Modulating autophagy: a strategy for cancer therapy

Jun-Lin Li¹, Shao-Liang Han² and Xia Fan³

Abstract

Autophagy is a process in which long-lived proteins, damaged cell organelles, and other cellular particles are sequestered and degraded. This process is important for maintaining the cellular microenvironment when the cell is under stress. Many studies have shown that autophagy plays a complex role in human diseases, especially in cancer, where it is known to have paradoxical effects. Namely, autophagy provides the energy for metabolism and tumor growth and leads to cell death that promotes tumor suppression. The link between autophagy and cancer is also evident in that some of the genes that regulate carcinogenesis, oncogenes and tumor suppressor genes, participate in or impact the autophagy process. Therefore, modulating autophagy will be a valuable topic for cancer therapy. Many studies have shown that autophagy can inhibit the tumor growth when autophagy modulators are combined with radiotherapy and/or chemotherapy. These findings suggest that autophagy may be a potent target for cancer therapy.

Key words Autophagy, chemotherapy, chemoresistance, nuclear factor-κB, P53, Bcl-2

In 1955, de Duve et al. [1] first described the term “autophagy” to distinguish lysosomal degradation, or cellular “eating” (phagy) of self (auto), from the breakdown of extracellular material (heterophagy). So-called autophagy is a genetically programmed, evolutionarily conserved process that degrades long-lived cellular proteins and organelles [2]. Autophagy contributes to the maintenance of the cellular energy homeostasis, clearance of damaged organelles, and adaptation to environmental stress. Although Seglen et al. [3] studied the early and intermediate steps of this process morphologically using electro-injected radioactive probes, significant breakthroughs in understanding the molecular basis of autophagy only occurred following analyses in the genetically facile yeast system. Since Takeshige et al. [4] carried out the first genetic screen for autophagy mutants, there has been a tremendous increase in autophagy research [5].

There are nearly 30 autophagy-related proteins (ATGs) in mammals, and these have been identified based on investigations in yeast [6], ATGs, through their role in signaling pathways, maintain normal physiological levels of autophagy. Recent studies have demonstrated that defective autophagy has a complicated correlation with many human diseases, including neuronal degeneration [7], immune disorders [8], myopathy, and cancer [9]. For example, the correlation between autophagy and tumorigenesis is ambiguous, and several studies have shown that autophagy regulators alone and in combination with radiotherapy and/or chemotherapy can inhibit tumor growth. Therefore, modulation of autophagy may be a useful strategy for cancer therapy.

The Classification, Mechanisms, and Regulation of Autophagy

Autophagy is a tightly regulated lysosome-dependent catabolic pathway. During this process, cytosolic particles are sequestered into autophagosomes that subsequently fuse with lysosomes, where their contents are degraded. Also, autophagy can be classified into chaperone-mediated autophagy (CMA), microautophagy, and macroautophagy, based on the pathway of substrate into the lysosome [10] (Figure 1). The...
Macroautophagy

Cytoplasm

Microautophagy

Chaperone-mediated autophagy

LAMP-2

Hsp70 family

Damaged cellular particles

KFERQ-like motif sequence proteins

Nucleus

Figure 1. The classification of autophagy. There are three types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). In macroautophagy, damaged cellular particles and long-lived proteins are sequestered and delivered to the lysosome by double-membrane vesicles called autophagosomes. In microautophagy, small particles enter the lysosome through tubular invaginations and undergo digestion. In CMA, substrate proteins are delivered into the lysosome by a member of the Hsp70 family of chaperones in cytosol.

type of autophagy that will function depends on the signals, cellular microenvironment, and organs. CMA is only described in mammals and involved in degradation of single, soluble proteins. Delivery of substrate proteins to the lysosome from CMA is not mediated by vesicular transport but executed by a protein translocation pathway through a proteinaceous pore in the lysosomal membrane. The proteins involved in the translocation pathway is a member of the Hsp70 family of chaperones in the cytosol (Hsc70) and the lysosomal lumen (Hsc73) as well as the lysosomal membrane protein LAMP-2A[10]. Cytosolic Hsc70 first recognizes the KFERQ-like motif sequence in proteins and then leads to formation of the Hsc70-cargo complex. In the presence of Hsc73 and other Hsp70 co-chaperones, such as Hsp40, Hsp90, and Hip, the Hsc70-cargo complex is targeted to the lysosomal membrane, where it binds to the cytosolic domain of LAMP-2A, after which degradation occurs. Microautophagy is characterized by the development of tubular invaginations involving the TOR signaling complex, EGO complex (Ego1, Ego3 and the GTPase Gtr2), and vacuolar transport chaperone (VTC) complex (Vtc1, Vtc2, Vtc3 and Vtc4), followed by digestion of small particles[11,12]. Compared with CMA and microautophagy, macroautophagy is the prevalent autophagy pathway in which long-lived proteins and cellular organelles are enveloped and sequestered in double-membrane vesicles called autophagosomes. Autophagosomes then fuse with lysosomes, where their components are degraded.

By means of the ATG pathway, autophagy occurs sequentially in several phases: induction; isolation membrane, or phagophore formation; membrane elongation, or autophagosome formation; autolysosome formation; and degradation (Figure 2). The phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT)–mammalian target of rapamycin (mTOR) axis is involved in autophagy initiation[13-15]. Cellular stresses,
such as nutrient deficiency, hypoxia, temperature or cell density changes, hormone or growth factor depletion, chemotherapy, and radiotherapy, trigger autophagy through several phosphorylation events within mTOR and drive Atg1-Atg13-Atg17 complex formation. Atgs, such as Vps15, Atg6, and Vps34, then accumulate in the PAS. During the autophagosome elongation phase, two conjugation systems, Atg12 and Atg8/LC, are indispensable for the formation of the autophagosome.

Figure 2. The autophagy process and signalling pathway. Autophagy occurs sequentially in phases: induction, phagophore formation, autophagosome elongation, autolysosome formation, and then degradation. Cellular stresses trigger the autophagic pathway by several phosphorylation events within mTOR and drive Atg1-Atg13-Atg17 complex formation. Atgs, such as Vps15, Atg6, and Vps34, then accumulate in the PAS. During the autophagosome elongation phase, two conjugation systems, Atg12 and Atg8/LC, are indispensable for the formation of the autophagosome.

The isolation membrane or so-called phagophore is a crescent-shaped, lipid bilayer membrane characterized by the accumulation of ATGs in pre-autophagosomal structures (PAS), and its generation results from a cascade of reactions induced by the ATG1 complex. In this phase of the autophagy process, the formation of the type III phosphatidylinositol 3-kinase (PtdIns3K) complex performs a key role in triggering autophagy and its applications in phagophore formation. In mammals, Beclin-1, the homolog of the autophagy-related gene Atg6/vacuolar protein sorting (Vps3), is closely correlated with tumorigenesis; mutations or allelic loss of Beclin-1 are frequently found in breast, ovarian and prostate cancers.[20]

Two conjugation systems involved in the elongation phase, ATG12 and ATG8/LC3, are indispensable for autophagosome formation. As the autophagosome matures, the ubiquitin-like protein ATG12 is covalently conjugated to ATG5 through the action of E1- and E2-like proteins ATG7 and ATG10, respectively. Upon the help of ATG7 and ATG10, ATG8 (mammalian homologue LC3) is lipidated by conjugation to

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phosphatidylethanolamine (PE) \[^{21}\]. Subsequently, the
ATG12-ATG5 dimer and ATG8-PE assemble and are
recruited to the autophagosomal membrane via
interaction with ATG16. Once the autophagosome is fully
expanded, ATG8 is deconjugated from PE through the
action of ATG4 and is released back to the cytosol \[^{20}\].
With this process underway, the autophagosomal
membrane becomes lengthened and sequesters
cytosolic particles and long-lived proteins further.
Through interactions with Rab7 and the SNARE protein
Vtilp \[^{23,24}\], the outer membrane of the autophagosome
fuses to the lysosome to form the autolysosome, where
the engulfed cytoplasmic proteins and organelles are
degraded by lysosomal hydrolases.

Autophagy occurs at a low level under normal
physiological conditions but significantly increases in
response to stress, including oxidative stress, chemotherapeutic
treatments, and nutrient deficiency, suggesting a precise and complicated mechanism in
the regulation of autophagy when adapted to the
environment change. Although the TOR/mTOR and
PI3K/AKT pathways were reported to negatively
influence autophagy \[^{5,25}\] and the class III PI3K was
found to be an efficient, promotive factor \[^{20}\], the precise
mechanisms underlying the autophagy process are still
ambiguous.

The Multifaceted and Paradox Correlation between Autophagy and Cancer

As shown in Figure 3, several interactions between
autophagy and other signaling pathways have been
recognized to play a functional role in tumorigenesis.
Many studies have shown that anti-cancer therapies can
induce autophagy in tumor cells, but the role of
autophagy in these cells may depend on the type of
tumor, the stage of tumorigenesis, and the nature and
extent of the insult, suggesting that appropriate
modification of autophagy, be it suppression of
cell-protective autophagy and enhancement of
cell-destructive autophagy, may augments cytotoxicity
induced by anti-cancer therapy.

The role of the cellular microenvironment and
its associated signaling pathways in tumorigenesis

Cell survival, growth, and proliferation require growth
factors, abundant nutrients, and oxygen. However, tumor
cells are generally deficient in these critical components.
For example, when a solid tumor reaches a size of
0.2–2.0 mm in diameter, oxygen, growth factors, and
nutrients, including glucose and small molecules like

![Figure 3. The multifaceted associations between autophagy and tumorigenesis.](chart)

Autophagy and its applications in cancer therapy

By Jun-Lin Li et al.
The involvement of ATGs and their signaling pathway in tumorigenesis

Autophagy is highly regulated and under the control of a number of signaling pathways. The following is a summary of recent research on the regulation of autophagy.

**PI3K-AKT-mTOR axis signaling pathway** The PI3K-AKT-mTOR axis, a vital process for initiating the autophagy pathway, regulates several biological events including cell cycle and proliferation and is mutated in many human malignancies.[15,33] In tumorigenesis, growth signaling constitutively activates receptor tyrosine kinases (RTKs), which then activate Rheb and PI3K. Rheb is a small GTP-binding protein that activates mTOR in its GTP-bound form, whereas Rheb and PI3K converge to activate mTOR to stimulate cell growth and inhibit autophagy.[44] Because most cancers can harbor activating mutations of master regulators, such as TSC1, TSC2, Akt, and ribosomal S6 kinase (RSK)[45], many cancers exhibit enhanced activation of mTOR and inhibit autophagy.

**The Vps34 complex signaling pathway** The Vps34 complex, which consists of Vps34, Vps15, ATG6, and ATG14 in yeast and Vps34, Vps15, Beclin-1, the WD domain protein Ambra1, and the endophilin Bif-1 in mammals, is essential for autophagy[46,47].

Emerging evidence suggests that submembers of Vps34 are involved in tumorigenesis. This is especially true for Beclin-1, a phylogenetically conserved protein that is essential for autophagy. In fact, the first association between autophagy and cancer was the landmark discovery of Beclin-1, which is also a haploinsufficient tumor suppressor[2]. In 1999, Liang et al. [44] used gene transfer techniques in human MCF7 breast carcinoma cells and found that the autophagy promoting activity of Beclin-1 in these cells was associated with inhibition of cellular proliferation. Furthermore, increasing studies show that the Beclin-1 locus (17q21) is frequently subjected to monoallelic deletions in human breast, ovarian, and prostate cancers as well as in brain tumors[46-49]. Further study demonstrated that Beclin-mediated tumor suppress involved a Beclin-1 domain. Through this domain, Beclin-1 directly interact with ultraviolet irradiation resistance-associated gene (UVRAG) and this interaction is purposed to promote binding of Vps34 to Beclin-1. In addition, Beclin-1, also known as SH3GLB1 or endophilin B1, was originally discovered as a Bax-binding protein, interacts with Beclin-1 via UVRAG and promotes Vps34 activation and autophagosome formation. In vivo, UVRAG has been reported to suppress cell proliferation and tumorigenesis, and monoallelic deletions or mutations in UVRAG occur.
in numerous human malignancies.\textsuperscript{[25,40]} Furthermore, reduction of Bif-1 expression was observed in gastric carcinomas, invasive urinary bladder, and gallbladder cancers, and mantle cell lymphomas.\textsuperscript{[46-48]}

Both ATG12 conjugation and LC3 modification (ATG8 lipidation in yeast) have been reported to take part in the dynamic process of autophagosome formation; ATG12 conjugation is essential for the formation of preautophagosomes, and LC3 modification is necessary for the formation of autophagosomes.\textsuperscript{[29]} Recent studies suggest that several key regulators of autophagosome in these two conjugation systems, ATG12 and LC3 conjugations, especially those also associated with apoptosis, are correlated with tumorigenesis. For example, ATG5, playing a role in ATG12 conjugation in the procedure of autophagosome membrane elongation and completion, is reported to interact with Bcl-xL. Kang et al.\textsuperscript{[44]} reported that frameshift mutations of ATG5 in gastric and colorectal cancers may contribute to cancer development by dysregulating the autophagy process. Lee et al.\textsuperscript{[59]} recently demonstrated that cellular and viral FLICE-like inhibitor protein (FLIPs), which protect cells from apoptosis mediated by death receptors, limit the ATG3-mediated step of LC3 modification to regulate autophagosome biogenesis. Nevertheless, the precise mechanism linking autophagy-related conjugations and tumorigenesis is still unknown and requires further investigation.

**Autophagy and apoptosis: a complex interaction through the Bcl-2 family and p53 signaling pathways**

*Bcl-2 family–mediated signaling pathway* The multifunctional Bcl-2 family of proteins contains members that inhibit (Bcl-2, Bcl-xL, Mcl-1, and Bcl-w) or promote (Bax and Bak) apoptosis. The anti-apoptotic members of this family have been reported to suppress autophagy, mainly by interacting with and therefore inhibiting Beclin-1, whereas the pro-apoptotic members of this family and other BH3-only proteins, including Bad, Bik, BNI-P3L, Noxa, Puma, and BimEL, promote autophagy by freeing Beclin-1 from inhibitory interactions with anti-apoptotic Bcl-2-like proteins. Such interactions involve the BH3 domain of Beclin-1 and the so-called "BH3 receptor" domain of anti-apoptotic Bcl-2 family members. Pattingre et al.\textsuperscript{[51]} demonstrated that activation of c-Jun N-terminal kinase 1 (JNK1) by tamoxifen-induced ceramide required both Bcl-2 phosphorylation and autophagy stimulation, which contributed to the development of anti-estrogen resistance.

*p53-mediated signaling pathway* p53, a typical tumor suppressor that is activated by DNA damage-induced stress, Arf activation, and re-expression of p53 in p53-negative tumor cells, has been found to be associated with autophagy.\textsuperscript{[22,53]} Tasdemir et al.\textsuperscript{[54,55]} showed that p53 inhibition in enucleated cells increased autophagy, whereas expression of cytoplasmic p53 repressed the enhanced autophagy in p53-null cells. p53 activation can trigger autophagy by up-regulating the transcription of damage-regulated autophagy modulator (DRAM) or by inhibiting mTOR.\textsuperscript{[56]} DRAM1 causes accumulation of autophagosomes, though the underlying mechanism is unknown. Furthermore, because it is specifically located in the lysosome, DRAM1 may regulate the autophagosome-lysosome fusion that is required for the generation of autophagolysosomes during a late stage of the autophagy process. Therefore, it is plausible that DRAM1 regulates the autophagosome-lysosome fusion that is required for the generation of autophagolysosomes.

**Autophagy and nuclear factor-kappa B**

The nuclear factor-kappa B (NF-κB) system is a critical signaling pathway induced to defend cells from cellular damage and environmental danger.\textsuperscript{[57]} Dysregulation of the NF-κB pathway is associated with cancer development, progression, and drug resistance, in addition to other human conditions, such as inflammatory diseases.\textsuperscript{[58]} Recently, autophagy has been reported to play a role in several cellular functions regulated by NF-κB. Djavaheri-Mergny et al.\textsuperscript{[59]} demonstrated that NF-κB activation mediates autophagy repression through effects on mTOR complex in tumor necrosis factor-alpha (TNF-α)-treated Ewing sarcoma cells. Further, Lee et al.\textsuperscript{[60]} reported that autophagy repression involved suppression of TSC1, which triggered the mTOR pathway. Dan et al.\textsuperscript{[61]} have also demonstrated that activation of mTOR in PTEN-deficient cancer cells involves IκB kinase (IKK)–α, a catalytic subunit of the IKK complex that controls NF-κB activation.

In addition to its role in repressing autophagy, NF-κB has recently been found to activate autophagy. Copetti et al.\textsuperscript{[62]} demonstrated that the NF-κB family member p65/RelA (v-rel reticuloendotheliosis viral oncogene homolog A) up-regulated Beclin-1 mRNA and protein levels in different cellular systems. Furthermore, they blocked p65 signaling pathway that could lead to a decrease in Beclin-1 transcription. Protein Beclin-1 can physically act in association with another protein (PI3KIII/Vps34) as a platform from which to recruit activators and inhibitors of autophagy, then to finely regulate autophagosome formation. Nevertheless, the precise link between NF-κB signaling and autophagic degradation remains to be elucidated.
Autophagy and cancer drug resistance

Acquired drug resistance in cancer cells is the major cause of failure for cancer therapy. Cancer drug resistance is complex, dynamic, and “elusive,” and it is affected by the following factors: (1) decreased influx and, because of drug transporters, increased efflux of anti-cancer drugs; (2) activation of DNA repair; (3) activation of detoxification, and (4) blockade of apoptosis[63,64]. Among these factors, current pharmacological approaches aim to restore the efficacy of the standard chemotherapy against drug-resistant cancers by reactivating apoptosis. However, resistance to apoptosis is considered a characteristic of many diverse cancer cells. Recent studies suggest that the autophagy and apoptosis pathways overlap[60]. Furthermore, many studies have shown that molecules that modulate or are involved in the autophagy process, when combined with chemotherapy agents, can reverse drug resistance[65,66].

5-fluorouracil (5-FU)–based chemotherapy has been reported to be an effective protocol for improving outcome and reducing tumor recurrence rate. Unfortunately, 5-FU resistance is a major cause of failure in colorectal cancer therapy[70]. Recently, Li et al.[88] showed that 5-FU induced apoptosis as well as autophagy, and combination treatment with 5-FU and 3-methyladenine (3-MA), which inhibits autophagy, significantly increased apoptotic cell death. Sasaki et al.[89] reported that combining chloroquine with 5-FU improved efficacy of 5-FU on colon cancer cells. O’Donovan et al.[90] inhibited early autophagy induction using siRNA targeting Beclin-1 and found that ATG7 significantly enhanced the effect of 5-FU and reduced the recovery of drug-treated esophageal cancer cells. These observations suggest that an autophagic response to chemotherapy may function as a survival mechanism that promotes chemoresistance and that selective inhibition of autophagy regulators has the potential to improve chemotherapeutic regimes.

Cancer therapy applications of autophagy regulators as single agents

Strategies to use regulators of autophagy as single agents to induce cytotoxicity in tumor cells have been developed in the last year. These agents include rapamycin[71,72], arsenic trioxide (As$_2$O$_3$)[73,74], temozolomide[75,76], kringles domains of plasminogen (endostatin kringle 5 )[77], phenethyl isothiocyanate (PEITC)[80], OSU-03012 (derivative of celecoxib)[81], NVP-BEZ235[82,83], and cell wall skeleton of Mycobacterium bovis Bacillus Calmette-Guerin (BCG/CWS)[84]. In addition, some autophagic inhibitors, such as 3-MA, chloroquine, bafilomycin A1, tamoxifen, and proteasome inhibitor MG-132[85,86] (Table 1), also inhibit tumorigenesis by playing a protective role in autophagy.

Utilization of the first prototype of an mTOR inhibitor, rapamycin, is limited due to the poor aqueous solubility and strong immunosuppressive properties[71]. However, its analogs, temsirolimus (CCI-779), everolimus (RAD-001), and deforolimus (AP23573), are used in the clinical and preclinical setting. In particular, temsirolimus was the first mTOR inhibitor approved by the US Food and Drug Administration for cancer treatment, and it is considered the first-line treatment for advanced renal cell carcinoma patients with poor prognostic features[85,86]. mTOR inhibitors bind to an intracellular protein, FK506 binding protein 12 (FKBP-12), forming a complex that inhibits the mTOR kinase. Randomized phase III trials have already demonstrated significant clinical benefits of treatment with single-agent temsirolimus in advanced renal cell carcinoma and relapsed and/or refractory mantle cell lymphomas[91,92]. Phase I and II trials have also been carried out in other malignancies, such as glioblastoma[93], breast cancer[94], endometrial cancer[95], non-Hodgkin lymphomas[96], and multiple myeloma[97].

In contrast to mTOR inhibitors, As$_2$O$_3$ has an elusive capacity for autophagy induction[72,73,75,76]. Kanzawa et al.[87,88] showed that As$_2$O$_3$ triggered autophagic cell death in U-373 malignant glioma cells with BNIP and BNIPL up-regulation. However, autophagy played complex roles in the As$_2$O$_3$-induced death of human acute myeloid leukemia cell line HL60 cells. A study by Yang et al.[74] showed that inhibiting autophagy at an early stage with 3-MA 1 h before As$_2$O$_3$ provoked As$_2$O$_3$-induced death of HL60 cells, whereas 3-MA administered 30 min after As$_2$O$_3$ attenuated As$_2$O$_3$-induced death. Therefore, they concluded that autophagy inhibits As$_2$O$_3$-induced apoptosis during the initiation stage of the autophagy process but amplifies the As$_2$O$_3$-mediated apoptotic program if it is persistently activated. In contrast, Charoenusk et al.[77] reported that As$_2$O$_3$ induced acute promyelocytic leukemia cell death in HL-60 cells via apoptosis but not autophagy. These findings suggest that the As$_2$O$_3$-induced effects depend on the tumor tissue
type: it triggers autophagy in solid tumors, whereas it induces cell death by apoptosis in hematological neoplasms. Currently, As₂O₃ is in clinical trials in gliomas, advanced solid tumors, metastatic liver cancer, and pediatric solid tumors.[60,100]

In addition to the aforementioned agents, new compounds have emerged as promising cancer chemopreventive agents because of their ability to induce autophagic cell death. These compounds include phenethyl isothiocyanate (PEITC), the celecoxib derivative OSU-03012, and kringles domains of plasminogen (endostatin kringles 5, K5). A study by Bommareddy et al.[80] showed that PEITC treatment triggered ATG5-dependent autophagic cell death in human prostate cancer cells, suggesting it may be an effective anti-tumor agent. The mechanism of action of OSU-03012 is presumably 3-phosphoinositide-dependent kinase 1 (PDK1) inhibition. Gao et al.[81] recently demonstrated that OSU-03012 induced autophagic cell death, which is related to the accumulation of reactive oxygen species (ROS) in hepatocellular carcinoma. Ramakrishnan et al.[82] reported that K5, a well-characterized and potential angiogenesis inhibitor, could induce autophagy in endothelial cells with alterations in the Beclin1–Bcl-2 complex.

Temozolomide (TMZ), a DNA alkylating agent, was reported to reduce the viability of malignant glioma cells in a dose-dependent manner and induce G2/M arrest.
and it has been used clinically for the treatment of malignant gliomas [100]. Although the current standard treatment for malignant gliomas is surgical resection followed by adjuvant radiotherapy plus TMZ, this type of cancer continues to maintain a dismal prognosis. O6-alkylguanine-DNA alkyltransferase (AGT) is a DNA repair enzyme that is known to limit the efficacy of TMZ in glioblastoma cells [100]. However, Fu et al. [100] reported that the possible molecular mechanisms underlying TMZ resistance in glioblastoma cells involve down-regulation of autophagy-related proteins in CD133+ cells. In contrast, a recent study carried out by Gao et al. [104] suggested that thalidomide enhanced the cytotoxicity of TMZ by promoting autophagy, which contributed to the up-regulation of PTEN by thalidomide. There is no doubt that more compounds that induce cell death through autophagy will be developed in the near future.

**Combined applications of two autophagic regulators to synergistically kill cancer cells**

A series of recent studies have reported that the combination of two or more autophagic regulators, especially proautophagic regulators, markedly enhance autophagic cell death. Oncolytic adenoviruses, promising tools in cancer therapy, induce autophagy as a part of their therapeutic effects [105]. Yokoyama et al. [105] jointly used OBP-405, an oncolytic adenovirus regulated by the human telomerase reverse transcriptase promoter with a tropism modification (RGD), as well as TMZ and rapamycin for an inhibition assay in glioblastoma cells. They found that tumor cells were synergistically sensitized to OBP-405 upon stimulation of the autophagic pathway. Ulasov et al. [107] used conditionally replicative adenoviruses (CRAds) with TMZ in the setting of experimental glioma in vivo and in vitro and observed, by Western blotting, increased expression of Bax and p53, elevated levels of Atg5, and decreased expression of Bcl-2. In addition to oncolytic adenoviruses, dasatinib, an ATP-competitive, small-molecule inhibitor, has also been used in combination therapies to induce autophagic cell death. Dasatinib is used to treat drug-resistant tumors expressing mutant BCR-ABL, KIT, or epidermal growth factor receptor (EGFR) by blocking tyrosine phosphorylation sites and inducing a significant increase in autophagic cell death. Milano et al. [108] demonstrated that combination treatment of glioma cells with dasatinib and TMZ resulted in a significant increase in cell cycle disruption and autophagic cell death, which resulted in increased therapeutic efficacy compared to the combination of dasatinib with carboplatin or irinotecan. Therefore, combination of two or more autophagic regulators may be helpful for cancer therapy and/or reverse the cancer drug resistance.

**Combined applications of autophagy regulators and chemotherapy in cancer treatment**

The idea of inhibiting tumor growth through autophagy blockade was conceived from observations of the role of autophagy and its cytoprotective effects during chemo- and radiotherapy in tumor cells. As mentioned above, malignant neoplasms are characterized by excessive proliferation, which results in an imbalance in supportive nutrients, hypoxia, and oxidative stress in tumor tissues. In these conditions, tumor cell and tissue survival is dependent upon the initiation of the autophagic process and glycolysis [109]. A number of conventional anti-tumor agents have been assayed and have been found to trigger autophagy as protective mechanism (Table 1).

Many specific autophagy inhibitors, such as 3-MA, chloroquine, bafilomycin A1, represent a general strategy to sensitize cancer cells to conventional chemotherapy [8,68,100]. Tamoxifen, the most commonly used anti-estrogen, exerts its pharmacological action by binding to estrogen receptor alpha (ERα) and blocking the growth-promoting action of the estrogen-bound receptor in breast cancer cells. However, the development of anti-estrogen resistance has become a major impediment in the treatment of ERα-positive breast cancer. Samaddar et al. [111] reported that autophagy plays a critical role in the development of anti-estrogen resistance. More specifically, overexpression of Beclin-1 down-regulated estrogenic signaling and growth response and contributed to the development of anti-estrogen resistance. Recently, Pattinget al. [51,112] demonstrated that tamoxifen stimulated ceramide synthesis de novo, which induced dissociation of the Beclin-1–Bcl-2 complex. Further, activation of JNK1 by ceramide was required both to phosphorylate Bcl-2 and to stimulate autophagy. Several compounds and chemotherapeutic agents have been reported to induce autophagy that protects against chemotherapy-induced cytotoxicity. However, autophagy inhibitors combined with these agents augment their killing capacity.

**Conclusions and Perspectives**

In summary, autophagy is a ubiquitous process in eukaryotic cells that results in the breakdown of cytoplasm within the lysosome in response to stress conditions, which allows the cell to adapt to environmental and/or developmental changes. However, autophagic cell death can result from excessive autophagy, which is associated with conditions such as neurodegenerative diseases, heart diseases, cancer, and
others. Therefore, further exploration of the role of autophagy in human disease will be important and promising work. The present research shows that appropriate modification of autophagy, that is, suppression of cell-protective autophagy or enhancement of cell-killing autophagy, can augment cytotoxicity caused by anti-cancer therapy. Hence, modulating autophagy will open new areas for cancer therapy.

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Tel: (20) 8734 3168
Fax: (20) 8734 3336
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