O_2 can activate the expression of *Atg4*, leading to the transformation of LC3 and promoting the formation of autophagosomes [62].

Glutamate-induced excitotoxicity is mediated by activation of *N*-methyl-D-aspartic acid receptors (NMDA), which plays a key role in many aspects of ischemic brain injury. NMDA agonists induce activation of autophagy in striatal damaged neurons. Excitotoxicity-mediated autophagy activation may be involved in the JNK signaling pathway, one of the most important pathways in the NMDA receptor-mediated signaling pathway. In cerebral ischemia, JNK has become a recognized target of neuroprotection [46]. The pathways involving above factors affecting post-stroke autophagy will be discussed in the following section.

5.2. The major regulatory pathways of autophagy in cerebral ischemic injury

5.2.1. Mammalian target of rapamycin (mTOR) pathway

The mTOR is a 289 kDa serine/threonine protein kinase involved in the regulation of transcription, cytoskeletal assembly, cell growth and survival by binding to different accessory molecules. Chong et al. [77] showed that PI3K/Akt/mTOR signaling pathway is involved in the

regulation of acute neuronal injury during cerebral ischemia. PI3K activates Akt through phosphorylation and inhibits tuberous sclerosis complex 1/2 (TSC1/2) activation. Inactivation of TSC1/2 activates Ras homolog enriched in brain (Rheb), after which mTOR is activated and autophagy is inhibited by activated mTOR.

The mTOR pathway is the primary pathway by which mammals regulate starvation-induced autophagy. Many signals, such as energy status, different forms of stress, growth factors, amino acids, glucose, can regulate its activities [78]. mTOR activity is reduced to activate autophagy during energy shortage, growth factor deficiency or the inhibition effect of rapamycin [79]. mTOR signaling pathway was activated in ischemic penumbra after cerebral ischemia–reperfusion injury in rats. mTOR inhibitor rapamycin significantly decreased the mTOR activation and infarct volume and subsequently improved neurological function. These results may relate to inhibition of neuron apoptosis and activation of autophagy [80].

5.2.2. Phosphatidylinositol 3-kinases (PI3K) pathway

Phosphatidylinositol 3-kinases (PI3K) is composed of I, II and III. Beclin-1 is a component of component III, which plays a vital role in the initial stage of autophagy, and interacts with other components in the PI3K signaling pathway to initiates autophagy during cerebral ischemia [81,82]. Netrin-1 ameliorated BBB impairment secondary to ischemic stroke by promoting tight junction function and endothelial survival. PI3K-mediated autophagy activation depending on UNC5H2 receptor could be an underlying mechanism [83].

The PI3K pathway is the main cascade signaling pathway that controls mTORC1. Different types of PI3K activation have different regulatory effects on autophagy: when cell surface receptors bind to growth factors (GF) or insulin, they activate type I PI3K, increasing their product phosphatidylinositol(3,4,5)-trisphosphate(PIP3). Autophagy is inhibited by activating the Akt-mTORC1 pathway [84]. Conversely, when type III PI3K is activated, its product PI3P activates autophagy. Therefore, type III PI3K inhibitors such as 3-MA, WM, can down-regulate autophagy levels [78]. In addition to the mTOR and PI3K pathways, studies have found that the p53 pathway inhibits autophagy under normal conditions while acting as an inducer of autophagy in conditions of nutrient deficiency or stress [23].

5.2.3. Peroxisome proliferators-activated receptors (PPAR-γ)

As a member of the nuclear hormone receptor superfamily, peroxisome proliferator-activated receptor-γ(PPAR-γ) is a ligand-activated transcription factor. PPAR-γ activation antagonizes Beclin-1 mediated autophagy by up-regulating the expression of B-cell lymphoma-2 (Bcl2)/B-cell lymphoma extra large (BCL-XL) [85]. Bcl2 phosphorylation activates autophagy and reduces mitochondrial damage [86]. In addition, binding of Bcl2 to Beclin-1 can inhibit autophagy, while hypoxia-inducible factor 1α (HIF-1α) competes with Beclin-1 for binding to Bcl2, thereby releasing Beclin-1 and promoting autophagy [87].

5.2.4. Adenosine 5′-monophosphate (AMP) -Activated Protein Kinase (AMPK)

AMPK is a serine/threonine protein kinase consisting of three subunits: α catalytic subunit, β and γ regulatory subunits [88]. Current studies suggest that α catalytic subunit contains a threonine phosphorylation site that activates AMPK when phosphorylated, and that activation of AMPK inhibits mTOR activity to induce autophagy [54]. Accumulating evidence indicates that the AMPK-mTOR signaling pathway regulates the activation of the autophagy pathway through the coordinated phosphorylation of Unc-51 like autophagy activating kinase (ULK1) [89].

5.2.5. Nuclear factor kappa B (NF-κB)

Nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression of multiple genes [90]. Li et al. reported that NF-κB1 (p50) knockdown inhibits mTOR activity and enhances autophagy during cerebral ischemia [91]. The NF-κB-dependent p53 signaling pathway is also associated with autophagy and apoptosis following cerebral ischemia/reperfusion [92]. MAPK is an upstream regulator of mTORC1, and MAPK-mTOR signaling pathway can also induce autophagy during cerebral I/R [93].

4.2.6 Hypoxia-Inducible Factor 1 (HIF-1).

Hypoxia-inducible factor 1 (HIF-1) is composed of a constitutively expressed HIF-1β subunit and an inducible expressed HIF-1α subunit, which responds to hypoxia-activated key transcription during cerebral ischemia [94]. Since ubiquitination is inhibited under hypoxic conditions, HIF-1α forms a dimer with HIF-1β, activating several downstream genes of hypoxia, such as vascular endothelial growth factor (VEGF), erythropoietin (EPO), Glucose transporter 1 (GLUT1) and glycolytic enzymes [95]. Bcl2 and adenovirus E1B 19 kDa interacting protein 3 (BNIP3) have a Bcl2 homology domain 3 (BH3), a subfamily of the Bcl2 family and an important target gene for HIF-1α [96]. BNIP3 competes with Beclin-1 for binding to Bcl2, in which situation Beclin-1 is released to trigger autophagy. BNIP3 also inhibits the upstream activator Rheb of mTOR and ultimately activates autophagy by inhibiting mTOR activity. However, the relative role of these factors still needs to be demonstrated in vivo [97]. HIF-1α also plays an important role in autophagy activation after ischemia by up-regulating another target gene, tumor protein p53 [95].

In summary, autophagy involved signal pathways during cerebral ischemic injury are summarized in Fig. 2.

6. Autophagy research methods after ischemic stroke

6.1. Common experimental indicators

Autophagy participates in several important pathophysiological processes of the body, and its positioning, qualitative and even quantitative detection can further deepen the understanding of the occurrence and development of some diseases. At present, the commonly used detection indicators in the basic research of autophagy after ischemic stroke are as follows: Autophagosomes, Microtubule associated protein 1 light chain 3(LC3), Cathepsin, Beclin-1, Lysosome Associated Membrane Protein (LAMP) and P62 protein.

The commonly used biomarkers for monitoring autophagy are not actually suitable for monitoring autophagic flux (autophagosome degradants and lysosomal inclusions). As a result, the results of many studies have been questioned because they are limited to monitoring only static markers. In addition to monitoring the degradation of autophagosomes, the degree of lipidation of LC3 before and after the use of lysosomal inhibitors such as BafA1 can also be compared. In addition, it is now possible to monitor the strength of autophagic flow in real time and in vivo by constructing a double-labeled fluorescent LC3 vector, which is crucial for the clinical monitoring of autophagy regulators [98].

Despite the challenges of the development of autophagy regulators, as technology and cognition escalate, we will see more selective autophagy modulators for clinical treatment.

6.2. Challenges in developing modulators of autophagy

Despite the huge potential of autophagy as a target, no drugs have been developed specifically for autophagy regulation. The obstacles to autophagy modulators development in clinical applications are mainly the lack of specific and accurate bioassays. Main modulators of autophagy available to date and their limitations are in Tables 1, 2.

Currently, many drugs lack specificity during the process of activating or inhibiting autophagy. For example, 3-MA and wortmannin are non-selective PI3K inhibitors Similarly, although rapamycin selectively inhibits mTORC1. Meanwhile, in addition to affecting autophagy, certain drugs also inhibit cell growth and proliferation. Chloroquine and HCQ [109] not only block the autophagy function of lysosomes, but

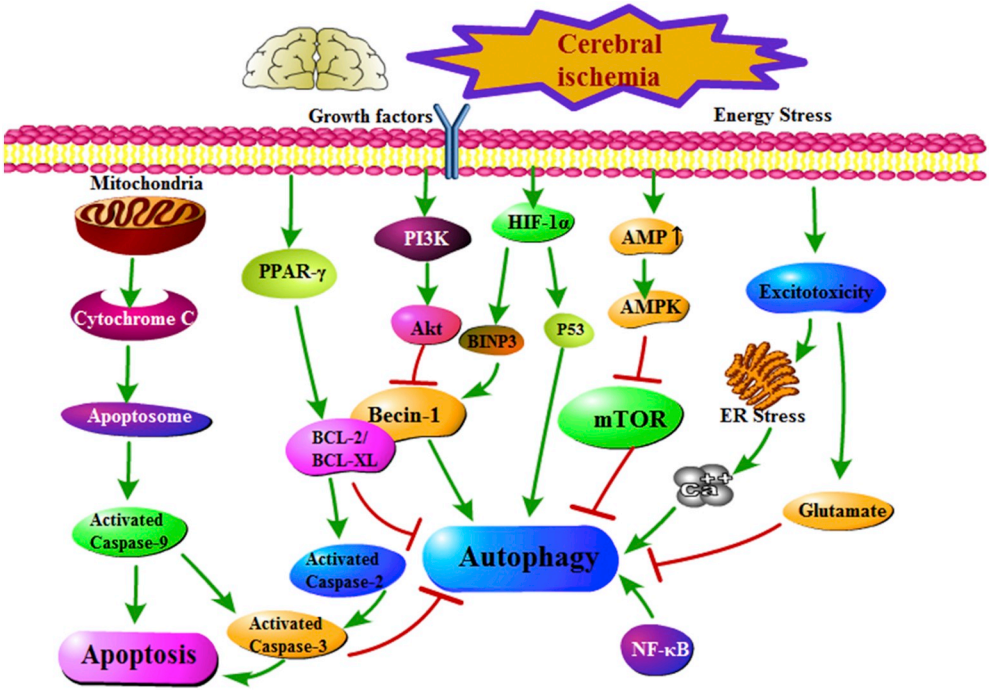

Fig. 2. Signaling pathway involved in autophagy during cerebral ischemia/hypoxia injury. (HIF-1α: hypoxia inducible factor 1, BNIP3: Bcl2 and adenovirus E1B 19 kDa interacting protein 3, Beclin-1: mammalian ortholog of the yeast autophagy-related gene 6 (Atg6), P53: tumor protein p53, PPAR-γ: peroxisome proliferator-activated receptor γ, BCL2: B lymphoma associated protein 2, BCL-XL: B lymphoma extra large protein, AMP: adenosine-5′-monophosphate, AMPK: AMP-activated protein kinase, PI3K: phosphoinositide 3-kinase, Akt: protease B, NF-κB: nuclear factor κB, ROS: reactive oxygen free radicals, ER: Endoplasmic reticulum, mTOR: mammalian target of rapamycin).

also degrade endosomes and inhibit vesicular transport. Besides, many autophagy modulators are not selectively targeted to a single cell type. Therefore, autophagy regulators may play a completely opposite role (activation/inhibition) in different cell types when we assess drug effects. In conclusion, adequate understanding of autophagy regulation on different cell types will help researchers develop more specific regulators.

7. Summary and outlook

In neurons, autophagy is of vital importance for the regulation of homeostasis and protein functions. Under normal conditions, autophagy is maintained at a relatively low level, and under pathophysiological conditions (such as cerebral ischemic injury), autophagy is activated. Whether autophagy activation is a manifestation of endogenous neuroprotective mechanisms, or just the opposite is still controversial. There is growing evidence supporting autophagy as a double-edged sword. With the deepening of research, the mechanism of autophagy in ischemic stroke will gradually become clear, which is of great significance for clinical treatment of ischemic brain injury. However, the complexity and heterogeneity of the experimental environment, including cell/animal models; animal strains and age; differences in the intensity of ischemia and duration of cerebral ischemia may lead to distinctions in experimental results. Well-regulated autophagy can react quickly to overcome various stresses and thereby enhance cell viability, while prolongation and excessive autophagy caused by ischemia are fatal.

In addition, several tool drugs such as 3-MA and rapamycin are widely used to evaluate the effect of autophagy inhibition on ischemic neuronal damage. The conclusions based on these studies are uncertain due to the low specificity of pharmacological agents that affect cell growth and secretion. It should be noted that the application of genetic techniques, such as gene knockout of autophagy genes, is also limited because many autophagy genes also regulate biological functions unrelated to autophagy. Therefore, a variety of methods including pharmacology and genetic manipulation should be considered to arrive at valid conclusions. Moreover, the role of neuroprotective factors secreted by brain and peripheral organs in autophagy in ischemic brain injury remains to be further studied. The development of highly specific autophagy manipulation reagents and better animal models of diseases may help researchers better understand the exact role of autophagy in disease progression.

Table 1
Activators of autophagy available to date and their limitations.

Target	Activators	Mechanism	Status	Limitation	References
AMPK	Hydrogen sulfide	Activation	Experimental agent	Potentially toxic for the respiratory tract	[99]
	Metformin	Activation	Approved for treatment of type 2 diabetes	Inhibition of respiratory complex I	[100]
	Simvastatin	Activation	Approved for treatment of obesity	Potentially mitochondriotoxic	[101]
mTORC1	Rapamycin	Inhibition	Approved for use in coronary stents	Excessive immunosuppressive effects	[28,102]
	Temsirolimus	Inhibition	Approved for cancer therapy	Excessive immunosuppressive effects	[103]
BECN1	BECN1-derived peptide	Activation	Preclinical development	Potential immunogenicity	[104]
ROS	Antimycobacterial antibiotics	Increase	Approved for treatment of mycobacterial infections	Potentially interferes with many ROS sensitive processes	[62]
MAPK	IFNγ	Activation	Clinical trials mainly for cancer immunotherapy	Unclear	[105]
Inositol	Lithium	Reduction	Approved for treatment of bipolar disorders	Inhibits various neuronal functions	[106]

Table 2
Inhibitions of autophagy available to date and their limitations.

Target	Inhibitors	Mechanism	Status	Limitation	References
VPS34	3-MA	Inhibition	Experimental agent	Inhibits various class III PI3Ks	[7]
	Wortmannin	Inhibition	Experimental agent	Inhibits various class III PI3Ks	[32]
ULK1	MRT68921	Inhibition	In preclinical development	Nonselective	[107]
ATG4B	NSC185058	Inhibition	In preclinical development	Unclear	[108]
Lysosomal	HCQ/Chloroquine	Inhibition	Extensively used as antimalarial agent	Inhibitor of lysosomal functions	[109]
	Lys05	Inhibition	Preclinical development	Unclear	[110]
Mitophagy	Mdivi-1	Inhibition	Preclinical development	Inhibitor of mitochondrial fragmentation	[111]
ROS	Edavarone	Scavenger	Experimental agent	Potentially interferes with many ROS sensitive processes	[112]
AMPK	Compound C(dorsomorphin)	Inhibition	AMPK inhibition	Potentially interferes with AMPK dependent processes	[113]
Na^+/K^+-ATPase	Cardiac glycosides	Inhibition	Extensively used for treatment of cardiac disorders	Narrow therapeutic window	[114]

3-MA:3-methyladenine;AMPK:AMP-activated protein kinase;ATG4B: autophagy-related 4B cysteine peptidase; BECN1 gene: Beclin-1 is a protein that in humans is encoded by the BECN1 gene.;HCQ:hydroxychloroquine;IFNγ, interferon-γ; MAPK, mitogen-activated protein kinase; mTORC: mechanistic target of rapamycin complex; NA:Not applicable; PI3K, phosphoinositide 3-kinase; ROS: reactive oxygen species; ULK: UNC-51-like autophagy activating kinase.

Author contributions

K.H. and D.X. performed most of the experiments and was involved in writing a draft manuscript; F.L. and S.C. were involved in writing and modification of the final manuscript. All authors read and approved the final manuscript.

Acknowledgments

This project was supported by the Priority Academic Program Development of Jiangsu Higher Education Institutions and the Policy Directive Program of Jiangsu Province [BY2015072-03] and National Science and Technology Major Project of the Ministry of Science and Technology of China (No. 2016ZX09101031).

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

[1] J.H. Lee, W.H. Yu, A. Kumar, S. Lee, P.S. Mohan, C.M. Peterhoff, D.M. Wolfe, M. Martinezvicente, A.C. Massey, G. Sovak, Lysosomal proteolysis and autophagy require Presenilin 1 and are disrupted by Alzheimer-related PS1 mutations, Cell 141 (7) (2010) 1146–1158.
[2] T. Hara, K. Nakamura, M. Matsui, A. Yamamoto, Y. Nakahara, R. Suzukimigishima, M. Yokoyama, K. Mishima, I. Saito, H. Okano, Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice, Nature 441 (7095) (2006) 885–889.
[3] M. Kroner, K.M. Weiss, B. Biedermann, S. Seidl, A.W. Holleitner, A. Badolato, P.M. Petroff, P. Hberg, R.J. Warburton, K. Karrai, Loss of autophagy in the central nervous system causes neurodegeneration in mice, Nature 441 (7095) (2006) 880–884.
[4] H. Hou, L. Zhang, L. Zhang, P. Tang, Acute spinal cord injury in rats should target activated autophagy, J. Neurosurg. Spine 20 (5) (2014) 568–577.
[5] H.Y. Zhang, Z.G. Wang, F.Z. Wu, X.X. Kong, J. Yang, B.B. Lin, S.P. Zhu, L. Lin, C.S. Gan, X.B. Fu, Regulation of autophagy and ubiquitinated protein accumulation by bFGF promotes functional recovery and neural protection in a rat model of spinal cord injury, Mol. Neurobiol. 48 (3) (2013) 452–464.
[6] Q. Zheng, J. Li, X. Wang, Interplay between the ubiquitin-proteasome system and autophagy in proteinopathies, Int J Physiol Pathophysiol Pharmacol 1 (2) (2009) 127–142.
[7] J.P. Tsai, C.H. Lee, T.H. Ying, C.L. Lin, C.L. Lin, J.T. Hsueh, Y.H. Hsieh, Licochalcone a induces autophagy through PI3K/Akt/mTOR inactivation and autophagy suppression enhances Licochalcone A-induced apoptosis of human cervical cancer cells, Oncotarget 6 (30) (2015) 28851–28866.
[8] E.J. Benjamin, M.J. Blaha, S.E. Chiuve, M. Cushman, S.R. Das, R. Deo, S.D. de Ferranti, J. Floyd, M. Fornage, C. Gillespie, Heart disease and stroke Statistics-2017 update: a report from the American Heart Association, Circulation 131 (4) (2017) e29.
[9] R.L. Medcalf, Plasminogen activation-based thrombolysis for ischaemic stroke: the diversity of targets may demand new approaches, Curr. Drug Targets 12 (12) (2011).
[10] S. Hafez, M.N. Hoda, X. Guo, M.H. Johnson, S.C. Fagan, A. Ergul, Comparative analysis of different methods of ischemia/reperfusion in Hyperglycemic stroke outcomes: interaction with tPA, Transl. Stroke Res. 6 (3) (2015) 171–180.
[11] F. Xu, J.H. Gu, Z.H. Qin, Neuronal autophagy in cerebral ischemia, Neurosci. Bull. 28 (5) (2012) 658–666, https://doi.org/10.1007/s12264-012-1268-9.
[12] G. He, W. Xu, L. Tong, S. Li, S. Su, X. Tan, C. Li, Gadd45b prevents autophagy and apoptosis against rat cerebral neuron oxygen-glucose deprivation/reperfusion injury, Apoptosis 21 (4) (2016) 390–403.
[13] M.V. Jain, A.M. Paczulla, T. Klonisch, F.N. Dimgba, S.B. Rao, K. Roberg, F. Schweizer, C. Lengerke, P. Davoodpour, V.R. Palicharla, Interconnections between apoptotic, autophagic and necrotic pathways: implications for cancer therapy development, J. Cell. Mol. Med. 17 (1) (2013) 12–29.
[14] Z. Jiang, L.T. Watts, S. Huang, Q. Shen, P. Rodriguez, C. Chen, C. Zhou, T.Q. Duong, The effects of methylene blue on autophagy and apoptosis in MRI-defined Normal tissue, ischemic penumbra and ischemic Core, PLoS One 10 (6) (2015) e0131929.
[15] Z. Yue, L. Friedman, M. Komatsu, K. Tanaka, The cellular pathways of neuronal autophagy and their implication in neurodegenerative diseases, Biochim. Biophys. Acta Mol. cell Res. 1793 (9) (2009) 1496–1507.
[16] S. Maday, K.E. Wallace, E.L.F. Holzbaur, Autophagosomes initiate distally and mature during transport toward the cell soma in primary neurons, Autophagy 196 (5) (2012) 407–417.
[17] S.T. Shibutani, T. Yoshimori, A current perspective of autophagosome biogenesis, Cell Res. 24 (1) (2014) 58–68.
[18] J.H. Kim, S.B. Hong, J.K. Lee, S. Han, K.H. Roh, K.E. Lee, Y.K. Kim, E.J. Choi, H.K. Song, Insights into autophagosome maturation revealed by the structures of ATG5 with its interacting partners, Autophagy 11 (1) (2015) 75–87.
[19] V. Ginet, A. Spiehlmann, C. Rummel, N. Rudinskiy, Y. Grishchuk, R. Luthi-Carter, P.G. Clarke, A.C. Truttmann, J. Puyal, Involvement of autophagy in hypoxic-excitotoxic neuronal death, Autophagy 10 (5) (2014) 846–860, https://doi.org/10.4161/auto.28264.
[20] T. Nitatori, N. Sato, S. Waguri, Y. Karasawa, H. Araki, K. Shibanai, E. Kominami, Y. Uchiyama, Delayed neuronal death in the CA1 pyramidal cell layer of the gerbil hippocampus following transient ischemia is apoptosis, Journal of Neuroscience the Official Journal of the Society for Neuroscience 15 (2) (1995) 1001.
[21] Y. Uchiyama, Autophagic cell death and its execution by lysosomal cathepsins, Arch. Histol. Cytol. 64 (3) (2001) 233–246.
[22] Y. Uchiyama, M. Shibata, M. Koike, K. Yoshimura, M. Sasaki, Autophagy–physiology and pathophysiology, Histochem. Cell Biol. 129 (4) (2008) 407–420.
[23] B. Gabryel, A. Kost, D. Kasprowska, Neuronal autophagy in cerebral ischemia–a potential target for neuroprotective strategies? Pharmacol. Rep. 64 (1) (2012) 1–15.
[24] B. Gabryel, H.I. Trzeciak, Role of astrocytes in pathogenesis of ischemic brain injury, Neurotox. Res. 3 (2) (2001) 205.
[25] B. Levine, J. Abrams, p53: the Janus of autophagy? Nat. Cell Biol. 10 (6) (2008) 637–639.
[26] N. Mizushima, Autophagy: process and function, Genes Dev. 21 (22) (2007) 2861.
[27] X. Zeng, J.H. Overmeyer, W.A. Maltese, Functional specificity of the mammalian Beclin-Vps34 PI 3-kinase complex in macroautophagy versus endocytosis and lysosomal enzyme trafficking, J. Cell Sci. 119 (2) (2006) 259–270.
[28] J. Bockaert, P. Marin, mTOR in brain physiology and pathologies, Physiol. Rev. 95 (4) (2015) 1157–1187.
[29] X.P. Huang, H. Ding, J.D. Lu, Y.H. Tang, B.X. Deng, C.Q. Deng, Autophagy in cerebral ischemia and the effects of traditional Chinese medicine, J. Integr. Med. 13 (5) (2015) 289–296.
[30] M. Yoshihiro, F. Norio, S.J. Hae, Y. Feng, L. Xiangrong, T. Yasukazu, L. Yumin, A. Ken, J. Xunming, E.H. Lo, Delayed inhibition of c-Jun N-terminal kinase worsens outcomes after focal cerebral ischemia, J. Neurosci. Off. J Soc. Neurosci. 32 (24) (2012) 8112.
[31] W. Balduini, S. Carloni, G. Buonocore, Autophagy in hypoxia-ischemia induced brain injury, J. Matern-Fetal Med. 25 (sup1) (2012) 30–34.

[32] H.K. Park, K. Chu, K.H. Jung, S.T. Lee, J.J. Bahn, M. Kim, K.L. Sang, J.K. Roh, Autophagy is involved in the ischemic preconditioning, Neurosci. Lett. 451 (1) (2009) 16–19.
[33] L. Zhan, S. Chen, K. Li, D. Liang, X. Zhu, L. Liu, Z. Lu, W. Sun, E. Xu, Autophagosome maturation mediated by Rab7 contributes to neuroprotection of hypoxic preconditioning against global cerebral ischemia in rats, Cell Death Dis. 8 (7) (2017) e2949.
[34] M. Papadakis, G. Hadley, M. Xilouri, L.C. Hoyte, S. Nagel, M.M. Mcmenamin, G. Tsaknakis, S.M. Watt, C.W. Drakesmith, R. Chen, Tsc1 (hamartin) confers neuroprotection against ischemia by inducing autophagy, Nat. Med. 19 (3) (2013) 351–357.
[35] Y. Yang, K. Gao, Z. Hu, W. Li, D. Henry, S. Ling, J.A. Rudd, M. Fang, Autophagy Upregulation and apoptosis Downregulation in DAHP and Triptolide treated cerebral ischemia, Mediat. Inflamm. 2015 (2) (2015) 120198.
[36] L. Zhang, W. Niu, Z. He, Q. Zhang, Y. Wu, C. Jiang, C. Tang, Y. Hu, J. Jia, Autophagy suppression by exercise pretreatment and p38 inhibition is neuroprotective in cerebral ischemia, Brain Res. 1587 (1) (2014) 127–132.
[37] L. Zhang, X. Hu, L. Jing, L. Li, X. Chen, R. Huang, P. Zhong, Physical exercise improves functional recovery through mitigation of autophagy, attenuation of apoptosis and enhancement of neurogenesis after MCAO in rats, BMC Neurosci. 14 (1) (2013) 46 (2013-04-08).
[38] G. Li, J. Teng, J. Guo, L. Yi, G. Cui, L. Gu, L. Su, Y. Zhang, Inhibition of autophagy contributes to ischemic Postconditioning-induced Neuroprotection against focal cerebral ischemia in rats, PLoS One 7 (9) (2012) e46092.
[39] S.H. Baek, A.R. Noh, K. Kim, M. Akram, Y.J. Shin, E.S. Kim, S.W. Yu, A. Majid, O.N. Bae, Modulation of mitochondrial function and autophagy mediates carnosine neuroprotection against ischemic brain damage, Stroke 45 (8) (2014) 2438–2443.
[40] Z.Q. Shao, Z.J. Liu, Neuroinflammation and neuronal autophagic death were suppressed via rosiglitazone treatment: new evidence on neuroprotection in a rat model of global cerebral ischemia, J. Neurol. Sci. 349 (1–2) (2015) 65.
[41] W. Yan, H. Zhang, X. Bai, Y. Lu, H. Dong, L. Xiong, Autophagy activation is involved in neuroprotection induced by hyperbaric oxygen preconditioning against focal cerebral ischemia in rats, Brain Res. 1402 (16) (2011) 109–121.
[42] R. Sheng, L.S. Zhang, R. Han, X.Q. Liu, B. Gao, Z.H. Qin, Autophagy activation is associated with neuroprotection in a rat model of focal cerebral ischemic preconditioning, Autophagy 6 (4) (2010) 482–494.
[43] J. Fan, Z. Zhang, X. Chao, J. Gu, W. Cai, W. Zhou, G. Yin, Q. Li, Ischemic preconditioning enhances autophagy but suppresses autophagic cell death in rat spinal neurons following ischemia-reperfusion, Brain Res. 1562 (20) (2014) 76–86.
[44] K. Wei, P. Wang, C.Y. Miao, A double-edged sword with therapeutic potential: an updated role of autophagy in ischemic cerebral injury, CNS Neurosci Ther. 18 (11) (2012) 879–886.
[45] S. Carloni, G. Buonocore, W. Balduini, Protective role of autophagy in neonatal hypoxia-ischemia induced brain injury, Neurobiol. Dis. 32 (3) (2008) 329–339.
[46] Y. Cheng, F. Qiu, S. Tashiro, S. Onodera, T. Ikejima, ERK and JNK mediate TNFalpha-induced p53 activation in apoptotic and autophagic L929 cell death, Biochem. Biophys. Res. Commun. 376 (3) (2008) 483–488.
[47] S. Zhou, B. Qiao, X. Chu, Q. Kong, Oxymatrine attenuates cognitive deficits through SIRT1-mediated autophagy in ischemic stroke, J. Neuroimmunol. 323 (2018) 136–142, https://doi.org/10.1016/j.jneuroim.2018.06.018.
[48] R. Sheng, X.Q. Liu, L.S. Zhang, B. Gao, R. Han, Y.Q. Wu, X.Y. Zhang, Z.H. Qin, Autophagy regulates endoplasmic reticulum stress in ischemic preconditioning, Autophagy 8 (3) (2012) 310–325.
[49] H. Li, A. Gao, D. Feng, Y. Wang, L. Zhang, Y. Cui, B. Li, Z. Wang, G. Chen, Evaluation of the protective potential of brain microvascular endothelial cell autophagy on blood-brain barrier integrity during experimental cerebral ischemia-reperfusion injury, Transl. Stroke Res. 5 (5) (2014) 618.
[50] S. Xing, Y. Zhang, J. Li, J. Zhang, Y. Li, C. Dang, C. Li, Y. Fan, J. Yu, Z. Pei, Beclin 1 knockdown inhibits autophagic activation and prevents the secondary neurodegenerative damage in the ipsilateral thalamus following focal cerebral infarction, Autophagy 8 (1) (2012) 63.
[51] F. Adhami, G. Liao, Y.M. Morozov, A. Schloemer, V.J. Schmithorst, J.N. Lorenz, R.S. Dunn, C.V. Vorhees, M. Wills-Karp, J.L. Degen, R.J. Davis, N. Mizushima, P. Rakic, B.J. Dardzinski, S.K. Holland, F.R. Sharp, C.Y. Kuan, Cerebral ischemia-hypoxia induces intravascular coagulation and autophagy, Am. J. Pathol. 169 (2) (2015) 566–583.
[52] T. Zhang, D. Lu, W. Yang, C. Shi, J. Zang, L. Shen, H. Mai, A. Xu, HMG-CoA Reductase inhibitors relieve endoplasmic reticulum stress by autophagy inhibition in rats with permanent brain ischemia, Front. Neurosci. 12 (2018) 405, https://doi.org/10.3389/fnins.2018.00405.
[53] L. Du, R.W. Hickey, H. Bayır, S.C. Watkins, V.A. Tyurin, F.L. Guo, P.M. Kochanek, L.W. Jenkins, J. Ren, G. Gibson, Starving neurons show sex difference in autophagy, J. Biol. Chem. 284 (4) (2009) 2383.
[54] J. Li, L.D. Mccullough, Effects of AMP-activated protein kinase in cerebral ischemia, J. Cereb. Blood Flow Metab. 30 (3) (2010) 480–492.
[55] Y.D. Wen, R. Sheng, L.S. Zhang, R. Han, X. Zhang, X.D. Zhang, F. Han, K. Fukunaga, Z.H. Qin, Neuronal injury in rat model of permanent focal cerebral ischemia is associated with activation of autophagic and lysosomal pathways, Autophagy 4 (6) (2008) 762–769.
[56] J.Y. Wang, Q. Xia, K.T. Chu, J. Pan, L.N. Sun, B. Zeng, Y.J. Zhu, Q. Wang, K. Wang, B.Y. Luo, Severe global cerebral ischemia-induced programmed necrosis of hippocampal CA1 neurons in rat is prevented by 3-methyladenine: a widely used inhibitor of autophagy, J. Neuropathol. Exp. Neurol. 70 (4) (2011) 314–322.
[57] M. Wang, J. Wang, Z. Liu, X. Guo, N. Wang, N. Jia, Y. Zhang, J. Yuan, Effects of intermedin on autophagy in cerebral ischemia/reperfusion injury, Neuropeptides 68 (2018) 15–21, https://doi.org/10.1016/j.npep.2017.10.004.
[58] F. Adhami, A. Schloemer, C.Y. Kuan, The roles of autophagy in cerebral ischemia, Autophagy 3 (1) (2007) 42.
[59] M. Koike, M. Shibata, M. Tadakoshi, K. Gotoh, M. Komatsu, S. Waguri, N. Kawahara, K. Kuida, S. Nagata, E. Kominami, Inhibition of autophagy prevents hippocampal pyramidal neuron death after hypoxic-ischemic injury, Am. J. Pathol. 172 (2) (2008) 454–469.
[60] Y. Zheng, J. Liu, X. Li, L. Xu, Y. Xu, RNA interference-mediated downregulation of Beclin1 attenuates cerebral ischemic injury in rats, Acta Pharmacol. Sin. 30 (7) (2009) 919–927.
[61] S. Swerdlow, K. Mccoll, Y. Rong, M. Lam, A. Gupta, C.W. Distelhorst, Apoptosis inhibition by Bcl-2 gives way to autophagy in glucocorticoid-treated lymphocytes, Autophagy 4 (5) (2008) 612–620.
[62] R. Scherzshouval, E. Shvets, E. Fass, H. Shorer, L. Gil, Z. Elazar, Reactive oxygen species are essential for autophagy and specifically regulate the activity of Atg4, EMBO J. 26 (7) (2007) 1749.
[63] B. Chelluboina, K.R. Nalamolu, G.G. Mendez, J.D. Klopfenstein, D.M. Pinson, D.Z. Wang, K.K. Veeravalli, Mesenchymal stem cell treatment prevents post-stroke Dysregulation of matrix Metalloproteinases and tissue inhibitors of Metalloproteinases, Cell. Physiol. Biochem. 44 (4) (2017) 1360–1369, https://doi.org/10.1159/000485533.
[64] X. Meng, G. Chu, Z. Yang, P. Qiu, Y. Hu, X. Chen, W. Peng, C. Ye, F.F. He, C. Zhang, Metformin protects neurons against oxygen-glucose deprivation/Reoxygenation -induced injury by Down-regulating MAD2B, Cell. Physiol. Biochem. 40 (3–4) (2016) 477–485, https://doi.org/10.1159/000452562.
[65] M. Ito, T. Shichita, M. Okada, R. Komine, Y. Noguchi, A. Yoshimura, R. Morita, Bruton's tyrosine kinase is essential for NLRP3 inflammasome activation and contributes to ischaemic brain injury, Nat. Commun. 6 (2015) 7360.
[66] Z. Yang, L. Zhong, S. Zhong, R. Xian, B. Yuan, Hypoxia induces microglia autophagy and neural inflammation injury in focal cerebral ischemia model, Exp. Mol. Pathol. 98 (2) (2015) 219–224.
[67] P. Wang, Y.F. Guan, H. Du, Q.W. Zhai, D.F. Su, C.Y. Miao, Induction of autophagy contributes to the neuroprotection of nicotinamide phosphoribosyltransferase in cerebral ischemia, Autophagy 8 (1) (2012) 77–87.
[68] T. Luo, G. Liu, H. Ma, B. Lu, H. Xu, Y. Wang, J. Wu, P. Ge, J. Liang, Inhibition of autophagy via activation of PI3K/Akt pathway contributes to the protection of ginsenoside Rb1 against neuronal death caused by ischemic insults, Int. J. Mol. Sci. 15 (9) (2014) 15426–15442.
[69] X. Yang, C. Hei, P. Liu, Y. Song, T. Thomas, S. Tshimanga, F. Wang, J. Niu, T. Sun, P.A. Li, Inhibition of mTOR pathway by Rapamycin reduces brain damage in rats subjected to transient forebrain ischemia, Int. J. Biol. Sci. 11 (12) (2015) 1424–1435.
[70] J. Xu, Y. Wang, X. Tan, H. Jing, MicroRNAs in autophagy and their emerging roles in crosstalk with apoptosis, Autophagy 8 (6) (2012) 873.
[71] W. Han, X. Fu, J. Xie, Z. Meng, Y. Gu, X. Wang, L. Li, H. Pan, W. Huang, miR-26a enhances autophagy to protect against ethanol-induced acute liver injury, J. Mol. Med. 93 (9) (2015) 1045–1055.
[72] C. Descloux, V. Ginet, P.G. Clarke, J. Puyal, A.C. Truttmann, Neuronal death after perinatal cerebral hypoxia-ischemia: focus on autophagy-mediated cell death, Int. J. Dev. Neurosci. 45 (2015) 75–85.
[73] Y. Zhu, Q. Bu, X. Liu, W. Hu, Y. Wang, Neuroprotective effect of TAT-14-3-3ε fusion protein against cerebral ischemia/reperfusion injury in rats, PLoS One 9 (3) (2014) e93334.
[74] S.B. Cullinan, J.A. Diehl, Coordination of ER and oxidative stress signaling: the PERK/Nrf2 signaling pathway, Int. J. Biochem. Cell Biol. 38 (3) (2006) 317–332.
[75] M. Høyerhansen, M. Jäättelä, Connecting endoplasmic reticulum stress to autophagy by unfolded protein response and calcium, Cell Death Differ. 14 (9) (2007) 1576.
[76] T. Yamashima, S. Oikawa, The role of lysosomal rupture in neuronal death, Prog. Neurobiol. 89 (4) (2009) 343–358.
[77] Z.Z. Chong, Y.C. Shang, S. Wang, K. Maiese, A critical kinase Cascade in neurological disorders: PI 3-K, Akt, and mTOR, Future Neurol. 7 (6) (2012) 733.
[78] B. Ravikumar, S. Sarkar, J.E. Davies, M. Futter, M. Garciaarencibia, Z.W. Greenthompson, M. Jimenezsanchez, V.I. Korolchuk, M. Lichtenberg, S. Luo, Regulation of mammalian autophagy in physiology and pathophysiology, Physiol. Rev. 90 (4) (2010) 1383–1435.
[79] J. Jiang, J. Dai, H. Cui, Vitexin reverses the autophagy dysfunction to attenuate MCAO-induced cerebral ischemic stroke via mTOR/Ulk1 pathway, Biomed. Pharmacother. 99 (2018) 583–590, https://doi.org/10.1016/j.biopha.2018.01.067.
[80] M. Wu, H. Zhang, J. Kai, F. Zhu, J. Dong, Z. Xu, M. Wong, L.H. Zeng, Rapamycin prevents cerebral stroke by modulating apoptosis and autophagy in penumbra in rats, Ann Clin Transl Neurol 5 (2) (2018) 138–146, https://doi.org/10.1002/acn3.507.
[81] D. Glick, S. Barth, K.F. Macleod, Autophagy: cellular and molecular mechanisms, J. Pathol. 221 (1) (2010) 3–12.
[82] C. Xingyong, S. Xicui, S. Huanxing, O. Jingsong, H. Yi, Z. Xu, H. Ruxun, P. Zhong, Upregulation of myeloid cell leukemia-1 potentially modulates beclin-1-dependent autophagy in ischemic stroke in rats, BMC Neurosci. 14 (1) (2013) 56.
[83] J. Yu, C. Li, Q. Ding, J. Que, K. Liu, H. Wang, S. Liao, Netrin-1 ameliorates blood-brain barrier impairment secondary to ischemic stroke via the activation of PI3K pathway, Front. Neurosci. 11 (2017) 700, https://doi.org/10.3389/fnins.2017.00700.
[84] S. Carloni, S. Girelli, C. Scopa, G. Buonocore, M. Longini, W. Balduini, Activation of autophagy and Akt/CREB signaling play an equivalent role in the

neuroprotective effect of rapamycin in neonatal hypoxia-ischemia, Autophagy 6 (3) (2010) 366–377.
[85] F. Xu, J. Li, W. Ni, Y. Shen, X. Zhang, Peroxisome proliferator-activated receptor-γ agonist 15d-prostaglandin J2 mediates neuronal autophagy after cerebral ischemia-reperfusion injury, PLoS One 8 (1) (2013) e55080.
[86] Z. Qi, D. Wen, W. Shi, R. Wang, C. Zhang, Y. Zhao, X. Ji, J.L. Ke, Y. Luo, Bcl-2 phosphorylation triggers autophagy switch and reduces mitochondrial damage in limb remote ischemic conditioned rats after ischemic stroke, Transl. Stroke Res. 6 (3) (2015) 198–206.
[87] M.C. Maiuri, G.L. Toumelin, A. Criollo, J.C. Rain, F. Gautier, P. Juin, E. Tasdemir, G. Pierron, K. Troulinaki, N. Tavernarakis, Functional and physical interaction between Bcl-XL and a BH3-like domain in Beclin-1, EMBO J. 26 (10) (2007) 2527–2539.
[88] S. Jiang, T. Li, T. Ji, W. Yi, Z. Yang, S. Wang, Y. Yang, C. Gu, AMPK: potential therapeutic target for ischemic stroke, Theranostics 8 (16) (2018) 4535–4551, https://doi.org/10.7150/thno.25674.
[89] J.F. Wang, Z.G. Mei, Y. Fu, S.B. Yang, S.Z. Zhang, W.F. Huang, L. Xiong, H.J. Zhou, W. Tao, Z.T. Feng, Puerarin protects rat brain against ischemia/reperfusion injury by suppressing autophagy via the AMPK-mTOR-ULK1 signaling pathway, Neural Regen. Res. 13 (6) (2018) 989–998, https://doi.org/10.4103/1673-5374.233441.
[90] C.H. Chen, P.R. Arany, Y.Y. Huang, E.M. Tomkinson, T. Saleem, F.E. Yull, T.S. Blackwell, Hamblin MR low level laser therapy activates NF-kB via generation of reactive oxygen species in mouse embryonic fibroblasts, SPIE BiOS Biomed. Optics 6 (7) (2011) e22453.
[91] W.L. Li, S.P. Yu, D. Chen, S.S. Yu, Y.J. Jiang, T. Genetta, L. Wei, The regulatory role of NF-κB in autophagy-like cell death after focal cerebral ischemia in mice, Neuroscience 244 (2013) 16–30.
[92] D.R. Cui, L. Wang, W. Jiang, A.H. Qi, Q.H. Zhou, X.L. Zhang, Propofol prevents cerebral ischemia-triggered autophagy activation and cell death in the rat hippocampus through the NF-κB/p53 signaling pathway, Neuroscience 246 (2013) 117.
[93] W. Peng-Ran, W. Jun-Song, Z. Chao, S. Xing-Fang, T. Na, K. Ling-Yi, Huang-Lian-Jie-Du-Decotion induced protective autophagy against the injury of cerebral ischemia/reperfusion via MAPK-mTOR signaling pathway, J. Ethnopharmacol. 149 (1) (2013) 270–280.
[94] J. Althaus, M. Bernaudin, E. Petit, J. Toutain, O. Touzani, A. Rami, Expression of the gene encoding the pro-apoptotic BNIP3 protein and stimulation of hypoxia-inducible factor-1α (HIF-1α) protein following focal cerebral ischemia in rats, Neurochem. Int. 48 (8) (2006) 687–695.
[95] X.Y. Xin, J. Pan, X.Q. Wang, J.F. Ma, J.Q. Ding, G.Y. Yang, S.D. Chen, 2-methoxyestradiol attenuates autophagy activation after global ischemia, Can. J. Neurol. Sci. 38 (4) (2011) 631–638.
[96] B. Cho, S.Y. Choi, O.H. Park, W. Sun, D. Geum, Differential expression of BNIP family members of BH3-only proteins during the development and after axotomy in the rat, Mol. Cells 33 (6) (2012) 605–610.
[97] J. Zhang, P.A. Ney, Mechanisms and biology of B-cell Leukemia/lymphoma 2/adenovirus E1B interacting protein 3 and nip-like protein X, Antioxid. Redox Signal. 14 (10) (2011) 1959.
[98] D.J. Klionsky, K. Abdelmohsen, A. Abe, M.J. Abedin, H. Abeliovich, A. Acevedo Arozena, H. Adachi, C.M. Adams, P.D. Adams, K. Adeli, P.J. Adhihetty, S.G. Adler, G. Agam, R. Agarwal, M.K. Aghi, M. Agnello, P. Agostinis, P.V. Aguilar, J. Aguirre-Ghiso, E.M. Airoldi, S. Ait-Si-Ali, T. Akematsu, E.T. Akporiaye, M. Al-Rubeai, G.M. Albaiceta, C. Albanese, D. Albani, M.L. Albert, J. Aldudo, H. Algul, M. Alirezaei, I. Alloza, A. Almasan, M. Almonte-Beceril, E.S. Alnemri, C. Alonso, N. Altan-Bonnet, D.C. Altieri, S. Alvarez, L. Alvarez-Erviti, S. Alves, G. Amadoro, A. Amano, C. Amantini, S. Ambrosio, I. Amelio, A.O. Amer, M. Amessou, A. Amon, Z. An, F.A. Anania, S.U. Andersen, U.P. Andley, C.K. Andreadi, N. Andrieu-Abadie, A. Anel, D.K. Ann, S. Anoopkumar-Dukie, M. Antonioli, H. Aoki, N. Apostolova, S. Aquila, K. Aquilano, K. Araki, E. Arama, A. Aranda, J. Araya, A. Arcaro, E. Arias, H. Arimoto, A.R. Ariosa, J.L. Armstrong, T. Arnould, I. Arsov, K. Asanuma, V. Askanas, E. Asselin, R. Atarashi, S.S. Atherton, J.D. Atkin, L.D. Attardi, P. Auberger, G. Auburger, L. Aurelian, R. Autelli, L. Avagliano, M.L. Avantaggiati, L. Avrahami, S. Awale, N. Azad, T. Bachetti, J.M. Backer, D.H. Bae, J.S. Bae, O.N. Bae, S.H. Bae, E.H. Baehrecke, S.H. Baek, S. Baghdiguian, A. Bagniewska-Zadworna, H. Bai, J. Bai, X.Y. Bai, Y. Bailly, K.N. Balaji, W. Balduini, A. Ballabio, R. Balzan, R. Banerjee, G. Banhegyi, H. Bao, B. Barbeau, M.D. Barrachina, E. Barreiro, B. Bartel, A. Bartolome, D.C. Bassham, M.T. Bassi, R.C. Bast Jr., A. Basu, M.T. Batista, H. Batoko, M. Battino, K. Bauckman, B.L. Baumgarner, K.U. Bayer, R. Beale, J.F. Beaulieu, G.R. Beck Jr., C. Becker, J.D. Beckham, P.A. Bedard, P.J. Bednarski, T.J. Begley, C. Behl, C. Behrends, G.M. Behrens, K.E. Behrns, E. Bejarano, A. Belaid, F. Belleudi, G. Benard, G. Berchem, D. Bergamaschi, M. Bergami, B. Berkhout, L. Berliocchi, A. Bernard, M. Bernard, F. Bernassola, A. Bertolotti, A.S. Bess, S. Besteiro, S. Bettuzzi, S. Bhalla, S. Bhattacharyya, S.K. Bhutia, C. Biagosch, M.W. Bianchi, M. Biard-Piechaczyk, V. Billes, C. Bincoletto, B. Bingol, S.W. Bird, M. Bitoun, I. Bjedov, C. Blackstone, L. Blanc, G.A. Blanco, H.K. Blomhoff, E. Boada-Romero, S. Bockler, M. Boes, K. Boesze-Battaglia, L.H. Boise, A. Bolino, A. Boman, P. Bonaldo, M. Bordi, J. Bosch, L.M. Botana, J. Botti, G. Bou, M. Bouche, M. Bouchecareilh, M.J. Boucher, M.E. Boulton, S.G. Bouret, P. Boya, M. Boyer-Guittaut, P.V. Bozhkov, N. Brady, V.M. Braga, C. Brancolini, G.H. Braus, J.M. Bravo-San Pedro, L.A. Brennan, E.H. Bresnick, P. Brest, D. Bridges, M.A. Bringer, M. Brini, G.C. Brito, B. Brodin, P.S. Brookes, E.J. Brown, K. Brown, H.E. Broxmeyer, A. Bruhat, P.C. Brum, J.H. Brumell, N. Brunetti-Pierri, R.J. Bryson-Richardson, S. Buch, A.M. Buchan, H. Budak, D.V. Bulavin, S.J. Bultman, G. Bultynck, V. Bumbasirevic, Y. Burelle, R.E. Burke, M. Burmeister, P. Butikofer, L. Caberlotto, K. Cadwell, M. Cahova, D. Cai, J. Cai, Q. Cai, S. Calatayud, N. Camougrand, M. Campanella, G.R. Campbell, M. Campbell, S. Campello, R. Candau, I. Caniggia, L. Cantoni, L. Cao, A.B. Caplan, M. Caraglia, C. Cardinali, S.M. Cardoso, J.S. Carew, L.A. Carleton, C.R. Carlin, S. Carloni, S.R. Carlsson, D. Carmona-Gutierrez, L.A. Carneiro, O. Carnevali, S. Carra, A. Carrier, B. Carroll, C. Casas, J. Casas, G. Cassinelli, P. Castets, S. Castro-Obregon, G. Cavallini, I. Ceccherini, F. Cecconi, A.I. Cederbaum, V. Cena, S. Cenci, C. Cerella, D. Cervia, S. Cetrullo, H. Chaachouay, H.J. Chae, A.S. Chagin, C.Y. Chai, G. Chakrabarti, G. Chamilos, E.Y. Chan, M.T. Chan, D. Chandra, P. Chandra, C.P. Chang, R.C. Chang, T.Y. Chang, J.C. Chatham, S. Chatterjee, S. Chauhan, Y. Che, M.E. Cheetham, R. Cheluvappa, C.J. Chen, G. Chen, G.C. Chen, G. Chen, H. Chen, J.W. Chen, J.K. Chen, M. Chen, M. Chen, P. Chen, Q. Chen, Q. Chen, S.D. Chen, S. Chen, S.S. Chen, W. Chen, W.J. Chen, W.Q. Chen, W. Chen, X. Chen, Y.H. Chen, Y.G. Chen, Y. Chen, Y. Chen, Y.J. Chen, Y.Q. Chen, Y. Chen, Z. Chen, Z. Chen, A. Cheng, C.H. Cheng, H. Cheng, H. Cheong, S. Cherry, J. Chesney, C.H. Cheung, E. Chevet, H.C. Chi, S.G. Chi, F. Chiacchiera, H.L. Chiang, R. Chiarelli, M. Chiariello, M. Chieppa, L.S. Chin, M. Chiong, G.N. Chiu, D.H. Cho, S.G. Cho, W.C. Cho, Y.Y. Cho, Y.S. Cho, A.M. Choi, E.J. Choi, E.K. Choi, J. Choi, M.E. Choi, S.I. Choi, T.F. Chou, S. Chouaib, D. Choubey, V. Choubey, K.C. Chow, K. Chowdhury, C.T. Chu, T.H. Chuang, T. Chun, H. Chung, T. Chung, Y.L. Chung, Y.J. Chwae, V. Cianfanelli, R. Ciarcia, I.A. Ciechomska, M.R. Ciriolo, M. Cirone, S. Claerhout, M.J. Clague, J. Claria, P.G. Clarke, R. Clarke, E. Clementi, C. Cleyrat, M. Cnop, E.M. Coccia, T. Cocco, P. Codogno, J. Coers, E.E. Cohen, D. Colecchia, L. Coletto, N.S. Coll, E. Colucci-Guyon, S. Comincini, M. Condello, K.L. Cook, G.H. Coombs, C.D. Cooper, J.M. Cooper, I. Coppens, M.T. Corasaniti, M. Corazzari, R. Corbalan, E. Corcelle-Termeau, M.D. Cordero, C. Corral-Ramos, O. Corti, A. Cossarizza, P. Costelli, S. Costes, S.L. Cotman, A. Coto-Montes, S. Cottet, E. Couve, L.R. Covey, L.A. Cowart, J.S. Cox, F.P. Coxon, C.B. Coyne, M.S. Cragg, R.J. Craven, T. Crepaldi, J.L. Crespo, A. Criollo, V. Crippa, M.T. Cruz, A.M. Cuervo, J.M. Cuezva, T. Cui, P.R. Cutillas, M.J. Czaja, M.F. Czyzyk-Krzeska, R.K. Dagda, U. Dahmen, C. Dai, W. Dai, Y. Dai, K.N. Dalby, L. Dalla Valle, G. Dalmasso, M. D'Amelio, M. Damme, A. Darfeuille-Michaud, C. Dargemont, V.M. Darley-Usmar, S. Dasarathy, B. Dasgupta, S. Dash, C.R. Dass, H.M. Davey, L.M. Davids, D. Davila, R.J. Davis, T.M. Dawson, V.L. Dawson, P. Daza, J. de Belleroche, P. de Figueiredo, R.C. de Figueiredo, J. de la Fuente, L. De Martino, A. De Matteis, G.R. De Meyer, A. De Milito, M. De Santi, W. de Souza, V. De Tata, D. De Zio, J. Debnath, R. Dechant, J.P. Decuypere, S. Deegan, B. Dehay, B. Del Bello, D.P. Del Re, R. Delage-Mourroux, L.M. Delbridge, L. Deldicque, E. Delorme-Axford, Y. Deng, J. Dengjel, M. Denizot, P. Dent, Deretic V. Der CJ, B. Derrien, E. Deutsch, T.P. Devarenne, R.J. Devenish, S. Di Bartolomeo, N. Di Daniele, F. Di Domenico, A. Di Nardo, S. Di Paola, A. Di Pietro, L. Di Renzo, A. Di Antonio, G. Diaz-Araya, I. Diaz-Laviada, M.T. Diaz-Meco, J. Diaz-Nido, C.A. Dickey, R.C. Dickson, M. Diederich, P. Digard, I. Dikic, S.P. Dinesh-Kumar, C. Ding, W.X. Ding, Z. Ding, L. Dini, J.H. Distler, A. Diwan, M. Djavaheri-Mergny, K. Dmytruk, R.C. Dobson, V. Doetsch, K. Dokladny, S. Dokudovskaya, M. Donadelli, X.C. Dong, X. Dong, Z. Dong, T.M. Donohue Jr., K.S. Doran, G. D'Orazi, G.W. Dorn 2nd, V. Dosenko, S. Dridi, L. Drucker, J. Du, Du LL, Du L, A. du Toit, P. Dua, L. Duan, P. Duann, V.K. Dubey, M.R. Duchen, M.A. Duchosal, H. Duez, I. Dugail, V.I. Dumit, M.C. Duncan, E.A. Dunlop, W.A. Dunn Jr., N. Dupont, L. Dupuis, R.V. Duran, T.M. Durcan, S. Duvezin-Caubet, U. Duvvuri, V. Eapen, D. Ebrahimi-Fakhari, A. Echard, L. Eckhart, C.L. Edelstein, A.L. Edinger, L. Eichinger, T. Eisenberg, A. Eisenberg-Lerner, N.T. Eissa, W.S. El-Deiry, V. El-Khoury, Z. Elazar, H. Eldar-Finkelman, C.J. Elliott, E. Emanuele, U. Emmenegger, N. Engedal, A.M. Engelbrecht, S. Engelender, J.M. Enserink, R. Erdmann, J. Erenpreisa, R. Eri, J.L. Eriksen, A. Erman, R. Escalante, E.L. Eskelinen, L. Espert, L. Esteban-Martinez, T.J. Evans, M. Fabri, G. Fabrias, C. Fabrizi, A. Facchiano, N.J. Faergeman, A. Faggioni, W.D. Fairlie, C. Fan, D. Fan, J. Fan, S. Fang, M. Fanto, A. Fanzani, T. Farkas, M. Faure, F.B. Favier, H. Fearnhead, M. Federici, E. Fei, T.C. Felizardo, H. Feng, Y. Feng, Y. Feng, T.A. Ferguson, A.F. Fernandez, M.G. Fernandez-Barrena, J.C. Fernandez-Checa, A. Fernandez-Lopez, M.E. Fernandez-Zapico, O. Feron, E. Ferraro, C.V. Ferreira-Halder, L. Fesus, R. Feuer, F.C. Fiesel, E.C. Filippi-Chiela, G. Filomeni, G.M. Fimia, J.H. Fingert, S. Finkbeiner, T. Finkel, F. Fiorito, P.B. Fisher, M. Flajolet, F. Flamigni, O. Florey, S. Florio, R.A. Floto, M. Folini, C. Follo, E.A. Fon, F. Fornai, F. Fortunato, A. Fraldi, R. Franco, A. Francois, A. Francois, L.B. Frankel, I.D. Fraser, N. Frey, D.G. Freyssenet, C. Frezza, S.L. Friedman, D.E. Frigo, D. Fu, J.M. Fuentes, J. Fueyo, Y. Fujitani, Y. Fujiwara, M. Fujiya, M. Fukuda, S. Fulda, C. Fusco, B. Gabryel, M. Gaestel, P. Gailly, M. Gajewska, S. Galadari, G. Galili, I. Galindo, M.F. Galindo, G. Galliciotti, L. Galluzzi, L. Galluzzi, V. Galy, N. Gammoh, S. Gandy, A.K. Ganesan, S. Ganesan, I.G. Ganley, M. Gannage, F.B. Gao, F. Gao, J.X. Gao, L. Garcia Nannig, E. Garcia Vescovi, M. Garcia-Macia, C. Garcia-Ruiz, A.D. Garg, P.K. Garg, R. Gargini, N.C. Gassen, D. Gatica, E. Gatti, J. Gavard, E. Gavathiotis, L. Ge, P. Ge, S. Ge, P.W. Gean, V. Gelmetti, A.A. Genazzani, J. Geng, P. Genschik, L. Gerner, J.E. Gestwicki, D.A. Gewirtz, S. Ghavami, E. Ghigo, D. Ghosh, A.M. Giammarioli, F. Giampieri, C. Giampietri, A. Giatromanolaki, D.J. Gibbings, L. Gibellini, S.B. Gibson, V. Ginet, A. Giordano, F. Giorgini, E. Giovannetti, S.E. Girardin, S. Gispert, S. Giuliano, C.L. Gladson, A. Glavic, M. Gleave, N. Godefroy, R.M. Gogal Jr., K. Gokulan, G.H. Goldman, D. Goletti, M.S. Goligorsky, A.V. Gomes, L.C. Gomes, H. Gomez, C. Gomez-Manzano, R. Gomez-Sanchez, D.A. Goncalves, E. Goncu, Q. Gong, C. Gongora, C.B. Gonzalez, P. Gonzalez-Alegre, P. Gonzalez-Cabo, R.A. Gonzalez-Polo, I.S. Goping, C. Gorbea, N.V. Gorbunov, D.R. Goring, A.M. Gorman, S.M. Gorski, S. Goruppi, S. Goto-Yamada, C. Gotor, R.A. Gottlieb, I. Gozes, D. Gozuacik, Y. Graba, M. Graef, G.E. Granato, G.D. Grant, S. Grant, G.L. Gravina, D.R. Green, A. Greenhough, M.T. Greenwood, B. Grimaldi, F. Gros, C. Grose, J.F. Groulx, F. Gruber, P. Grumati, T. Grune, J.L. Guan, K.L. Guan, B. Guerra, C. Guillen, K. Gulshan, J. Gunst, C. Guo, L. Guo, M. Guo, W. Guo, X.G. Guo, A.A. Gust, A.B. Gustafsson, E. Gutierrez,

M.G. Gutierrez, H.S. Gwak, A. Haas, J.E. Haber, S. Hadano, M. Hagedorn, D.R. Hahn, A.J. Halayko, A. Hamacher-Brady, K. Hamada, A. Hamai, A. Hamann, M. Hamasaki, I. Hamer, Q. Hamid, E.M. Hammond, F. Han, W. Han, J.T. Handa, J.A. Hanover, M. Hansen, M. Harada, L. Harhaji-Trajkovic, J.W. Harper, A.H. Harrath, A.L. Harris, J. Harris, U. Hasler, P. Hasselblatt, K. Hasui, R.G. Hawley, T.S. Hawley, C. He, C.Y. He, F. He, G. He, R.R. He, X.H. He, Y.W. He, Y.Y. He, J.K. Heath, M.J. Hebert, R.A. Heinzen, G.V. Helgason, M. Hensel, E.P. Henske, C. Her, P.K. Herman, A. Hernandez, C. Hernandez, S. Hernandez-Tiedra, C. Hetz, P.R. Hiesinger, K. Higaki, S. Hilfiker, B.G. Hill, J.A. Hill, W.D. Hill, K. Hino, D. Hofius, P. Hofman, G.U. Hoglinger, J. Hohfeld, M.K. Holz, Y. Hong, D.A. Hood, J.J. Hoozemans, T. Hoppe, C. Hsu, C.Y. Hsu, L.C. Hsu, D. Hu, G. Hu, H.M. Hu, H. Hu, M.C. Hu, Y.C. Hu, Z.W. Hu, F. Hua, Y. Hua, C. Huang, H.L. Huang, K.H. Huang, K.Y. Huang, S. Huang, S. Huang, W.P. Huang, Y.R. Huang, Y. Huang, Y. Huang, T.B. Huber, P. Huebbe, W.K. Huh, J.J. Hulmi, G.M. Hur, J.H. Hurley, Z. Husak, S.N. Hussain, S. Hussain, J.J. Hwang, S. Hwang, T.I. Hwang, A. Ichihara, Y. Imai, C. Imbriano, M. Inomata, T. Into, V. Iovane, J.L. Iovanna, R.V. Iozzo, N.Y. Ip, J.E. Irazoqui, P. Iribarren, Y. Isaka, A.J. Isakovic, H. Ischiropoulos, J.S. Isenberg, M. Ishaq, H. Ishida, I. Ishii, J.E. Ishmael, C. Isidoro, K. Isobe, E. Isono, S. Issazadeh-Navikas, K. Itahana, E. Itakura, A.I. Ivanov, A.K. Iyer, J.M. Izquierdo, Y. Izumi, V. Izzo, M. Jaattela, N. Jaber, D.J. Jackson, W.T. Jackson, T.G. Jacob, T.S. Jacques, C. Jagannath, A. Jain, N.R. Jana, B.K. Jang, A. Jani, B. Janji, P.R. Jannig, P.J. Jansson, S. Jean, M. Jendrach, J.H. Jeon, N. Jessen, E.B. Jeung, K. Jia, L. Jia, H. Jiang, H. Jiang, L. Jiang, T. Jiang, X. Jiang, X. Jiang, X. Jiang, Y. Jiang, Y. Jiang, A. Jimenez, C. Jin, H. Jin, L. Jin, M. Jin, S. Jin, U.K. Jinwal, E.K. Jo, T. Johansen, D.E. Johnson, G.V. Johnson, J.D. Johnson, E. Jonasch, C. Jones, L.A. Joosten, J. Jordan, A.M. Joseph, B. Joseph, A.M. Joubert, D. Ju, J. Ju, H.F. Juan, K. Juenemann, G. Juhasz, H.S. Jung, J.U. Jung, Y.K. Jung, H. Jungbluth, M.J. Justice, B. Jutten, N.O. Kaakoush, K. Kaarniranta, A. Kaasik, T. Kabuta, B. Kaeffer, K. Kagedal, A. Kahana, S. Kajimura, O. Kakhlon, M. Kalia, D.V. Kalvakolanu, Y. Kamada, K. Kambas, V.O. Kaminskyy, H.H. Kampinga, M. Kandouz, C. Kang, R. Kang, T.C. Kang, T. Kanki, T.D. Kanneganti, H. Kanno, A.G. Kanthasamy, M. Kantorow, M. Kaparakis-Liaskos, O. Kapuy, V. Karantza, M.R. Karim, P. Karmakar, A. Kaser, S. Kaushik, T. Kawula, A.M. Kaynar, P.Y. Ke, Z.J. Ke, J.H. Kehrl, K.E. Keller, J.K. Kemper, A.K. Kenworthy, O. Kepp, A. Kern, S. Kesari, D. Kessel, R. Ketteler, C. Kettelhut Ido, B. Khambu, M.M. Khan, V.K. Khandelwal, S. Khare, J.G. Kiang, A.A. Kiger, A. Kihara, A.L. Kim, C.H. Kim, D.R. Kim, D.H. Kim, E.K. Kim, H.Y. Kim, H.R. Kim, J.S. Kim, J.H. Kim, J.C. Kim, J.H. Kim, K.W. Kim, M.D. Kim, M.M. Kim, P.K. Kim, S.W. Kim, S.Y. Kim, Y.S. Kim, Y. Kim, A. Kimchi, A.C. Kimmelman, T. Kimura, J.S. King, K. Kirkegaard, V. Kirkin, L.A. Kirshenbaum, S. Kishi, Y. Kitajima, K. Kitamoto, Y. Kitaoka, K. Kitazato, R.A. Kley, W.T. Klimecki, M. Klinkenberg, J. Klucken, H. Knaevelsrud, E. Knecht, L. Knuppertz, J.L. Ko, S. Kobayashi, J.C. Koch, C. Koechlin-Ramonatxo, U. Koenig, Y.H. Koh, K. Kohler, S.D. Kohlwein, M. Koike, M. Komatsu, E. Kominami, D. Kong, H.J. Kong, E.G. Konstantakou, B.T. Kopp, T. Korcsmaros, L. Korhonen, V.I. Korolchuk, N.V. Koshkina, Y. Kou, M.I. Koukourakis, C. Koumenis, A.L. Kovacs, T. Kovacs, W.J. Kovacs, D. Koya, C. Kraft, D. Krainc, H. Kramer, T. Kravic-Stevovic, W. Krek, C. Kretz-Remy, R. Krick, M. Krishnamurthy, J. Kriston-Vizi, G. Kroemer, M.C. Kruer, R. Kruger, N.T. Ktistakis, K. Kuchitsu, C. Kuhn, A.P. Kumar, A. Kumar, A. Kumar, D. Kumar, D. Kumar, R. Kumar, S. Kumar, M. Kundu, H.J. Kung, A. Kuno, S.H. Kuo, J. Kuret, T. Kurz, T. Kwok, T.K. Kwon, Y.T. Kwon, I. Kyrmizi, A.R. La Spada, F. Lafont, T. Lahm, A. Lakkaraju, T. Lam, T. Lamark, S. Lancel, T.H. Landowski, D.J. Lane, J.D. Lane, C. Lanzi, P. Lapaquette, L.R. Lapierre, J. Laporte, J. Laukkarinen, G.W. Laurie, S. Lavandero, L. Lavie, LaVoie MJ, B.Y. Law, H.K. Law, K.B. Law, R. Layfield, P.A. Lazo, L. Le Cam, K.G. Le Roch, H. Le Stunff, V. Leardkamolkarn, M. Lecuit, B.H. Lee, C.H. Lee, E.F. Lee, G.M. Lee, H.J. Lee, H. Lee, J.K. Lee, J. Lee, J.H. Lee, J.H. Lee, M. Lee, M.S. Lee, P.J. Lee, S.W. Lee, S.J. Lee, S.J. Lee, S.Y. Lee, S.H. Lee, S.S. Lee, S.J. Lee, S. Lee, Y.R. Lee, Y.J. Lee, Y.H. Lee, C. Leeuwenburgh, S. Lefort, R. Legouis, J. Lei, Q.Y. Lei, D.A. Leib, G. Leibowitz, I. Lekli, S.D. Lemaire, J.J. Lemasters, M.K. Lemberg, A. Lemoine, S. Leng, G. Lenz, P. Lenzi, L.O. Lerman, D. Lettieri Barbato, J.I. Leu, H.Y. Leung, B. Levine, P.A. Lewis, F. Lezoualc'h, C. Li, F. Li, F.J. Li, J. Li, K. Li, L. Li, M. Li, M. Li, Q. Li, R. Li, S. Li, W. Li, W. Li, X. Li, Y. Li, J. Lian, C. Liang, Q. Liang, Y. Liao, J. Liberal, P.P. Liberski, P. Lie, A.P. Lieberman, H.J. Lim, K.L. Lim, K. Lim, R.T. Lima, C.S. Lin, C.F. Lin, F. Lin, F. Lin, F.C. Lin, K. Lin, K.H. Lin, P.H. Lin, T. Lin, W.W. Lin, Y.S. Lin, Y. Lin, R. Linden, D. Lindholm, L.M. Lindqvist, P. Lingor, A. Linkermann, L.A. Liotta, M.M. Lipinski, V.A. Lira, M.P. Lisanti, P.B. Liton, B. Liu, C. Liu, C.F. Liu, F. Liu, H.J. Liu, J. Liu, J.J. Liu, J.L. Liu, K. Liu, L. Liu, L. Liu, Q. Liu, R.Y. Liu, S. Liu, S. Liu, W. Liu, X.D. Liu, X. Liu, X.H. Liu, X. Liu, X. Liu, X. Liu, Y. Liu, Y. Liu, Z. Liu, Z. Liu, J.P. Liuzzi, G. Lizard, M. Ljujic, I.J. Lodhi, S.E. Logue, B.L. Lokeshwar, Y.C. Long, S. Lonial, B. Loos, C. Lopez-Otin, C. Lopez-Vicario, M. Lorente, P.L. Lorenzi, P. Lorincz, M. Los, M.T. Lotze, P.E. Lovat, B. Lu, B. Lu, J. Lu, Q. Lu, S.M. Lu, S. Lu, Y. Lu, F. Luciano, S. Luckhart, J.M. Lucocq, P. Ludovico, A. Lugea, N.W. Lukacs, J.J. Lum, A.H. Lund, H. Luo, J. Luo, S. Luo, C. Luparello, T. Lyons, J. Ma, Y. Ma, Y. Ma, Z. Ma, J. Machado, G.M. Machado-Santelli, F. Macian, MacIntosh GC, MacKeigan JP, K.F. Macleod, MacMicking JD, MacMillan-Crow LA, F. Madeo, M. Madesh, J. Madrigal-Matute, A. Maeda, T. Maeda, G. Maegawa, E. Maellaro, H. Maes, M. Magarinos, K. Maiese, T.K. Maiti, L. Maiuri, M.C. Maiuri, C.G. Maki, R. Malli, W. Malorni, A. Maloyan, F. Mami-Chouaib, N. Man, J.D. Mancias, E.M. Mandelkow, M.A. Mandell, A.A. Manfredi, S.N. Manie, C. Manzoni, K. Mao, Z. Mao, Z.W. Mao, P. Marambaud, A.M. Marconi, Z. Marelja, G. Marfe, M. Margeta, E. Margittai, M. Mari, F.V. Mariani, C. Marin, S. Marinelli, G. Marino, I. Markovic, R. Marquez, A.M. Martelli, S. Martens, K.R. Martin, S.J. Martin, S. Martin, M.A. Martin-Acebes, P. Martin-Sanz, C. Martinand-Mari, W. Martinet, J. Martinez, N. Martinez-Lopez, U. Martinez-Outschoorn, M. Martinez-Velazquez, M. Martinez-Vicente, W.K. Martins, H. Mashima, J.A. Mastrianni, G. Matarese, P. Matarrese, R. Mateo, S. Matoba, N. Matsumoto, T. Matsushita, A. Matsuura, T. Matsuzawa, M.P. Mattson, S. Matus, N. Maugeri, C. Mauvezin, A. Mayer, D. Maysinger, G.D. Mazzolini, McBrayer MK, K. McCall, C. McCormick, McInerney GM, McIver SC, S. McKenna, J.J. McMahon, I.A. McNeish, F. Mechta-Grigoriou, J.P. Medema, D.L. Medina, K. Megyeri, M. Mehrpour, J.L. Mehta, Y. Mei, U.C. Meier, A.J. Meijer, A. Melendez, G. Melino, S. Melino, E.J. de Melo, M.A. Mena, M.D. Meneghini, J.A. Menendez, R. Menezes, L. Meng, L.H. Meng, S. Meng, R. Menghini, A.S. Menko, R.F. Menna-Barreto, M.B. Menon, M.A. Meraz-Rios, G. Merla, L. Merlini, A.M. Merlot, A. Meryk, S. Meschini, J.N. Meyer, M.T. Mi, C.Y. Miao, L. Micale, S. Michaeli, C. Michiels, A.R. Migliaccio, A.S. Mihailidou, D. Mijaljica, K. Mikoshiba, E. Milan, L. Miller-Fleming, G.B. Mills, I.G. Mills, G. Minakaki, B.A. Minassian, X.F. Ming, F. Minibayeva, E.A. Minina, J.D. Mintern, S. Minucci, A. Miranda-Vizuete, C.H. Mitchell, S. Miyamoto, K. Miyazawa, N. Mizushima, K. Mnich, B. Mograbi, S. Mohseni, L.F. Moita, M. Molinari, M. Molinari, A.B. Moller, B. Mollereau, F. Mollinedo, M. Mongillo, M.M. Monick, S. Montagnaro, C. Montell, D.J. Moore, M.N. Moore, R. Mora-Rodriguez, P.I. Moreira, E. Morel, M.B. Morelli, S. Moreno, M.J. Morgan, A. Moris, Y. Moriyasu, J.L. Morrison, L.A. Morrison, E. Morselli, J. Moscat, P.L. Moseley, S. Mostowy, E. Motori, D. Mottet, J.C. Mottram, C.E. Moussa, V.E. Mpakou, H. Mukhtar, J.M. Mulcahy Levy, S. Muller, R. Munoz-Moreno, C. Munoz-Pinedo, C. Munz, M.E. Murphy, J.T. Murray, A. Murthy, I.U. Mysorekar, I.R. Nabi, M. Nabissi, G.A. Nader, Y. Nagahara, Y. Nagai, K. Nagata, A. Nagelkerke, P. Nagy, S.R. Naidu, S. Nair, H. Nakano, H. Nakatogawa, M. Nanjundan, G. Napolitano, N.I. Naqvi, R. Nardacci, D.P. Narendra, M. Narita, A.C. Nascimbeni, R. Natarajan, L.C. Navegantes, S.T. Nawrocki, T.Y. Nazarko, V.Y. Nazarko, T. Neill, L.M. Neri, M.G. Netea, R.T. Netea-Maier, B.M. Neves, P.A. Ney, I.P. Nezis, H.T. Nguyen, H.P. Nguyen, A.S. Nicot, H. Nilsen, P. Nilsson, M. Nishimura, I. Nishino, M. Niso-Santano, H. Niu, R.A. Nixon, V.C. Njar, T. Noda, A.A. Noegel, E.M. Nolte, E. Norberg, K.K. Norga, S.K. Noureini, S. Notomi, L. Notterpek, K. Nowikovsky, N. Nukina, T. Nurnberger, V.B. O'Donnell, O'Donovan T, P.J. O'Dwyer, I. Oehme, C.L. Oeste, M. Ogawa, B. Ogretmen, Y. Ogura, Y.J. Oh, M. Ohmuraya, T. Ohshima, R. Ojha, K. Okamoto, T. Okazaki, F.J. Oliver, K. Ollinger, S. Olsson, D.P. Orban, P. Ordonez, I. Orhon, L. Orosz, E.J. O'Rourke, H. Orozco, A.L. Ortega, E. Ortona, L.D. Osellame, J. Oshima, S. Oshima, H.D. Osiewacz, T. Otomo, K. Otsu, J.H. Ou, T.F. Outeiro, D.Y. Ouyang, H. Ouyang, M. Overholtzer, M.A. Ozbun, P.H. Ozdinler, B. Ozpolat, C. Pacelli, P. Paganetti, G. Page, G. Pages, U. Pagnini, B. Pajak, S.C. Pak, K. Pakos-Zebrucka, N. Pakpour, Z. Palkova, F. Palladino, K. Pallauf, N. Pallet, M. Palmieri, S.R. Paludan, C. Palumbo, S. Palumbo, O. Pampliega, H. Pan, W. Pan, T. Panaretakis, A. Pandey, A. Pantazopoulou, Z. Papackova, D.L. Papademetrio, I. Papassideri, A. Papini, N. Parajuli, J. Pardo, V.V. Parekh, G. Parenti, J.I. Park, J. Park, O.K. Park, R. Parker, R. Parlato, J.B. Parys, K.R. Parzych, J.M. Pasquet, B. Pasquier, K.B. Pasumarthi, D. Patschan, C. Patterson, S. Pattingre, S. Pattison, A. Pause, H. Pavenstadt, F. Pavone, Z. Pedrozo, F.J. Pena, M.A. Penalva, M. Pende, J. Peng, F. Penna, J.M. Penninger, A. Pensalfini, S. Pepe, G.J. Pereira, P.C. Pereira, V. Perez-de la Cruz, M.E. Perez-Perez, D. Perez-Rodriguez, D. Perez-Sala, C. Perier, A. Perl, D.H. Perlmutter, I. Perrotta, S. Pervaiz, M. Pesonen, J.E. Pessin, G.J. Peters, M. Petersen, I. Petrache, B.J. Petrof, G. Petrovski, J.M. Phang, M. Piacentini, M. Pierdominici, P. Pierre, V. Pierrefite-Carle, F. Pietrocola, F.X. Pimentel-Muinos, M. Pinar, B. Pineda, R. Pinkas-Kramarski, M. Pinti, P. Pinton, B. Piperdi, J.M. Piret, L.C. Platanias, H.W. Platta, E.D. Plowey, S. Poggeler, M. Poirot, P. Polcic, A. Poletti, A.H. Poon, H. Popelka, B. Popova, I. Poprawa, S.M. Poulose, J. Poulton, S.K. Powers, T. Powers, M. Pozuelo-Rubio, K. Prak, R. Prange, M. Prescott, M. Priault, S. Prince, R.L. Proia, T. Proikas-Cezanne, H. Prokisch, V.J. Promponas, K. Przyklenk, R. Puertollano, S. Pugazhenthi, L. Puglielli, A. Pujol, J. Puyal, D. Pyeon, X. Qi, W.B. Qian, Z.H. Qin, Y. Qiu, Z. Qu, J. Quadrilatero, F. Quinn, N. Raben, H. Rabinowich, F. Radogna, M.J. Ragusa, M. Rahmani, K. Raina, S. Ramanadham, R. Ramesh, A. Rami, S. Randall-Demllo, F. Randow, H. Rao, V.A. Rao, B.B. Rasmussen, T.M. Rasse, E.A. Ratovitski, P.E. Rautou, S.K. Ray, B. Razani, B.H. Reed, F. Reggiori, M. Rehm, A.S. Reichert, T. Rein, D.J. Reiner, E. Reits, J. Ren, X. Ren, M. Renna, J.E. Reusch, J.L. Revuelta, L. Reyes, A.R. Rezaie, R.I. Richards, D.R. Richardson, C. Richetta, M.A. Riehle, B.H. Rihn, Y. Rikihisa, B.E. Riley, G. Rimbach, M.R. Rippo, K. Ritis, F. Rizzi, E. Rizzo, P.J. Roach, J. Robbins, M. Roberge, G. Roca, M.C. Roccheri, S. Rocha, C.M. Rodrigues, C.I. Rodriguez, S.R. de Cordoba, N. Rodriguez-Muela, J. Roelofs, V.V. Rogov, T.T. Rohn, B. Rohrer, D. Romanelli, L. Romani, P.S. Romano, M.I. Roncero, J.L. Rosa, A. Rosello, K.V. Rosen, P. Rosenstiel, M. Rost-Roszkowska, K.A. Roth, G. Roue, M. Rouis, K.M. Rouschop, D.T. Ruan, D. Ruano, D.C. Rubinsztein, E.B. Rucker 3rd, A. Rudich, E. Rudolf, R. Rudolf, M.A. Ruegg, C. Ruiz-Roldan, A.A. Ruparelia, P. Rusmini, D.W. Russ, G.L. Russo, G. Russo, R. Russo, T.E. Rusten, V. Ryabovol, K.M. Ryan, S.W. Ryter, D.M. Sabatini, M. Sacher, C. Sachse, M.N. Sack, J. Sadoshima, P. Saftig, R. Sagi-Eisenberg, S. Sahni, P. Saikumar, T. Saito, T. Saitoh, K. Sakakura, M. Sakoh-Nakatogawa, Y. Sakuraba, M. Salazar-Roa, P. Salomoni, A.K. Saluja, P.M. Salvaterra, R. Salvioli, A. Samali, A.M. Sanchez, J.A. Sanchez-Alcazar, R. Sanchez-Prieto, M. Sandri, M.A. Sanjuan, S. Santaguida, L. Santambrogio, G. Santoni, C.N. Dos Santos, S. Saran, M. Sardiello, G. Sargent, P. Sarkar, S. Sarkar, M.R. Sarrias, M.M. Sarwal, C. Sasakawa, M. Sasaki, M. Sass, K. Sato, M. Sato, J. Satriano, N. Savaraj, S. Saveljeva, L. Schaefer, U.E. Schaible, M. Scharl, H.M. Schatzl, R. Schekman, W. Scheper, A. Schiavi, H.M. Schipper, H. Schmeisser, J. Schmidt, I. Schmitz, B.E. Schneider, E.M. Schneider, J.L. Schneider, E.A. Schon, M.J. Schonenberger, A.H. Schonthal, D.F. Schorderet, B. Schroder, S. Schuck, R.J. Schulze, M. Schwarten, T.L. Schwarz, S. Sciarretta, K. Scotto, A.I. Scovassi, R.A. Screaton, M. Screen, H. Seca, S. Sedej, L. Segatori, N. Segev, P.O. Seglen, J.M. Segui-Simarro, J. Segura-Aguilar, E. Seki, C. Sell, I. Seiliez, C.F. Semenkovich, G.L. Semenza, U. Sen, A.L. Serra, A. Serrano-Puebla,

H. Sesaki, T. Setoguchi, C. Settembre, J.J. Shacka, A.N. Shajahan-Haq, I.M. Shapiro, S. Sharma, H. She, C.K. Shen, C.C. Shen, H.M. Shen, S. Shen, W. Shen, R. Sheng, X. Sheng, Z.H. Sheng, T.G. Shepherd, J. Shi, Q. Shi, Q. Shi, Y. Shi, S. Shibutani, K. Shibuya, Y. Shidoji, J.J. Shieh, C.M. Shih, Y. Shimada, S. Shimizu, D.W. Shin, M.L. Shinohara, M. Shintani, T. Shintani, T. Shioi, K. Shirabe, R. Shiri-Sverdlov, O. Shirihai, G.C. Shore, C.W. Shu, D. Shukla, A.A. Sibirny, V. Sica, C.J. Sigurdson, E.M. Sigurdsson, P.S. Sijwali, B. Sikorska, W.A. Silveira, S. Silvente-Poirot, G.A. Silverman, J. Simak, T. Simmet, A.K. Simon, H.U. Simon, C. Simone, M. Simons, A. Simonsen, R. Singh, S.V. Singh, S.K. Singh, D. Sinha, S. Sinha, F.A. Sinicrope, A. Sirko, K. Sirohi, B.J. Sishi, A. Sittler, P.M. Siu, E. Sivridis, A. Skwarska, R. Slack, I. Slaninova, N. Slavov, S.S. Smaili, K.S. Smalley, D.R. Smith, S.J. Soenen, S.A. Soleimanpour, A. Solhaug, K. Somasundaram, J.H. Son, A. Sonawane, C. Song, F. Song, H.K. Song, J.X. Song, W. Song, K.Y. Soo, A.K. Sood, T.W. Soong, V. Soontornniyomkij, M. Sorice, F. Sotgia, D.R. Soto-Pantoja, A. Sotthibundhu, M.J. Sousa, H.P. Spaink, P.N. Span, A. Spang, J.D. Sparks, P.G. Speck, S.A. Spector, C.D. Spies, W. Springer, D.S. Clair, A. Stacchiotti, B. Staels, M.T. Stang, D.T. Starczynowski, P. Starokadomskyy, C. Steegborn, J.W. Steele, L. Stefanis, J. Steffan, C.M. Stellrecht, H. Stenmark, T.M. Stepkowski, S.T. Stern, C. Stevens, B.R. Stockwell, V. Stoka, Z. Storchova, B. Stork, V. Stratoulias, D.J. Stravopodis, P. Strnad, A.M. Strohecker, A.L. Strom, P. Stromhaug, J. Stulik, Y.X. Su, Z. Su, C.S. Subauste, S. Subramaniam, C.M. Sue, S.W. Suh, X. Sui, S. Sukseree, D. Sulzer, F.L. Sun, J. Sun, J. Sun, S.Y. Sun, Y. Sun, Y. Sun, Y. Sun, V. Sundaramoorthy, J. Sung, H. Suzuki, K. Suzuki, N. Suzuki, T. Suzuki, Y.J. Suzuki, M.S. Swanson, C. Swanton, K. Sward, G. Swarup, S.T. Sweeney, P.W. Sylvester, Z. Szatmari, E. Szegezdi, P.W. Szlosarek, H. Taegtmeyer, M. Tafani, E. Taillebourg, S.W. Tait, K. Takacs-Vellai, Y. Takahashi, S. Takats, G. Takemura, N. Takigawa, N.J. Talbot, E. Tamagno, J. Tamburini, C.P. Tan, L. Tan, M.L. Tan, M. Tan, Y.J. Tan, K. Tanaka, M. Tanaka, D. Tang, D. Tang, G. Tang, I. Tanida, K. Tanji, B.A. Tannous, J.A. Tapia, I. Tasset-Cuevas, M. Tatar, I. Tavassoly, N. Tavernarakis, A. Taylor, G.S. Taylor, G.A. Taylor, J.P. Taylor, M.J. Taylor, E.V. Tchetina, A.R. Tee, F. Teixeira-Clerc, S. Telang, T. Tencomnao, B.B. Teng, R.J. Teng, F. Terro, G. Tettamanti, A.L. Theiss, A.E. Theron, K.J. Thomas, M.P. Thome, P.G. Thomes, A. Thorburn, J. Thorner, T. Thum, M. Thumm, T.L. Thurston, L. Tian, A. Till, J.P. Ting, V.I. Titorenko, L. Toker, S. Toldo, S.A. Tooze, I. Topisirovic, M.L. Torgersen, L. Torosantucci, A. Torriglia, M.R. Torrisi, C. Tournier, R. Towns, V. Trajkovic, L.H. Travassos, G. Triola, D.N. Tripathi, D. Trisciuoglio, R. Troncoso, I.P. Trougakos, A.C. Truttmann, K.J. Tsai, M.P. Tschan, Y.H. Tseng, T. Tsukuba, A. Tsung, A.S. Tsvetkov, S. Tu, H.Y. Tuan, M. Tucci, D.A. Tumbarello, B. Turk, V. Turk, R.F. Turner, A.A. Tveita, S.C. Tyagi, M. Ubukata, Y. Uchiyama, A. Udelnow, T. Ueno, M. Umekawa, R. Umemiya-Shirafuji, B.R. Underwood, C. Ungermann, R.P. Ureshino, R. Ushioda, V.N. Uversky, N.L. Uzcategui, T. Vaccari, M.I. Vaccaro, L. Vachova, H. Vakifahmetoglu-Norberg, R. Valdor, E.M. Valente, F. Vallette, A.M. Valverde, G. Van den Berghe, L. Van Den Bosch, G.R. van den Brink, F.G. van der Goot, I.J. van der Klei, L.J. van der Laan, W.G. van Doorn, M. van Egmond, K.L. van Golen, L. Van Kaer, M. van Lookeren Campagne, P. Vandenabeele, W. Vandenberghe, I. Vanhorebeek, I. Varela-Nieto, M.H. Vasconcelos, R. Vasko, D.G. Vavvas, I. Vega-Naredo, G. Velasco, A.D. Velentzas, P.D. Velentzas, T. Vellai, E. Vellenga, M.H. Vendelbo, K. Venkatachalam, N. Ventura, S. Ventura, P.S. Veras, M. Verdier, B.G. Vertessy, A. Viale, M. Vidal, H.L. Vieira, R.D. Vierstra, N. Vigneswaran, N. Vij, M. Vila, M. Villar, V.H. Villar, J. Villarroya, C. Vindis, G. Viola, M.T. Viscomi, G. Vitale, D.T. Vogl, O.V. Voitsekhovskaja, C. von Haefen, K. von Schwarzenberg, D.E. Voth, V. Vouret-Craviari, K. Vuori, J.M. Vyas, C. Waeber, C.L. Walker, M.J. Walker, J. Walter, L. Wan, X. Wan, B. Wang, C. Wang, C.Y. Wang, C. Wang, C. Wang, C. Wang, D. Wang, F. Wang, F. Wang, G. Wang, H.J. Wang, H. Wang, H.G. Wang, H. Wang, H.D. Wang, J. Wang, J. Wang, M. Wang, M.Q. Wang, P.Y. Wang, P. Wang, R.C. Wang, S. Wang, T.F. Wang, X. Wang, X.J. Wang, X.W. Wang, X. Wang, X. Wang, Y. Wang, Y. Wang, Y. Wang, Y.J. Wang, Y. Wang, Y. Wang, Y.T. Wang, Y. Wang, Z.N. Wang, P. Wappner, C. Ward, D.M. Ward, G. Warnes, H. Watada, Y. Watanabe, K. Watase, T.E. Weaver, C.D. Weekes, J. Wei, T. Weide, C.C. Weihl, G. Weindl, S.N. Weis, L. Wen, X. Wen, Y. Wen, B. Westermann, C.M. Weyand, A.R. White, E. White, J.L. Whitton, A.J. Whitworth, J. Wiels, F. Wild, M.E. Wildenberg, T. Wileman, D.S. Wilkinson, S. Wilkinson, D. Willbold, C. Williams, K. Williams, P.R. Williamson, K.F. Winklhofer, S.S. Witkin, S.E. Wohlgemuth, T. Wollert, E.J. Wolvetang, E. Wong, G.W. Wong, R.W. Wong, V.K. Wong, E.A. Woodcock, K.L. Wright, C. Wu, D. Wu, G.S. Wu, J. Wu, J. Wu, M. Wu, M. Wu, S. Wu, W.K. Wu, Y. Wu, Z. Wu, C.P. Xavier, R.J. Xavier, G.X. Xia, T. Xia, W. Xia, Y. Xia, H. Xiao, J. Xiao, S. Xiao, W. Xiao, C.M. Xie, Z. Xie, Z. Xie, M. Xilouri, Y. Xiong, C. Xu, C. Xu, F. Xu, H. Xu, H. Xu, J. Xu, J. Xu, J. Xu, L. Xu, X. Xu, Y. Xu, Y. Xu, Z.X. Xu, Z. Xu, Y. Xue, T. Yamada, A. Yamamoto, K. Yamanaka, S. Yamashina, S. Yamashiro, B. Yan, B. Yan, X. Yan, Z. Yan, Y. Yanagi, D.S. Yang, J.M. Yang, L. Yang, M. Yang, P.M. Yang, P. Yang, Q. Yang, W. Yang, W.Y. Yang, X. Yang, Y. Yang, Y. Yang, Z. Yang, Z. Yang, M.C. Yao, P.J. Yao, X. Yao, Z. Yao, Z. Yao, L.S. Yasui, M. Ye, B. Yedvobnick, B. Yeganeh, E.S. Yeh, P.L. Yeyati, F. Yi, L. Yi, X.M. Yin, C.K. Yip, Y.M. Yoo, Y.H. Yoo, S.Y. Yoon, K. Yoshida, T. Yoshimori, K.H. Young, H. Yu, J.J. Yu, J.T. Yu, J. Yu, L. Yu, W.H. Yu, X.F. Yu, Z. Yu, J. Yuan, Z.M. Yuan, B.Y. Yue, J. Yue, Z. Yue, D.N. Zacks, E. Zacksenhaus, N. Zaffaroni, T. Zaglia, Z. Zakeri, V. Zecchini, J. Zeng, M. Zeng, Q. Zeng, A.S. Zervos, D.D. Zhang, F. Zhang, G. Zhang, G.C. Zhang, H. Zhang, H. Zhang, H. Zhang, H. Zhang, J. Zhang, J. Zhang, J. Zhang, J. Zhang, J.P. Zhang, L. Zhang, L. Zhang, L. Zhang, L. Zhang, M.Y. Zhang, X. Zhang, X.D. Zhang, Y. Zhang, Y. Zhang, Y. Zhang, Y. Zhang, Y. Zhang, M. Zhao, W.L. Zhao, X. Zhao, Y.G. Zhao, Y. Zhao, Y. Zhao, Y.X. Zhao, Z. Zhao, Z.J. Zhao, D. Zheng, X.L. Zheng, X. Zheng, B. Zhivotovsky, Q. Zhong, G.Z. Zhou, G. Zhou, H. Zhou, S.F. Zhou, X.J. Zhou, H. Zhu, H. Zhu, W.G. Zhu, W. Zhu, X.F. Zhu, Y. Zhu, S.M. Zhuang, X. Zhuang, E. Ziparo, C.E. Zois, T. Zoladek, W.X. Zong, A. Zorzano, S.M. Zughaier, Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edn.), Autophagy 12 (1) (2016) 1–222, https://doi.org/10.1080/15548627.2015.1100356.

[99] L. Sun, S. Zhang, C. Yu, Z. Pan, Y. Liu, J. Zhao, X. Wang, F. Yun, H. Zhao, S. Yan, Hydrogen sulfide reduces serum triglyceride by activating liver autophagy via the AMPK-mTOR pathway, Am. J. Physiol. Endocrinol. Metab. 309 (11) (2015) 925–935.

[100] Y.M. Song, Y.H. Lee, J.W. Kim, D.S. Ham, E.S. Kang, B.S. Cha, H.C. Lee, B.W. Lee, Metformin alleviates hepatosteatosis by restoring SIRT1-mediated autophagy induction via an AMP-activated protein kinase-independent pathway, Autophagy 11 (1) (2015) 46–59.

[101] J. Kim, M. Kundu, B. Viollet, K.L. Guan, AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1, Nat. Cell Biol. 13 (2) (2011) 132–141.

[102] S. Erlich, A. Alexandrovich, E. Shohami, R. Pinkas-Kramarski, Rapamycin is a neuroprotective treatment for traumatic brain injury, Neurobiol. Dis. 26 (1) (2007) 86.

[103] B. Ravikumar, C. Vacher, Z. Berger, J.E. Davies, S. Luo, L.G. Oroz, F. Scaravilli, D.F. Easton, R. Duden, C.J. O'Kane, Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease, Nat. Genet. 36 (6) (2004) 585–595.

[104] L. Cinque, A. Forrester, R. Bartolomeo, M. Svelto, R. Venditti, S. Montefusco, E. Polishchuk, E. Nusco, A. Rossi, D.L. Medina, FGF signalling regulates bone growth through autophagy, Nature 528 (7581) (2015) 272–275.

[105] M.G. Gutierrez, M.I. Colombo, S.S. Master, Autophagy is a defense mechanism inhibiting BCG and mycobacterium tuberculosis survival in infected macrophages, Cell 119 (6) (2004) 753–766.

[106] X.Z. Li, X.P. Chen, K. Zhao, L.M. Bai, H. Zhang, X.P. Zhou, Therapeutic effects of valproate combined with Lithium carbonate on MPTP-induced parkinsonism in mice: possible mediation through enhanced autophagy, Int. J. Neurosci. 123 (2) (2013) 73–79.

[107] K.J. Petherick, O.J.L. Conway, C. Mpamhanga, S.A. Osborne, A. Kamal, B. Saxty, I.G. Ganley, Pharmacological inhibition of ULK1 kinase blocks mammalian target of Rapamycin (mTOR)-dependent autophagy, J. Biol. Chem. 290 (18) (2015) 11376–11383.

[108] D. Akin, S.K. Wang, P. Habibzadegahtari, B. Law, D. Ostrov, M. Li, X.M. Yin, J.S. Kim, N. Horenstein, D.W. Jr, A novel ATG4B antagonist inhibits autophagy and has a negative impact on osteosarcoma tumors, Autophagy 10 (11) (2014) 2021–2035.

[109] E.L. Flannery, A.K. Chatterjee, E.A. Winzeler, Antimalarial drug discovery — approaches and progress towards new medicines, Nat. Rev. Microbiol. 11 (12) (2013) 849–862.

[110] Q. Mcafee, Z. Zhang, A. Samanta, S.M. Levi, X.H. Ma, S. Piao, J.P. Lynch, T. Uehara, A.R. Sepulveda, L.E. Davis, Autophagy inhibitor Lys05 has single-agent antitumor activity and reproduces the phenotype of a genetic autophagy deficiency, Autophagy 109 (21) (2012) 8253–8258.

[111] G.L. Semenza, Mitochondrial autophagy: life and breath of the cell, Autophagy 4 (4) (2008) 534–536.

[112] R. Scherz-Shouval, E. Shvets, E. Fass, H. Shorer, L. Gil, Z. Elazar, Reactive oxygen species are essential for autophagy and specifically regulate the activity of Atg4, EMBO J. 26 (7) (2007) 1749–1760.

[113] J. Poels, M.R. Spasić, P. Callaerts, K.K. Norga, Expanding roles for AMP-activated protein kinase in neuronal survival and autophagy, Bioessays 31 (9) (2009) 944–952.

[114] Y. Liu, S. Shojikawata, S.R. Jr, Y. Wei, V. Ginet, L. Zhang, B. Posner, K.A. Tran, D.R. Green, R.J. Xavier, Autosis is a Na+,K+-ATPase-regulated form of cell death triggered by autophagy-inducing peptides, starvation, and hypoxia-ischemia, Pnas 110 (51) (2013) 20364–20371.