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Review

The role of autophagy in cancer chemotherapy drug resistance

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Abstract: About 650,000 cancer patients are treated with chemotherapy drugs each year. There have been tremendous advances in this field over the past several decades. However, major obstacles remain. One of these obstacles is that cancer cells become drug resistant. 90% of clinical failures in chemotherapy treatment are because of drug resistance. In this review, we focus on the role of autophagy in cancer cell drug resistance. In non-cancerous cells, autophagy is constitutively active, but can be augmented by nutrient deprivation, reactive oxygen species (ROS), and pathogen invasion. It can either keep cells alive or trigger apoptosis, depending on the degree of disruption of cell homeostasis. These are critical considerations in cancer treatment: autophagy can either kill cells or it can keep cancer cells alive, furthering drug resistance. In cancer cells, chemotherapy typically triggers ROS. ROS then activate autophagy through several pathways. Thus, understanding how autophagy works in cancer cells that have been exposed to drugs can be a valuable weapon to combat drug resistance.

Keywords: autophagy; chemotherapy; drug resistance; cancer; reactive oxygen species

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Introduction

Tumor cells can become resistant to chemotherapy drugs [1]. At the gross anatomy scale, resistance is due mainly to the limited amount of drug that can be administered to a patient because of toxicity [2]. Thus, cells deep in tumors are usually exposed to less-than-lethal doses of drugs that do not kill them. By being exposed to low doses of a chemical, the surviving cells become resistant through a variety of mechanisms. A key question is how this resistance occurs on the cellular and molecular levels. Answers to this question can be found, in part, in the cellular response mechanism autophagy. Autophagy is a conserved process that engulfs and degrades either seemingly random areas of the cytosol or targeted proteins and organelles [3]. The material to be broken down is engulfed in a double membrane structure that matures from the endoplasmic reticulum (ER) as an omegasome, grows into a phagophore, which then elongates into an autophagosome [4]. The autophagosome surrounds its cargo and then merges with a lysosome to form an autolysosome [5]. The contents of the autolysosome are degraded, and their fundamental moieties are reused [6]. A comprehensive guide to the molecular mechanisms of autophagy has been recently published [7].

Autophagy plays at least two roles in cancer progression and cancer chemotherapy drug resistance. First, it keeps eukaryotic cells alive in times of nutrient deprivation. Since cancer cells need reagents for unregulated growth, autophagy helps them thrive when nutrients are scarce. Second, certain chemotherapy drugs cause the generation of reactive oxygen species (ROS). ROS in turn trigger autophagy. This also helps keep cancer cells alive. The goal of this review is to highlight the effects of a subset of cancer chemotherapy treatments on ROS and autophagy that were reported in recent years. More than one-third of the references are from studies within the last five years. We focus mainly on the mechanisms by which chemotherapy drugs alter the states of proteins involved in the ROS-autophagy axis and provide a glimpse of the possibilities of co-treatments of anti-cancer and anti-autophagy agents.

Autophagy

Initiation of autophagy involves the formation of two protein complexes, the serine/threonine Unc-51-like kinase 1 (ULK1) complex and the class III phosphoinositide 3-kinase complex 1 (PI3KC3-C1) [7,8] (Fig. 1). Under nutrient deprivation, phosphoinositide 3-kinase class 1 (PI3K1) turns on a signaling cascade involving protein kinase B (AKT) that inhibits mechanistic target of rapamycin kinase (mTOR) and ultimately activates ULK1-mediated ULK1/autophagy-related protein 13 (ATG13)/focal adhesion kinase family interacting protein of 200 kDa (FIP200) dephosphorylation [9,10]. ULK1/ATG13/FIP200 complex cooperates with Beclin-1/PI3KC3/vacuolar protein sorting-associated protein 34 (Vps34) and promotes phagophore nucleation. Activation of Beclin-1/PI3KC3 leads to hydrogen peroxide (H_2O_2) accumulation in mitochondria because of stress conditions and nutrition deprivation, ultimately leading to the generation of ROS [11]. ROS further induce autophagy through several pathways [11]. These include 5' adenosine monophosphate-activated protein kinase (AMPK) activation, which leads to the activation of the ULK1/ATG13/FIP200 complex.

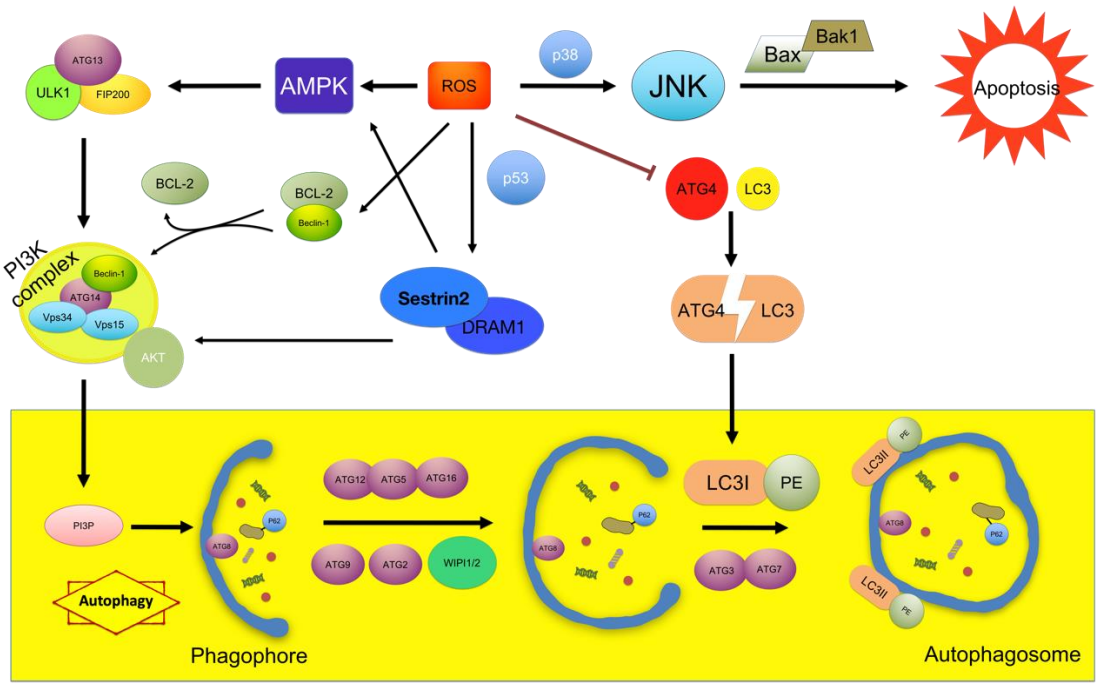

Figure 1. Proteins involved in autophagy initiation, phagophore formation, elongation and autophagosome formation. Autophagy and ROS levels are positively correlated.

The term autophagy encompasses a broad class of cellular responses. One classification strategy is for autophagy to be described as selective or non-selective. In the former, organelles and pathogens are directly targeted for degradation. In this form of autophagy, cargo adaptor proteins Sequestosome 1 (SQSTM1)/p62, neighbor of BRCA1 gene 1 (NBR1), or B-cell lymphoma 2 (BCL-2)/adenovirus E1B 19-kDa-interacting protein 3 longform (NIX/BNIP3L) bind both the cargo and ATG8 family proteins such as microtubule-associated protein 1A/1B-light chain 3 (LC3) and gamma-aminobutyric acid receptor-associated protein (GABARAP), which are on the phagophore [12–15]. In the latter, volumes of the cytosol are engulfed and recycled. We focus on the subsets of autophagy that have been found to be important in cancer cells, with ROS-induced autophagy at the forefront. It is mechanistically unclear if ROS generate selective, non-selective, or both types of autophagy [16].

ROS

ROS are unstable, partially reduced oxygen derivatives, which are byproducts of metabolic processes. They are continually being generated during normal metabolic processes [17]. They include H_2O_2, superoxide anion (O_2^-), hypochlorous acid (HClO), singlet oxygen ($^1O_2$), and hydroxyl radical (·OH) [18]. ROS-producing enzymes include NADPH oxidases, cyclooxygenases (COX), and lipoxygenases (LOX). ROS are generated from oxygen mostly in mitochondria, during oxidative phosphorylation [19,20]. Peroxisomes generate O_2^- and H_2O_2, contributing to ROS production. Chemotherapy drugs also contribute to ROS production, as discussed below.

ROS regulate autophagy

The main downstream autophagic effectors of ROS are ATG4 (at Cys-81), AMPK, ULK1/ATG1 (through AMPK), and the transcription factor nuclear factor of κ light polypeptide gene enhancer in B-cells (NF-κB), which leads to the expression of Beclin-1 and SQSTM1/p62 [11,21–26]. ATG4 oxidized by ROS at specific cysteine residues is unable to delipidate LC3 [27,28]. Since lipidated LC3 is part of the autophagosome, ROS interaction with ATG4 leads to the sustained presence of autophagosomes [11,21–26]. Because mitochondria produce ROS, autophagy of mitochondria, a process called mitophagy, is crucial for regulating ROS levels. Mitophagy initiation involves either the ubiquitin-mediated phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1)-Parkin pathway or the receptor-mediated FUN14 domain containing 1 (FUNDC1)/BCL-2 interacting protein 3 (BNIP3)/BNIP3-like protein X (NIX) pathway [29]. In the former, PINK1 accumulates in the outer mitochondrial membrane [30]. A phosphorylation cascade involving PINK1 and Parkin activates Parkin's ubiquitin ligase activity [31]. Parkin then ubiquitylates the outer mitochondrial membrane proteins Mfn1, Mfn2, VDAC, and MIRO1 [32]. Ubiquitinated proteins are then recognized by the ATG8-family junction proteins SQSTM1/p62, OPTN, NDP52, TAX1BP1, and NBR1. Interestingly, PINK1-PRKN-dependent mitophagy requires GABARAP, not LC3 [33,34]. The phagophore then nucleates around the damaged mitochondria and autophagy is initiated. In the latter case, the mitochondrial receptor proteins FUNDC1, BNIP3, NIX, FKBP8, Bcl2L13, Ambra1, PHB2, and NLRX1 contain a conserved LC3-interacting receptor domain that can bind LC3 and thus be engulfed in a developing autophagosome [35–43].

ROS in cancer cells

Cancer cells have high ROS levels [44]. This is due mainly to augmented cell proliferation, differentiation, protein synthesis, glucose metabolism, and inflammation [45]. Increased metabolism in cancer cells results in respiratory dysfunction and electron leakage from mitochondria [46]. In fact, cancer cells often have dysfunctional mitochondria. ROS levels can further increase by oncogene activation, or cytokine/growth factor signaling [28,47]. During ROS-induced tumor cell progression, ROS activate the Wnt signaling pathway. Wnt activation leads to the epithelial-mesenchymal transition [48]. It also upregulates the transcription factor c-Myc [49]. Overexpression of c-Myc is a hallmark of cervical carcinomas, leukemias, lymphomas, colon, and testicular cancers [50,51]. In turn, c-Myc overexpression can generate additional ROS [52]. With this background in autophagy and ROS, we now focus on the mechanisms by which chemotherapy drugs trigger additional ROS production, which in turn triggers pro-survival autophagy in cancer cells.

Autophagy plays different roles in cancer cells, depending on the stage of tumor progression [53]. Autophagy can help reduce the probability of DNA mutations by suppressing ROS in the early stages of oxidative cell stress [54]. This occurs mainly through mitophagy. In primary tumor cells, autophagy can cause p53-dependent apoptosis, thus preventing accumulation of oncogenic p62 protein aggregates and metastasis [55]. p53 plays pro- and anti-autophagic roles, depending on its localization in cells [56]. p53 is usually localized to the cytosol. Cytosolic p53 suppresses autophagosome formation by interacting with FIP200, which leads to inhibition of the ULK1/ATG13/FIP200 complex [56]. When p53 translocates to the nucleus, it initiates autophagy. In the nucleus, p53 activates autophagy inducers, including DNA damage regulated autophagy modulator 1 (DRAM1) and Sestrin2 [57]. In these cells, downregulation of BCL-2/BCL-xL induces pro-apoptotic autophagy [58]. At this point in cancer progression, when cells are adapting to stress (e.g., nutrient deprivation, hypoxia, metabolic stress, and chemotherapy), autophagy reduces both DNA and ROS damage, and removes damaged organelles [59]. In metastasis, autophagy helps migrating cells overcome hypoxia, nutrient deprivation, and autophagic gene mutations that lead to chemotherapy resistance [55]. Thus, depending on the stage of the cancer, with more advanced cancers needing more nutrients, cancer cells should naturally trigger ROS production [60].

The effects of chemotherapy on ROS production

Chemotherapy can cause ROS generation by disrupting and/or by inhibiting the cellular antioxidant system [61–67]. In the former, chemotherapy drugs can destabilize mitochondrial membranes, disrupting the mitochondrial electron transport chain. This leads to electron leakage, which elevates ROS production [61–67]. Thus, mitophagy could play a central role in chemotherapy drug resistance. In the latter, chemotherapy agents can cause the depletion of antioxidants such as glutathione (GSH) and the superoxide dismutase (SOD) enzyme [61–67].

Since autophagy can sustain cell viability, it is important to determine if there are functional overlaps or interactions with autophagy gene products and the anti-apoptotic proteins that cancer cells use for survival [68]. BCL-2 family members are a prominent class of anti-apoptotic genes [69]. During stress conditions, Beclin-1 interacts with BCL-2/xL/w/myeloid cell leukemia 1 (MCL-1), thereby activating autophagy via the interaction of Beclin-1 with Vps15 and Vps34 [70] (Fig. 2). This complex promotes phagophore nucleation [69]. Thus, we see that anti-apoptotic genes work with autophagy genes to maintain cell viability.

However, BCL-2 proteins can also be apoptotic. BCL-2, BCL-xL, BCL-w, and MCL-1 inhibit survival autophagy when BCL-2 interacts with Beclin-1. This complex blocks the action of BCL-2 associated X, apoptosis regulator (Bax)/BCL-2 antagonist/killer 1 (Bak1) [69]. The activated Bax/Bak1 complex causes mitochondrial membrane permeabilization and rupture by interacting with ceramide channel-forming sphingolipids or form putative cytochrome c release channels on the outer membrane of mitochondria to induce permeabilization [71].

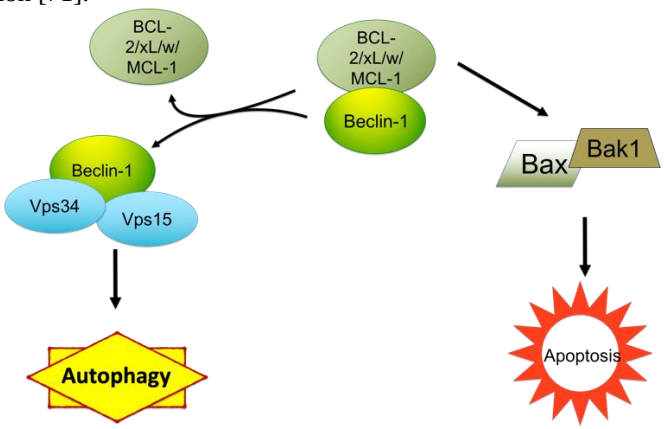

Figure 2. Different functions of BCL-2 family members. Beclin-1 dissociation from BCL-2, BCL-xL, BCL-w, MCL-1 during stress conditions causes phagophore nucleation and triggers autophagy, while pro-apoptotic BCL-2 (Bax and Bak1) causes mitochondrial membrane rupture. Cell survival genes coordinate with autophagic genes to promote viability.

Certain chemotherapy drugs cause autophagy

The main link between cancer chemotherapy drug resistance and autophagy is that drugs trigger ROS production, which triggers autophagy, keeping certain cancer cells viable. Table 1 summarizes drugs that are involved in chemotherapy treatments that trigger autophagic pathways.

Piperlongumine. Piperlongumine is used as an anti-cancer drug for lung, breast, prostate, and gastric cancers. Piperlongumine causes p38 and c-Jun *N*-terminal kinase (JNK) phosphorylation via a ROS-dependent pathway. This leads to increased expression of Bax and Beclin-1 [72,73]. It also inhibits AKT/mTOR phosphorylation, triggering autophagy. Piperlongumine activation of p38 inhibits ATG5 and the formation of autophagosomes (Fig. 3). In piperlongumine-treated androgen-independent human PC-3 prostate cancer cells and renal carcinoma 786-O cells, stimulation of ROS inhibits the phosphorylation of AKT [74].

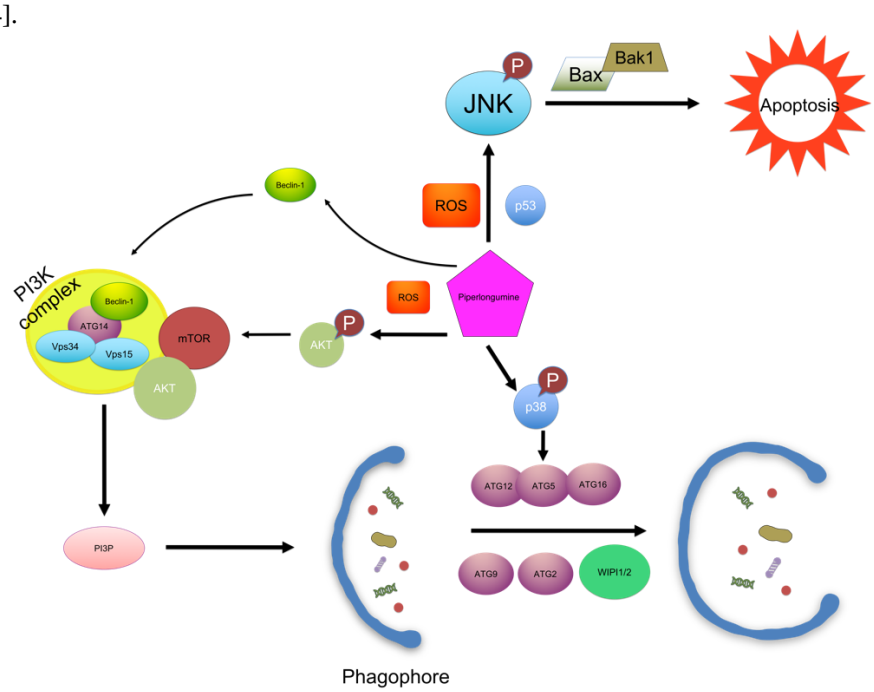

Figure 3. Role of piperlongumine in the autophagic pathway. Piperlongumine activates p38 phosphorylation, leading to autophagosome formation. It also triggers autophagy via ROS promotion and AKT/mTOR inhibition. Piperlongumine also phosphorylates JNK, leading to the triggering of apoptosis by Bax and Beclin-1. Piperlongumine triggers a combination of autophagic and apoptotic pathways.

Sorafenib. Sorafenib inhibits protein kinases including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and rapidly accelerated fibrosarcoma (RAF) kinases [75]. Rodríguez-Hernández *et al.* have shown that a low dose of sorafenib, a drug to treat advanced hepatocellular carcinoma (HCC), increased autophagy in HepG2 liver cells *in vitro* [76,77]. The survival role of autophagy has been seen in lower doses of sorafenib, through activation of caspase-9 [76,77]. Caspase-9 is activated by adenosine uptake into mammalian cells, followed by conversion to AMP, and ultimately AMPK activation [78]. In contrast, higher doses of sorafenib induced cell death through the caspase-3 pathway, by inhibiting BCL-2 family proteins [76,77] (Fig. 4). Forkhead box protein O3a (FOXO3a) is an important transcriptional factor that regulates stress responses, such as hypoxia and nutrition deprivation, in the cells. Phosphorylation of FOXO3a occurs under starvation conditions via the PI3K-AKT signaling pathway [79]. mTOR is upregulated by sustained sorafenib and AKT activation; therefore, it leads to autophagy induction and cell apoptosis [80].
FOXO3a knockout inhibits hypoxia-induced autophagy; therefore, to eliminate sorafenib resistance, FOXO3a plays a pivotal role in HCC cells [81].

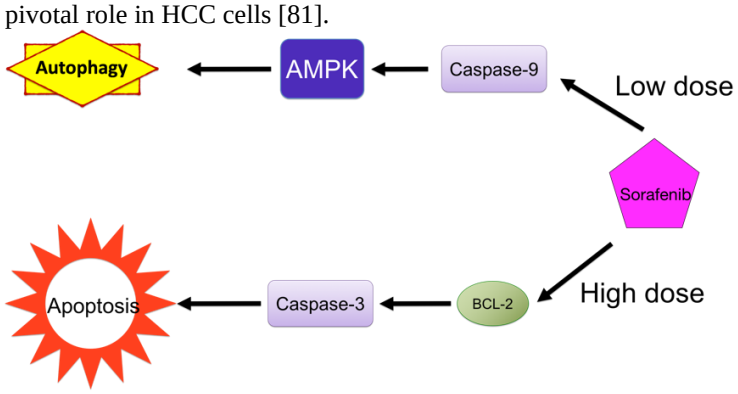

Figure 4. Role of sorafenib in the autophagic pathway. The extent of autophagy and apoptosis by sorafenib is dose-dependent.

miRNAs and lncRNAs. MicroRNAs (miRNAs or miRs) are non-coding RNAs that regulate gene expression, cell proliferation, and apoptosis [82]. miRNAs are involved in the initiation, progression, and drug resistance of HCC [83]. Similarly, miR-212 downregulates lethal autophagy through the AKT/PTEN pathway in sorafenib-resistant cells [84]. Xie *et al.* have confirmed the downregulation of the AKT/PTEN/NF-κB signaling pathway by miR-132, which blocks resistance by doxorubicin (DOX) in HCC cells [85,86]. miR-132 targets PI3K regulatory subunit 3 (PIK3R3) and inhibits autophagy and drug resistance in HCC cells [87]. Also, miR-223 overexpression induced non-lethal autophagy in cisplatin-resistant cells; therefore, miR-223 inhibition enhanced cisplatin efficacy *in vivo* [88]. In another example of HCC treatment, it was shown that cisplatin-induced downregulation of miR-199a-5p increased drug resistance by activating ATG7, another autophagy associated gene that interacts with LC3 [81] (Fig. 5). miR-22 increases the sensitivity of osteosarcoma cells to cisplatin [89]. A miR-22 mimic that was transfected into osteosarcoma cells downregulated ATG5, Beclin-1, and LC3 [90]. Thus, miR-22 may improve cisplatin sensitivity by inhibiting autophagy. This is an example where the combination of anti-cancer drugs and autophagy modulators may improve chemotherapy treatment outcomes.
Long non-coding RNA (lncRNA) LUCAT1 contributes to cisplatin resistance by regulating the miR-514a-3p/ULK1 axis in human non-small cell lung cancer (NSCLC) [91]. LUCAT1 was upregulated in cisplatin-resistant cancer cells. ULK1 was determined to be the target gene of miR-514a-3p. LUCAT1 positively regulated ULK1 expression by targeting miR-514a-3p. Gene ontology analysis of lung cancer cells revealed that autophagy plays a protective role against cisplatin [92]. That study showed that autophagy is more active in cisplatin-resistant small cell lung cancer cells; that autophagy protects cisplatin-resistant small cell lung cancer cells; and that anti-malaria drugs, which increase the pH of lysosomes, enhance cisplatin effectiveness. miR-17 binds ATG7 mRNA and negatively regulates ATG7 expression [93]. High expression of ATG7 leads to chemotherapy resistance [94]. Temozolomide, a brain cancer treatment, showed the most resistance in cells of the T98G glioblastoma cell line [95]. Inhibition of miR-17 combined with temozolomide decreases drug resistance in T98G cells via the autophagic pathway underlying ATG7 regulation [96].
In human lung adenocarcinoma cells, miR-24-3p was found to regulate cisplatin resistance in small-cell lung cancer by targeting ATG4 and, finally, miR-200b participated in autophagy regulation through ATG12 signaling [89,97] (Fig. 5). MiR-133a also plays a prominent role in tumorigenesis, progression, autophagy, and drug-resistance in various malignancies [98]. It could incorporate DOX and cisplatin to improve drug efficiency in breast cancer cell line MCF-7 and Hep-2v cells, respectively [99,100]. MiR-133a-3p can promote proliferation and autophagy in gastric cancer (GC) cell lines by binding the 3'-UTR of forkhead protein 3 (FOXP3) [101].

Table 1. Drugs and their effect on autophagy.

References	Drugs/Proteins	Disease/Cell line	Effect on autophagy	Pathway
[74]	Piperlongumine	Prostate cancer (786-O and PC-3)	Generating ROS	mTOR inhibition signaling via AKT phosphorylation
[72,73]	Piperlongumine	Leukemia (U937)	Promoting ROS	p38 and JNK phosphorylation, Bax and Beclin-1 upregulation
[77]	Sorafenib	HCC (HepG2 cells)	Reducing caspase-9 activity	AMPK signaling
[91]	Cisplatin	NSCLC	Activating autophagy by targeting ATG7	Downregulated miRNA cells and PI3K complex
[102]	Bortezomib	MM cells (MM1.R)	Suppressing MARCKS	Initiating Beclin-1/BCL-xL complex
[103]	Trim14	GC cells (SGC)	Promoting autophagy by FGFR inhibition	PI3K/mTOR/AMPK complex
[104]	DHA/Epirubicin	Breast cancer (MDA and MCF-7)	Inducing autophagy by blocking Beclin-1/BCL-2 complex	mTOR autophagic signaling
[105]	DHA/DOX	Breast cancer (MDA and MCF-7)	Enhancing DOX localization in the nucleus, generating ROS	AKT/mTOR signaling
[106]	PTX	Ovarian, esophageal, breast, lung, Kaposi's sarcoma, cervical, and pancreatic cancers	Inhibiting autophagy, but co-treatment of breast cancer cells with the autophagy blocker CQ improves PTX resistance	LC3-II and SQSTM1 signaling
[107]	Trastuzumab emtansine	HER2-positive breast cancer	Promoting autophagy	Caspase-3/7 activation and AKT/mTOR signaling
[108]	Vemurafenib/Mibefradil	MM cells (Vem-R and Vem-S)	Promoting autophagy	Activation of PI3K/AKT pathway

AKT: protein kinase B [serine/threonine kinase]; AMPK: 5' adenosine monophosphate-activated protein kinase; ATG7: autophagy-related protein 7; Bax: BCL-2 associated X, apoptosis regulator; Caspases: cysteine-dependent aspartate-directed proteases; CQ: chloroquine; DHA: dihydroartemisinin; DOX: doxorubicin; FGFR: fibroblast growth factor receptor; GC: gastric cancer; HCC: hepatocellular carcinoma; HER2: human epidermal growth factor receptor 2; JNK: c-Jun *N*-terminal kinase; LC3-II: microtubule-associated protein 1A/1B-light chain 3-II; MARCKS: myristoylated alanine-rich C kinase substrate; miRNA: microRNA; MM: multiple myeloma; mTOR: mechanistic target of rapamycin [serine/threonine kinase]; NSCLC: non-small cell lung cancer; PTX: paclitaxel; PI3K1: phosphoinositide 3-kinase class 1; ROS: reactive oxygen species; SQSTM1: sequestosome 1; Trim14: tripartite motif-containing 14

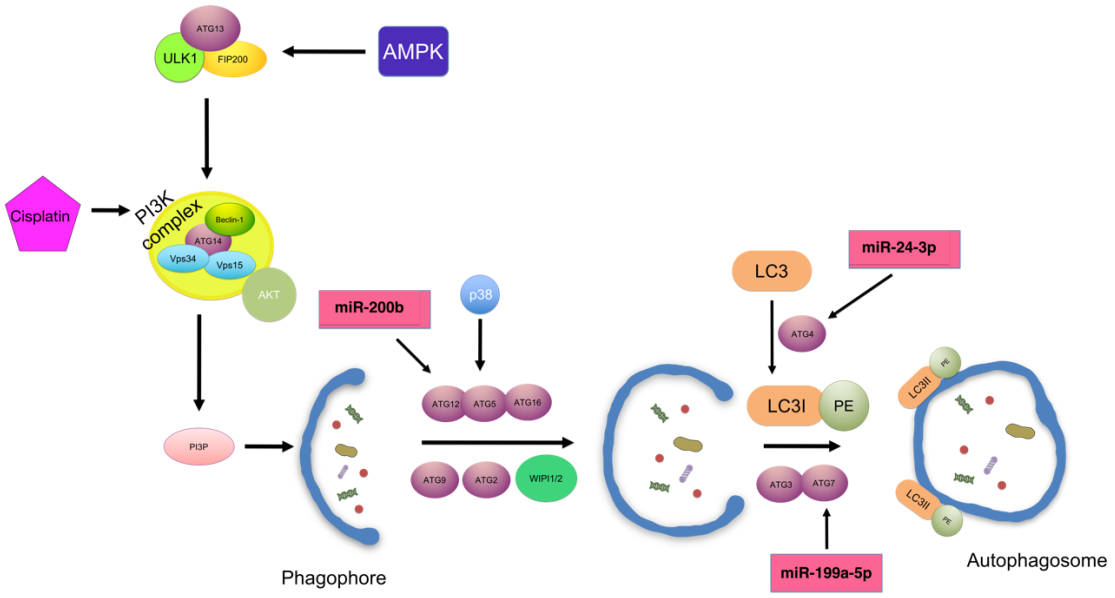

Figure 5. Inhibiting non-lethal autophagy by miRs to overcome drug resistance in cisplatin-treated cells. miR-200b, miR-24-3p, and miR-199a-5p respectively inhibit ATG12, ATG4, and ATG7 in different stages of autophagy.

Bortezomib and Carfilzomib. Bortezomib and carfilzomib – two drugs that are used for the treatment of multiple myeloma (MM) – activate AMPK, which promotes prosurvival autophagy [74] (Fig. 6). Similarly, Zhang and colleagues showed that bortezomib suppressed myristoylated alanine-rich C kinase substrate (MARCKS), causing p53 upregulation, which released the autophagy initiating Beclin-1/Vps34 complex from BCL-2 family proteins [109]. They also showed that the interaction between Beclin-1 and BCL-xL is weakened in MARCKS-silenced cells. The reduced Beclin-1/BCL-xL interaction suggest a mechanism whereby MARCKS suppression induces autophagy [92]. Combining the drugs mentioned above, bortezomib and carfilzomib, with MARCKS knocked-down cells, led to increased MARCKS suppression. Therefore, the triggering of lethal autophagy with MARCKs suppression seems to help to combat drug resistance in the MM cells [92] (Fig. 6).

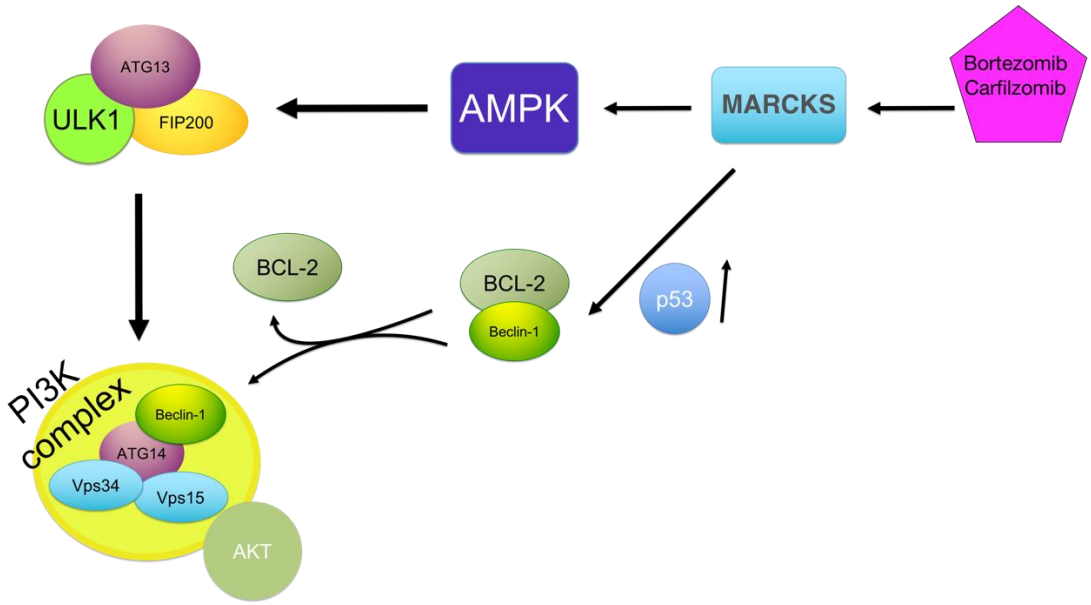

Figure 6. Role of bortezomib and carfilzomib in the autophagic pathway. These drugs trigger autophagy by activating the AMPK pathway and increasing nuclear p53 via MARCKS suppression.

Further studies on HCC have shown the regulation of autophagy by lncRNAs. In response to drug-resistance to DOX and sorafenib, long intergenic non-coding RNA 00160 (LINC00160) triggers autophagy by targeting PI3K and ATG5 [110]. LINC00160 correlates with breast cancer survival and regulates the expression of PIK3R3, whose main function is ATG5 activation at the transcriptional level, and, by binding to miR-132, inhibits cell viability and drug resistance in HCC cells [109] (Fig. 7).

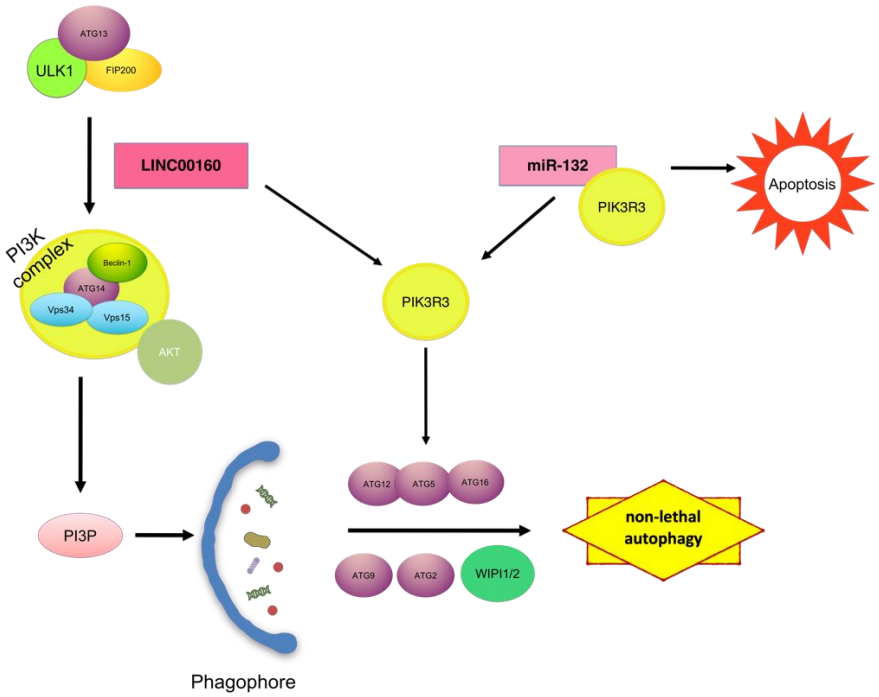

Figure 7. LINC00160 upregulates PIK3R3, while miR-132 is downregulated. Silencing of LINC00160 suppresses autophagy by decreasing PIK3R3 and miR-132 promotion in DOX- and sorafenib-resistant cells to overcome drug resistance.

LINC00160 silencing suppresses non-lethal autophagy and cell proliferation by decreasing PIK3R3 and miR-132 promotion [94]. In terms of the key autophagy regulator, ATG7, lncRNA BLACAT is up-regulated in cisplatin-resistant NSCLC cells and acts as a competing endogenous RNA (ceRNA) in reducing miR-17 expression. This leads to increased expression of ATG7 and autophagy promotion [111]. LncRNA XIST also causes autophagy and drug resistance to chemotherapy by regulating ATG7 expression through miR-17 [112].

However, lncRNAs have different effects on liver cancer cells and are highly upregulated in HCC tissues and human HCC cell lines, including HepG2, Hep3B, PLC, Huh7, and smmc7721 [94,113]. In a similar study on HCC and sorafenib, Lin and colleagues have represented autophagy suppression by an RNA complex. Methyltransferase-like 3 (METTL3) is an RNA methyltransferase complex that inhibits autophagy under hypoxia environment through the PI3K/AKT signaling pathway. METTL3-knockdown provides another solution to minimize sorafenib drug resistance in NSCLC, via upregulation of LC3-II, ATG5, Beclin-1 and Vps34, and downregulation of BCL-2 [80,114] (Fig. 8).

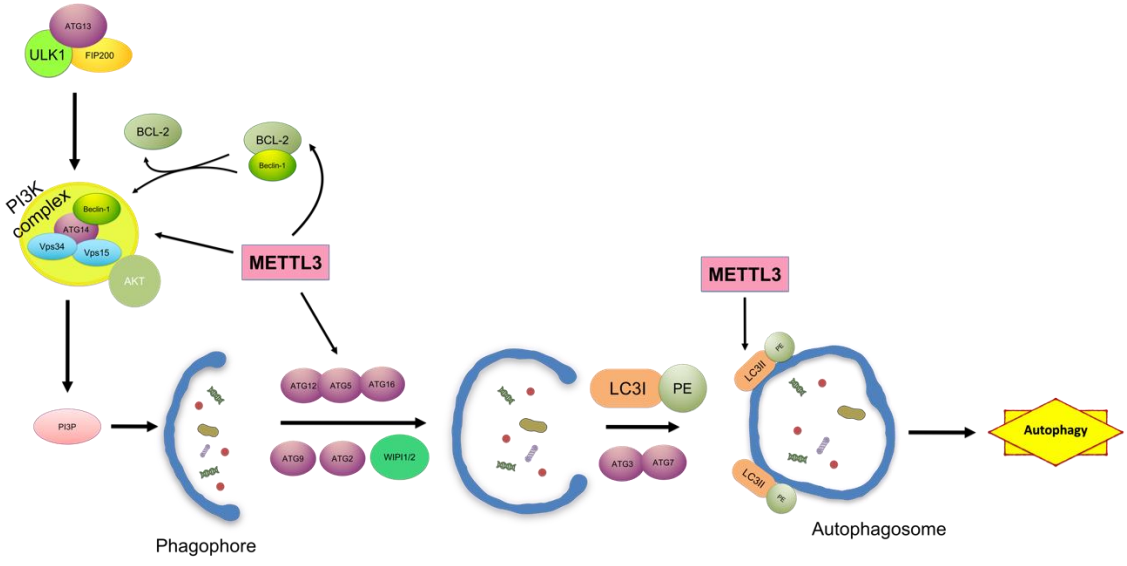

Figure 8. The role of METTL3 in autophagy induction in sorafenib-resistant cells. Depletion of METTL3 in hypoxia conditions activates the autophagic pathway in HCC cells.

Gemcitabine and Asparaginase. Gemcitabine is used to treat prostate cancer. Zhang and colleagues demonstrated that gemcitabine treatment in hormone-independent prostate cancer (HIPC) has a dose-dependent outcome on the protein level of high mobility group box 1 (HMGB1) [115]. HMGB1 upregulates the Beclin-1/2 complex by dissolving it from BCL-2 to initiate and regulate autophagy in the cytosol. Nuclear localization of HMGB1 activates heat shock protein β-1 (HSPB1) expression and autophagy. HMGB1-overexpression or -knockdown affects HSPB1 level but does not have any effect on Beclin-1 level. This leads to the postulate that gemcitabine sensitivity is due to HSPB1-initiated autophagy. Nevertheless, the exact pathway of Beclin-1 autophagy induction is still unclear [84] (Fig. 9).

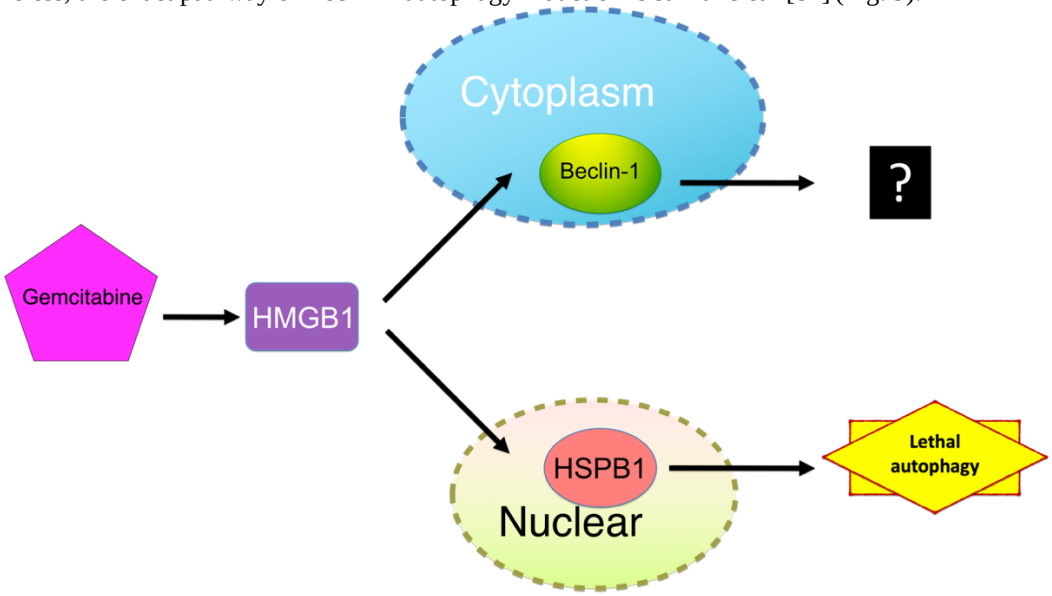

Figure 9. Role of gemcitabine in the autophagic pathway. HMGB1 regulates non-lethal autophagy in the cytosol. Nuclear localization of HMGB1 expresses HSPB1 and induces autophagy.

Asparaginase is a common drug in the treatment of natural killer/T-cell lymphoma. As the name suggests, asparaginase kills these target cells by depriving them of L-asparagine [116]. Patients with higher levels of the non-messenger RNA factor brain cytoplasmic RNA 1 (BCYRN1) had markedly lower progression-free survival than patients with lower levels [117]. The authors found that asparaginase increased degradation of p53 through ubiquitination. This resulted in the increase of autophagy via the PI3K/AKT/mTOR and p53/mTOR pathways, ultimately leading to asparaginase resistance. In this case, drug resistance was reversed by drug-induced autophagy inhibition in a xenograph model.

Tripartite motif-containing 14 (Trim14), a protein that has been expressed in GC cells, has promoted autophagy and increased the proliferation of chemotherapy resistance. The autophagic pathway that has been involved here consists of the PI3K/mTOR/AMPK complex. As it was mentioned before, the activation of AMPK reversibly regulates the activation of mTOR [103].

In advanced stages of GC, human fibroblast growth factor receptor (FGFR) protein inhibition has been reported to activate autophagy and improve therapeutic strategies [110]. FGFR activates mitogen-activated protein kinase (MAPK), and the PI3K/AKT complex [118,119]. Peng *et al.* have shown that the FGFR inhibitor is connected with autophagy by targeting the AMPK/mTOR signaling pathway in GC cells [110]. Previous studies have shown the role of transforming growth factor-β-activated kinase 1 (TAK1) in autophagy induction via AMPK/mTOR signaling pathway [106,120,121]. In sum, with the combination of FGFR and TAK1 inhibitors, chemotherapy resistance could potentially be overcome [86].

Cancer stem cells and autophagy

Cancer is in large part a stem cell disease. Recently, mechanistic links between cancer stem cell factors and autophagy have been uncovered. In the context of our discussion of GC and colorectal cancer, it was recently determined that Beclin-1 is partially responsible for chemoresistance, stemness, and the epithelial-mesenchymal transition [122]. In that work, the sex-determining region Y-box2 (SOX2), a master regulator of embryonic and induced pluripotent stem cells, increases the expression of Beclin-1. This increases autophagy and activates a malignant phenotype. Furthermore, xenograph mouse models showed that SOX2 inhibition reduced autophagy and abated tumor growth and decreased chemotherapy resistance *in vivo*. These results confirm those of a previous study suggesting that SOX2 plays a crucial role in maintaining GC stem cell properties [123]. Certainly, more links between stemness and autophagy will be uncovered that will hopefully be able to be exploited as drug targets.

Targeting autophagy to overcome drug resistance

Combining chemotherapy drugs with autophagy inhibitors can optimize drug concentration, accelerate binding with the targets and/or transporters, and inhibit autophagy, leading to cell apoptosis and eventually more efficient anticancer treatment. Table 2 provides a list of complementary enhancers to minimize drug resistance in cancer. Ramirez and colleagues saw an increase in ATGs, SQSTM1, Beclin-1, and ULK1 after 5-fluorouracil (5-FU) treatment of the human colon cancer cell line HCT-116 *in vitro* [124]. However, when they added chloroquine (CQ), an autophagy suppressor, LC3-II and SQSTM1 levels increased, indicating that autophagy was blocked at autophagosome formation. It should always be noted that autophagy is a dynamic process and can be halted at certain gateway points [3]. Incomplete autophagy and autophagosome accumulation can cause oxidative stress and lead to organelle dysfunction and, ultimately, cell death [104,125]. Indeed, adding CQ to 5-FU increases cell apoptosis [124].

In the following, more examples of multidrug resistance and autophagy are discussed. In some recent studies on cancer treatment by dihydroartemisinin (DHA), apoptosis has been noticed widely in autophagy induction and tumor cells. For example, in breast cancer, a combination of DHA and epirubicin, another breast cancer drug, improved the treatment due to higher drug concentration and prolonged drug interference to the cells through the mTOR autophagic signaling pathway [104,115].

DHA interacts with BCL-2, therefore blocking the Beclin-1/BCL-2 complex. Beclin-1 activates the PI3K complex to promote autophagy. On the other hand, DHA suppresses binding of BCL-2 with Bax, resulting in Bax association with the mitochondria, to activate the apoptosis cascade via the mitochondria pathway. Epirubicin intercalates DNA strands, resulting in apoptosis of cancer cells. Moreover, DHA enhances the uptake of epirubicin due to the disruption of the cell membrane upon exposure to DHA [105].

Similarly, in colon cancer, DHA+DOX enhanced the localization of DOX in the nucleus, followed by autophagy enhancement and, finally, cancer cell apoptosis [110]. Other than Bax, DHA contributes with other cell mechanisms, such as inhibition of NF-κB, generation of active oxygen radicals, autophagy regulation, and apoptosis induction [126–128]. Downregulation of NF-κB promotes ROS and suppresses mTOR signaling, leading to autophagy induction [129]. In an *in vivo* study on rat ventricular cardiomyocytes, DOX-induced autophagy was proven through GATA binding protein 4 (GATA4) pathway. In response to DOX treatment, the GATA4 protein is depleted, which results in BCL-2 inhibition and ATG5, ATG7, ATG12, and Beclin-1 upregulation (Fig. 10). Ultimately, it leads to autophagy activation, contributing to cardiomyocyte death [130]. The drug combination also resulted in downregulation of BCL-xL [129]. Recent strategies for overcoming autophagy-based resistance to DOX include the co-delivery of DOX with mirror siRNA that knocked down ATG7 [131]. Another study has shown that alteration of paclitaxel (PTX) with CQ caused autophagy inhibition in lung adenocarcinoma cells and ovarian carcinoma cells [99].

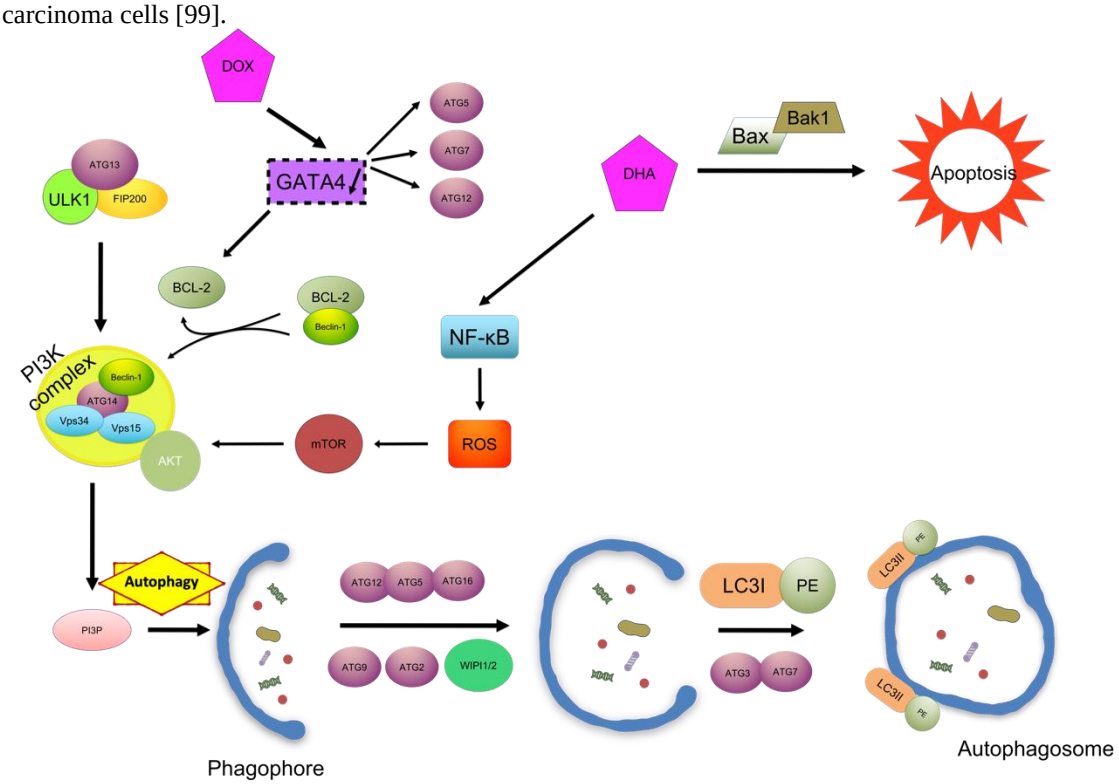

Figure 10. Role of DHA and DOX in the autophagic pathway. Combination of these drugs enhances autophagy by downregulation of BCL-xL.

Table 2. The effect of drug enhancer co-treatment with chemotherapy on autophagy.

References	Drugs	Drug Enhancers	Cell lines	Pathway
[109]	Bortezomib	Carfilzomib	MM cells (MM1.R)	MARCKS knocked-down Upregulating p53, initiating Beclin-1/Vps34 complex
[84]	Sorafenib	miR-212	HCC (HCCLM3-SR)	AKT/PTEN signaling
[85]	DOX	miR-132	HCC (MHCC97 cells)	Downregulating AKT/PTEN/NF-κB signaling pathway
[132]	DOX and Sorafenib	LINC00160 suppression	HCC	Targeting PI3K and ATG5
[114]	Sorafenib	METTL3	HCC (HepG2)	PI3K/AKT signaling pathway
[115]	Gemcitabine	HMGB1	HIPC cells	Beclin-1 and -2 complex and HSPB1 expression
[115]	5-FU	CQ	HCT-116 colon cancer	Increasing ATGs/SQSTM1/Beclin-1/ULK1; and LC3-II/SQSTM1
[106]	PTX	CQ	Human lung adenocarcinoma (A549/T) cells and ovarian carcinoma (A2780/T) cells	Increasing LC3-II and SQSTM1 levels
[108]	Vemurafenib	TTCC and BRAF inhibitor	MM cells (Vem-R and Vem-S)	Activation of PI3K/AKT pathway
[133]	Sertraline	TRAIL	Lung A549 cells	Downregulation of AMPK and BCL-2, increase in caspase-3 activity

AKT: protein kinase B [serine/threonine kinase]; AMPK: 5' adenosine monophosphate-activated protein kinase; ATG5: autophagy-related protein 5; BCL-2: B-cell lymphoma 2; BRAF: B-Raf proto-oncogene [serine/threonine kinase]; Caspases: cysteine-dependent aspartate-directed proteases; CQ: chloroquine; DOX: doxorubicin; 5-FU: 5-fluorouracil; HCC: hepatocellular carcinoma; HMGB1: high mobility group box 1; HSPB1: heat shock protein β-1; LC3-II: microtubule-associated protein 1A/1B-light chain 3-II; LINC00160: long intergenic non-coding RNA 00160; MARCKS: myristoylated alanine-rich C kinase substrate; METTL3: methyltransferase like 3; miR: microRNA; MM: multiple myeloma; NF-κB: nuclear factor of κ light polypeptide gene enhancer in B-cells; PI3K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homolog; PTX: paclitaxel; SQSTM1: sequestosome 1; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; TTCC: T-type calcium channel; Vps34: vacuolar protein sorting-associated protein 34; ULK1: Unc-51-like autophagy activating kinase 1

In a different approach to breast cancer, Liu and colleagues precisely demonstrated the notable result on trastuzumab emtansine (T-DM1) autophagy induction in a type of breast cancer cells [131]. Human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients who have progressed after prior treatment with trastuzumab and taxane received T-DM1, an antibody-drug conjugate (ADC) of trastuzumab [107]. T-DM1 has triggered autophagy inhibition and cell apoptosis through the caspase-3/7 activation pathway and showed therapeutic improvement. They also revealed a molecular pathway for T-DM1, in which T-DM1 reduces p-mTOR-S2448 expression in cells. Then, mTOR and AKT regulators are dephosphorylated and trigger autophagy [80].

Hormone therapy has also been reported for HCC treatment with underlying autophagy [134]. Thyroid hormone is involved in the phosphatase and tensin homolog (PTEN)-induced kinase 1 pathway and triggers selective mitophagy, autophagy of mitochondria [135]. Therefore, it can be an option for liver cancer treatment while further investigations are required.

Another chemotherapy-resistant disease is malignant melanoma, which is affected by autophagy activation. Vemurafenib tends to reduce the standard type of this tumor, and melanomas harbor B-Raf proto-oncogene (*BRAF*) gene mutation kinase inhibitors. However, these tumors repeatedly face drug resistance through chronic vemurafenib-induced autophagy [108]. It has been observed in a study on mutant melanoma cells that it is possible to overcome resistance development by blocking autophagy. Barceló *et al.* have proposed an autophagy blocker complex to treat melanomas. This complex consists of a T-type

calcium channel (TTCC) biomarker blocker, and a BRAF inhibitor. The results have shown a successful progression in post-therapeutic levels with mibefradil, the chemical used to block TTCCs [135].

Oleanolic acid, a chemical found in food and plants, is used in the treatment of leukemia, breast, lung, and liver cancer [136]. Oleanolic acid can inhibit the phosphorylation of PI3K in leukemia cells through the AKT/PI3K/mTOR signaling pathway and ROS pathway, or it dephosphorylates mTOR in prostate cancer cells [137–139]. Zhou *et al.* also revealed the autophagy inhibition role of oleanolic acid in HCC cells. Their results confirm that oleanolic acid has induced autophagy through the AKT/mTOR pathway by downregulating the Beclin-2/Beclin-1 ratio, followed by mitochondrial dysfunction, and eventually cell apoptosis [140].

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) enhances cancer cell apoptosis via binding with death receptors and caspase cascade activation. Cancer cells are often resistant to TRAIL due to their insufficient expression of death receptors (DR4/DR5), excessive expression of decoy receptors, or genetic and epigenetic modification of TRAIL receptors [133,141]. In an *in vitro* study of lung A549 cells, it was shown that small doses of sertraline in combination with TRAIL notably enhance apoptosis [106]. Sertraline is an antidepressant drug that has proved anti-tumor activities against cancers [142]. Sertraline mediates apoptosis through the inhibition of autophagy via the downregulation of AMPK phosphorylation and activation of DR5 in TRAIL-resistant lung A549 cells. Besides, sertraline was demonstrated to decrease the expression of BCL-2 and increase caspase-3 activity [143].

As an example of lethal autophagy enhancer, irinotecan (IRI) has an anti-tumor activity for second-line treatment of advanced GC. IRI promotes MAPK signaling proteins p-JNK and p-p38 associated with ROS and induces lethal autophagy [94]. Furthermore, after IRI treatment in MGC803 and SGC7901 cells, two GC cell lines, it has been observed that ROS generation promotes autophagosome formation by phosphorylating BCL-2 and disrupting the BCL-2/Beclin-1 complex [144].

Current clinical trials

There are currently nine clinical trials of cancer chemotherapy drugs that have an autophagy aspect. Eight of the nine chemotherapy treatments group an anti-cancer drug with hydroxychloroquine. Thus, the approach is to block autophagy by inhibiting the merger of the autophagosome with the lysosome. This will lead to the accumulation of autophagosomes in any cell that takes up hydroxychloroquine. It will be interesting to see how these combination therapies affect the normal autophagic process in healthy cells, which is so crucial to organism-wide homeostasis.

Conclusions

Treating malignant cells with chemotherapy drugs can result in the increase in ROS generation, which leads to autophagy and cancer cell survival. This is one of many defenses cancer cells trigger to maintain viability and to proliferate. Combination therapies that utilize cytotoxic anti-cancer drugs along with autophagy inhibitors may increase positive outcomes for patients. However, as always, targeting mostly cancer cells and avoiding healthy tissues is a major challenge. Off-target autophagy inhibition could trigger several side effects, including increased susceptibility to infection, increased fatty acid accumulation, and cellular senescence. Recently, immunotherapy such as checkpoint strategies have shown success in the clinic. Programmed cell death protein 1 (PD-1) is a prominent target in these strategies. Reduction of PD-1 increases autophagy. Therefore, checkpoint therapies may also benefit from co-administration of autophagy-reducing agents.

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Author Contributions

MA and PD drafted the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no competing interests.

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