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REVIEW
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Combination of an Autophagy Inducer and an Autophagy Inhibitor: A Smarter Strategy Emerging in Cancer Therapy

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Autophagy is considered a cytoprotective function in cancer therapy under certain conditions and is a drug resistance mechanism that represents a clinical obstacle to successful cancer treatment and leads to poor prognosis in cancer patients. Because certain clinical drugs and agents in development have cytoprotective autophagy effects, targeting autophagic pathways has emerged as a potential smarter strategy for cancer therapy. Multiple preclinical and clinical studies have demonstrated that autophagy inhibition augments the efficacy of anticancer agents in various cancers. Autophagy inhibitors, such as chloroquine and hydroxychloroquine, have already been clinically approved, promoting drug combination treatment by targeting autophagic pathways as a means of discovering and developing more novel and more effective cancer therapeutic approaches. We summarize current studies that focus on the antitumor efficiency of agents that induce cytoprotective autophagy combined with autophagy inhibitors. Furthermore, we discuss the challenge and development of targeting cytoprotective autophagy as a cancer therapeutic approach in clinical application. Thus, we need to facilitate the exploitation of appropriate autophagy inhibitors and coadministration delivery system to cooperate with anticancer drugs. This review aims to note optimal combination strategies by modulating autophagy for therapeutic advantage to overcome drug resistance and enhance the effect of antitumor therapies on cancer patients.

Keywords: autophagy inducer, cytoprotective autophagy, autophagy inhibitor, drug resistance, cancer therapy

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HIGHLIGHTS

1. A number of agents in development and even clinical drugs for cancer treatment have cytoprotective autophagy effects that contribute to drug resistance.
2. Combination treatment with an autophagy inducer and inhibitor is a good opportunity for discovery and development of more novel and effective therapeutic approaches for cancer treatment.

INTRODUCTION

Macroautophagy (hereafter termed autophagy) is a physiological and dynamic process dependent on the formation of double-membrane vesicles to maintain metabolic homeostasis by capturing intracellular constituents, including redundant or unnecessary proteins, injured or aged organelles, and later degrading them in lysosomes. Basal autophagy is widely accepted as a mechanism of cell survival under conditions of nutrient deprivation because the lysosome-released breakdown products are recycled into metabolic and biosynthetic pathways (White et al., 2015). Autophagy is also a cytoprotective mechanism against various environmental stresses, such as oxidant stress, endoplasmic reticulum stress, and viral or bacterial infection, by eliminating damaged and toxic cellular components and products. However, autophagy plays a dual role in both tumor-suppressing and -promoting activity in cancer initiation, development, progression, and treatment by preventing the toxic accumulation of oncogenic signaling substances from carcinogenic factors, such as genomic injury to suppress cancer initiation. By contrast, cancer cells tend to utilize autophagy-mediated recyclable biomolecules to meet the increased metabolic energy demand of survival and proliferation and take advantage of the engulfment capability to overcome micro-environmental stress, which facilitates tumorigenesis and aggressiveness (Galati et al., 2019). It has been shown that cancer cells are more autophagy-dependent than normal tissues. Thus, targeting autophagy directly is a therapeutic strategy for cancer therapy (White, 2015).

Autophagy in cancer treatment is also context-dependent and complicated. There are generally two effects of autophagy in response to anticancer drugs or ionizing radiation treatment in cancer cells (Thorburn et al., 2014). One effect is the cytotoxic function known as autophagic cell death, also named type II programmed cell death (Fulda and Kögel, 2015; Denton and Kumar, 2019). It is a nonapoptotic form of programmed cell death caused by overactivated autophagy (Booth et al., 2019; Zhu et al., 2020). Anticancer treatment induces robust autophagy of cancer cells to self-digestion until death (Simonet et al., 2020; Ganesher et al., 2020). Many natural compounds and synthetic agents exhibit their anticancer effects through triggering autophagic cell death (Law et al., 2017; Xu et al., 2019; Kiruthiga et al., 2020; Pellerito et al., 2020). Moreover, the activation of autophagy-related signaling may implicate the suppression of certain other cancer therapeutic target to help against cancer, such as tumor invasion and migration and tumor angiogenesis (Wang et al., 2019; Jiang et al., 2019; Song et al., 2019).

The other effect is the cytoprotective function, which is a drug resistance mechanism resulting in a clinical obstacle to successful cancer treatment and leads to a poor prognosis of the patients. The cancer cells initiate autophagy to escape from the damage of drugs or radiation. Efforts to inhibit treatment-induced autophagy has therefore attracted great interest to improve cancer therapy efficiency (Nagelkerke et al., 2015). By combining the antineoplastic agents, the application of autophagy inhibitors is considered beneficial to increase the susceptibility of cancer cells to therapeutic agents that induce autophagy (Dalby et al., 2010; Kleger et al., 2014). Thus, it is critical to determine if anticancer drugs and radiation treatment actually promote cytoprotective autophagy in patient tumors (G, 2014).

Multiple agents in development in preclinical and clinical trials and even many clinical drugs have been found to trigger cytoprotective autophagy, including mTOR inhibitors, kinase inhibitors, natural products, and antiangiogenic agents (Haiyang Yu et al., 2019; Mei-Chuan Chen et al., 2019). Meanwhile, various signaling pathways and molecules have been identified in regulating drug-induced autophagy that impact the outcome of anticancer therapy, such as the PI3K-Akt-mTOR pathway, one of the main regulators of autophagy. The anticancer drug-triggered DNA damage may play a crucial role in the initiation of autophagy signaling cascades to elevate DNA repair levels and promote cellular survival (Zhang et al., 2015). Research has demonstrated autophagy as a universal cytoprotective response after DNA damage induced by chemotherapeutic drugs, including cisplatin, BO-1051, and doxorubicin (DOX) in hepatocellular carcinoma cell lines (Chen et al., 2011). High mobility group box 1 (HMGB1) is associated with the hallmarks of cancer. Autophagy-associated HMGB1 has been revealed to protect various cancer cells, such as osteosarcoma, lung adenocarcinoma, neuroblastoma and ovarian cancer, from many chemotherapeutics, including DOX, cisplatin and etoposide (Wang et al., 2015). HMGB1-mediated autophagy through the mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway promotes docetaxel resistance in human lung adenocarcinoma (Pan et al., 2014). HMGB1 release is also a key regulator of autophagy and promotes tumor resistance to chemotherapy in leukemia (Liu et al., 2011). Additionally, in gastric cancer cells, after vincristine, a microtubule-targeting drug treatment, HMGB1 released into the extracellular space to protect cancer cells from apoptosis by upregulating the transcription of Mcl-1 (Zhan et al., 2012). VEGF-C/NRP-2 axis is another signaling pathway involved in autophagy activation through inhibition of mTOR complex 1 activity, results in aiding cancer cell survival under therapeutic treatment (Stanton et al., 2013). Protective autophagy regulated by PP2Ac and ERK are at least parts of the mechanism that contribute to cisplatin resistance in certain ovarian cancer cells (Yin et al., 2013; Wang and GS, 2014). The autophagic response regulated by JNK-Bcl-2 pathway plays a role in limiting the anticancer activity and toxicity of CA-4 in clinical application for various cancers. Thus, a JNK inhibitor or a Bcl-2 inhibitor (ABT-737) could promote CA-4-elicited apoptosis due to inhibition of autophagy (Li et al., 2014). Effective targeting of these pathways may intervene in therapy to render cancer cells resistant to cell inhibition, such as cell death, cell proliferation and tumor angiogenesis, as well as leading to the development of novel cancer therapies.

AUTOPHAGY INHIBITORS

Not surprisingly, increasing research has demonstrated that drug resistance in cancer therapy can be abrogated by the inhibition of

autophagy *via* genomic interference against autophagic genes (siRNA targeting Atg3, Atg5, Atg7, and Beclin 1) or pharmacological inhibitors of key components within the autophagy pathway in cancer resistance (Kumar et al., 2015) (**Table 1**). Additionally, there is also a growing interest in exploring more potent and specific pharmacological autophagy inhibitors (Golden et al., 2015; Li et al., 2016).

3-Methyladenine (3-MA), LY294002, and Bafilomycin A1 (Baf A1) are common autophagy inhibitors that function in early autophagy by PI3K inhibition and in late autophagy by blocking vacuolar-type H(+)-ATPase, respectively (Feng et al., 2018; Yang et al., 2013). Chloroquine (CQ), a 4-alkylamino-substituted quinoline family member, is a clinically available antimalarial agent which is also an autophagy inhibitor function by blocking the fusion of autophagosomes and lysosomes. Because CQ has been approved by the U.S. Food and Drug administration (FDA) for use as an antimalarial agent, it is commonly used in clinical trials as an inhibitor of autophagy (Kimura et al., 2012; Kuroda et al., 2013), as well as another more toxic safety agent for autophagy inhibition, hydroxychloroquine (HCQ) (Wolpin et al., 2014).

Except the classical autophagy inhibitors mentioned above, more agents with function of autophagy inhibition in certain cases have been proved. This kind of autophagy inhibitors may have multiple biological activities and exhibit promising inhibitory effect of therapy-induced cytoprotective autophagy that facilitate overcoming acquired resistance to antitumor therapy. The Bcl-2 family of proteins are not only regulators of apoptosis signaling, but also involved in autophagy processes (Duffy et al., 2015). The Bcl-2 inhibitor ABT-737 has been identified as an autophagy inhibitor (Yang et al., 2016). Moreover, obatoclax which exhibits pan-Bcl-2 inhibition effect has been demonstrated to cause a striking inhibition of autophagy at late-stage in colorectal cancer and bladder cancer cells (Huang and Sinicrope, 2010; Koehler et al., 2015; Jiménez-Guerrero et al., 2018). Clarithromycin is a macrolide antibiotic frequently utilized in the treatment of upper and lower respiratory tract infections and Helicobacter pylori that has demonstrated inhibitory effects on autophagy (Altman and Platanias, 2012; Giulia Petroni et al., 2020). Resveratrol is a natural polyphenolic compound derived from plants which has proapoptotic effects on various cancer cells. Interestingly, resveratrol showed synergistic anticancer efficacy by blocking temozolomide or doxorubicin induced cytoprotective autophagy flux (Lin et al., 2012; Rai et al., 2016). Quinacrine also known as mepacrine which is a synthetic antimalarial drug belonging to the quinoline-based drugs class and have been demonstrated to inhibit autophagy at late stage (Golden et al., 2015). 4-Acetylantroquinonol B is a novel compound derived from antroquinonol by the addition of an acetyl group. It had been first demonstrated by a group that it could enhance the drug susceptibility of the epithelial cancerous cells to cisplatin by inhibition of autophagic flux (Liu et al., 2017). Epigallocatechin gallate (EGCG) is a bioactive catechin derived from green tea which has been employed to overcome drug resistance by inhibiting therapy-induced autophagic flux (Meng et al., 2019).

ANTITUMOR AGENTS WITH CYTOPROTECTIVE AUTOPHAGY

Accumulating evidence has shown that targeting autophagy in combination with antitumor agents has been effective at enhancing cell death and improving the efficacy of cancer therapies in various cancer types. The antitumor agents are currently under investigation with a cytoprotective autophagy effect that is mainly classified into several types according to distinct characteristic (**Table 2**).

Natural Compounds

Multiple plant-derived natural compounds have obvious anticancer potential. However, autophagy-associated chemoresistance limits the development of novel natural drugs in clinical cancer treatment (Zhang et al., 2014; Guo et al., 2015). Polyphyllin I (PPI) is a bioactive phytochemical isolated from the rhizoma of *Paris polyphyllin*. Preclinical studies revealed PPI has anticancer efficacy with autophagy induction in various cancer models. Further combined PPI with CQ to block PPI-induced autophagy in HCC cells resulted in augmenting the cytotoxicity and antiproliferation effects of PPI *via* the caspase-dependent

TABLE 1 | Autophagy inhibitors in cancer cells.

Autophagy inhibitor	Target point	Inhibition stage	References
3-MA	PI3K inhibition	Early	(Horwacik et al., 2015; Zhang et al., 2015)
LY294002	PI3K/mTOR inhibition	Early	(Feng et al., 2018; Shen et al., 2017)
Baf A1	Vacuolar-type H(+)-ATPase inhibition	Late	(Miyazawa, 2011)
CQ	Lysosomal inhibition	Late	(Kimura et al., 2012; Fukuda et al., 2015; Liu et al., 2016)
HCQ	Lysosomal inhibition	Late	(Vogl et al., 2014; Rangwala et al., 2014)
ABT-737	Bcl-2 inhibition	Early	(Huang and Sinicrope, 2010; Yang et al., 2016)
Obatoclax	Lysosomal inhibition	Late	(Koehler et al., 2015; Jiménez-Guerrero et al., 2018)
Clarithromycin	Block autophagy flux	Late	(Altman and Platanias, 2012; Sugita et al., 2015)
Resveratrol	Autophagy regulator -S6K1	Early	(Lin et al., 2012; Alayev et al., 2015; Rai et al., 2016)
Quinacrine	Lysosomal inhibition	Late	(Lobo et al., 2013; Golden et al., 2015)
4-Acetylantroquinonol B	Block autophagy flux	Late	(Liu et al., 2017)
EGCG	Block autophagy flux	Late	(Meng et al., 2019)

3-MA, 3-methyladenine; Baf A1, bafilomycin A1; PI3K, phosphatidylinositol 3 kinase; mTOR, mammalian target of rapamycin; CQ, chloroquine; HCQ, hydroxychloroquine; ATPase, adenosine triphosphatase; EGCG, Epigallocatechin gallate.

TABLE 2 | Subset of the preclinical research targeting drug-induced autophagy in various cancers.

Drug Classification	Drug name	Targeting cancer cells	Autophagy inhibitor	References
Natural compounds	Polyphyllin I	Hepatoma	CQ	(Shi et al., 2015)
	Ursolic acid	Prostate cancer	3-MA	(Shin et al., 2012; Junco et al., 2015)
	Paclitaxel	Cervical cancer	2-deoxyD-glucose	(Peng et al., 2014)
		Renal cancer	3-MA or BafA1	(Zhang et al., 2013)
		Bladder cancer	Obatoclax	(Jiménez-Guerrero et al., 2018)
	Tetrandrine	Various cancers	CQ	(Mei et al., 2015)
	Pterostilbene	Lung cancer	3-MA or BafA1	(Hsieh et al., 2013)
		Breast cancer	3-MA or BafA1	(Wei-Chih Chen et al., 2014)
	Topotecan	Lung cancer	CQ	(Wang Y et al., 2011)
	Cucurbitacin	Glioblastoma	CQ	(Yuan et al., 2014)
	Sulforaphane	Neuroblastoma	3-MA	(Horwacik et al., 2015)
	Honokiol	Lung cancer	CQ	(Lv et al., 2015)
	Combretastatin A-4	Various cancers	ABT-737, 3-MA or BafA1	(Li et al., 2014)
Tyrosine kinase inhibitor	Imatinib	Leukemia	CQ or Clarithromycin	(Altman and Platanias, 2012; Zeng et al., 2015)
		Glioblastoma	BafA1	(Shingu et al., 2009)
	Sorafenib	Hepatoma	3-MA	(Yuan et al., 2014)
		Glioblastoma	CQ	(Liu et al., 2016)
	Sunitinib	Various cancers	CQ	(Abdel-Aziz et al., 2014)
	Linifanib	Hepatoma	CQ, HCQ or 3-MA	(Pan et al., 2014)
	Gefitinib	Breast cancer	HCQ, BafA1 or 3-MA	(Dragowska et al., 2013; Liu et al., 2017)
		Lung cancer	Clarithromycin, EGCG	(Sugita et al., 2015; Meng et al., 2019)
	Erlotinib	Lung cancer	CQ	(Zou et al., 2013)
	Cediranib	Glioblastoma	Quinacrine	(Lobo et al., 2013)
Conventional cytotoxic drugs	Cisplatin	Lung cancer	3-MA or CQ	(Wu et al., 2015; Liu et al., 2015)
		Ovarian cancer	3-MA or CQ	(Zhang et al., 2012; Wang and GS, 2014; Bao et al., 2015)
		Glioblastoma	3-MA	
		Gastric cancer	CQ	(Zhang et al., 2015)
		Bladder cancer	3-MA or CQ	(Zhang et al., 2015)
		Endometrial cancer	CQ	(Ojha et al., 2016)
		Epithelial cancer	4-Acetylantroquinonol B	(Fukuda et al., 2015)
	Oxaliplatin	Colorectal cancer	3-MA	(Liu et al., 2017)
	Temozolomide	Glioblastoma	Resveratrol or CQ	(Liu et al., 2015)
	5-Fluorouracil	Cholangiocarcinoma	Quinacrine	(Lin et al., 2012; Yan et al., 2016)
		Colon cancer	Capsaicin	(Buccarelli et al., 2018)
	Cytarabine	Acute myeloid	3-MA or CQ	(Hong et al., 2015)
	Doxorubicin	Hepatoma,	Baf A1 or CQ	(Sasaki et al., 2010; Li et al., 2010)
		osteosarcoma	EGCG	(Bosnjak et al., 2014)
		leukemia	3-MA	(Chen et al., 2014; Wang and Ding Chen, 2018)
		Osteosarcoma	Resveratrol	(Zhao et al., 2014)
		Breast cancer	HCQ or 3-MA	(Rai et al., 2016)
	Pirarubicin	Bladder cancer	HCQ or 3-MA	(Pan et al., 2015) (Li et al., 2015)
Proteasome inhibitor	Carfilzomib	Myeloma	CQ, HCQ	(Jarauta et al., 2016; Baranowska et al., 2016)
	Bortezomib	Myeloma	Macrolide antibiotics BafA1,	(Moriya et al., 2013)
		Myeloma	HCQ	(Di Lernia et al., 2020; Miyazawa, 2011)
		Glioblastoma	3-MA	(Zhang et al., 2014)
	Ixazomib	Colorectal cancer	ABT-737	(Yang et al., 2016)

CQ, chloroquine; HCQ, hydroxychloroquine; 3-MA, 3-methyladenine; Baf A1, bafilomycin A1; EGCG, Epigallocatechin gallate.

apoptosis pathway (Shi et al., 2015). By the Beclin-1 and Akt/mTOR pathway, ursolic acid (UA), a pentacyclic triterpenoid derived from natural plants, showed an autophagic response as a survival mechanism in PTEN-deficient PC3 prostate cancer cells. Blockade of autophagy by 3-MA enhanced UA-induced apoptosis (Shin et al., 2012). Additionally, UA and resveratrol have been shown to synergize with CQ to enhance melanoma cell death (Junco et al., 2015). By interfering with the normal breakdown of microtubules during cell division, paclitaxel is a medication used to treat several cancer types, including breast cancer, lung cancer and ovarian cancer. Acquired resistance mediated by autophagy of paclitaxel functions as a major obstacle to successful anticancer effects. 2-Deoxy-D-glucose or 3-MA could enhance the preferential toxicity on paclitaxel resistant HeLa cervical cancer cells *via* decreasing autophagy (Peng et al., 2014). Moreover, the blockade of autophagy with 3-MA and Baf A1 strengthen sensitivity of folliculin-deficient renal cancer cells to paclitaxel (Zhang et al., 2013). Obatoclax could also promote paclitaxel induced apoptosis in synergistic manner by blockade of the autophagic flux in bladder cancer (Jiménez-Guerrero et al., 2018). Tetrandrine is a natural product study in our laboratory, and we found that tetrandrine combined with CQ has synergistic antitumor activity (Mei et al., 2015). It was also reported that pterostilbene in combination with 3-MA or

BafA1 may enhance the efficiency of chemotherapeutic approaches in both chemo-sensitive and chemo-resistant lung cancer cells and in triple-negative breast cancer cells (Hsieh et al., 2013; Wei-Chih Chen et al., 2014). The anticancer effect of another natural substance product, chaetocin, is enhanced by Baf A1(Jung et al., 2016). Moreover, CQ potentiated the cytotoxicity of topotecan in lung cancer cells by interfering with autophagy (Wang Y et al., 2011), and the antitumor efficiency of cucurbitacin I is promoted with synergetic treatment of CQ in glioblastoma (Yuan et al., 2014). Additionally, cell death of BE (2)-C human neuroblastoma cells following sulforaphane treatment could be promoted by 3-MA *via* inhibition of autophagy (Horwacik et al., 2015). Honokiol is isolated from the bark, seed cones, and leaves of trees belonging to the genus Magnolia and is a kind of lignan. Honokiol-induced cell death increased with CQ by inhibiting autophagy that finally exhibits augmented antitumor effects in human nonsmall cell lung cancer cells (Lv et al., 2015). Combretastatin A-4 (CA-4) is a drug isolated from combretum caffrum which has been applied in clinical trials for solid tumors therapy in past over ten years. However, the CA-4-elicited autophagic response in various cancer cells restricts its clinical application. Autophagy inhibition by autophagy inhibitors (3-MA and Baf A1), the JNK inhibitor or the Bcl-2 inhibitor ABT-737 could promote CA-4-induced apoptosis (Li et al., 2014).

Synthetic Compounds

Conventional Cytotoxic Drugs

Cytotoxic drugs are used in the treatment of tumors to trigger the death of tumor cells by preventing DNA replication and cell division. Cisplatin-based chemotherapy frequently results in acquired resistance, which is a major challenge in the clinical control of various cancers. The underlying mechanism is demonstrated in relation to the autophagic response. Combined treatment of cisplatin with 3-methyladenosine or CQ promotes the chemotherapeutic sensitivity of various cancers, including lung cancer, ovarian cancer, glioma cancer, gastric cancer, bladder cancer, and endometrial cancer cells (Zhang et al., 2012; Wang and GS, 2014; Bao et al., 2015; Wu et al., 2015; Zhang et al., 2015; Zhang et al., 2015; Fukuda et al., 2015; Ojha et al., 2016). Coadministration of CQ and cisplatin to abolish the suppression of mTORC1 activity-mediated autophagy significantly re-sensitized cisplatin-resistant EC109/CDDP cells (Yu et al., 2014). 4-Acetylantroquinonol B can also act as an autophagy inhibitor by blocking autophagic flux and improving the sensitivity of highly aggressive epithelial cancer to cisplatin *via* the PI3K/Akt/mTOR/p70S6K signaling pathway (Liu et al., 2017). Another platinum-based antineoplastic agent, oxaliplatin, shows the drug resistance *via* the MEK/ERK signaling pathway and HMGB1-mediated autophagy in colorectal cancer cells, and the sensitivity can be restored by 3-MA (Liu et al., 2015). Temozolomide (TMZ) is an alkylating agent used for the clinical treatment of glioblastoma multiforme and melanoma. Studies have revealed that cytoprotective autophagy induced by TMZ contributes to therapy resistance in malignant glioma which can be suppressed by resveratrol, chrysin, or CQ and its analog quinacrine, resulting in a decrease in autophagy and an increase in apoptosis (Buccarelli et al., 2018; Lin et al., 2012; Yan et al., 2016). 5-Fluorouracil (5-FU) is a pyrimidine analog for cancer treatment that works through irreversible inhibition of thymidylate synthase. Capsaicin is a major pungent ingredient found in hot red chili peppers of the genus capsicum, emerges as a chemotherapeutic augmenter for 5-FU's anticancer effects in cholangiocarcinoma (Hong et al., 2015). In addition, CQ and 3-MA potentiate the cytotoxic effect of 5-fluorouracil on colon cancer cells (Sasaki et al., 2010; Li et al., 2010). Cytarabine is a chemotherapy agent used mainly in killing acute myeloid leukemia (AML) and non-Hodgkin lymphoma cancer cells by interfering with DNA synthesis. Baf A1 and CQ can markedly increase apoptotic death in cytarabine-treated human leukemic cells (Bosnjak et al., 2014).

Anthracycline drugs derived from Streptomyces bacterium Streptomyces peucetius var. caesius, which are used in cancer chemotherapy to treat several cancers, including breast, ovarian, uterine, bladder, lung cancers, and leukemias, and lymphomas. Doxorubicin (DOX) is an anthracycline antibiotic derived by chemical semisynthesis from bacterial species and works by intercalating DNA for the treatment of various cancers. EGCG, one of the highest catechins from green tea, promisingly showed the capability to augment the antitumor efficacy of DOX in HCC and osteosarcoma treatment involving autophagy inhibition (Chen et al., 2014; Wang and Ding Chen, 2018). As a classic chemotherapeutic agent for osteosarcoma, autophagy-mediated resistance of DOX can be reversed by 3-MA (Zhao et al., 2014). Resveratrol can enhance the chemotherapeutic potential of DOX by inducing apoptosis mediated through down regulation of autophagy in breast cancer cell lines (Rai et al., 2016). Additionally, HCQ or 3-MA can partially reverse the drug resistance of myeloma RPMI8226/DOX cells by inhibition of autophagy (Pan et al., 2015). Pirarubicin is widely used in clinical chemotherapy for bladder cancer. However, emerging evidence has shown that the efficacy of pirarubicin is limited by the cytoprotective role of autophagy in bladder cancer cells, and inhibition of autophagy by 3-MA or HCQ increased cell apoptosis, suggesting an efficiency over traditional pirarubicin chemotherapy in bladder cancer patients (Li et al., 2015).

Tyrosine Kinase Inhibitors

Tyrosine kinases play a pivotal role in oncogenesis, but emerging studies have report compromised cytotoxicity of tyrosine kinase inhibitors used as monotherapy in cancer (Carew et al., 2008). Imatinib (INN) is a frontline tyrosine-kinase inhibitor notably used in the targeted therapy of Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) by targeting BCR-Abl-expressing leukemic cells. Autophagy induction has been identified as the imatinib resistance mechanism during therapeutic process. CQ could markedly promote CML cell apoptosis induced by Hedgehog pathway suppression of imatinib-sensitive or -resistant BCR-ABL+ cells (Zeng et al., 2015). Additionally, clarithromycin, which blocks autophagy, could also restore the sensitivity of CML cells to imatinib (Altman and Platanias, 2012). In human malignant

glioma cells, the imatinib-elicited cytotoxicity has been enhanced by induction of apoptosis with Baf A1 which trigger inhibition of autophagy at a late stage (Shingu et al., 2009). Sorafenib, which is a multikinase inhibitor that inhibits serine/threonine kinases and receptor tyrosine kinases (RTKs), was shown to have survival benefits in advanced HCC. Inhibition of cytoprotective autophagy by 3-MA treatment enhances sorafenib-mediated cell death *via* necrosis and significantly augments the combination antitumor effect with sorafenib and the HDAC inhibitor vorinostat in hepatocellular carcinoma cells (Honma and Harada, 2013; Yuan et al., 2014). Additionally, sorafenib has shown antitumor activity in glioblastoma multiforme (U373 and LN229 cells). Further study demonstrated that combination treatment with sorafenib and CQ exhibited inhibition of cell proliferation and migration and induction of cell apoptosis by blockade of autophagy *in vitro* and *in vivo* (Liu et al., 2016). Sunitinib is a multitargeted receptor tyrosine kinase inhibitor that was approved for the treatment of renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumor. CQ has been shown to synergize with sunitinib by switching off autophagy then enhanced the cytotoxicity of sunitinib *via* inducing apoptosis (Abdel-Aziz et al., 2014). Linifanib (ABT-869) is a structurally novel and potent multikinase inhibitor of RTK, vascular endothelial growth factor (VEGF), and platelet-derived growth factor. Autophagy was found to impair the sensitivity of HCC cells to linifanib-targeted therapy by the suppression of Akt/mTOR and Mek/Erk signaling pathways and CQ, HCQ, or 3-MA greatly augments the anti-HCC effect of linifanib (Pan et al., 2014). Gefitinib is a small-molecule inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase used for certain breast, lung, and other cancers with mutated and overactive EGFR. HCQ or Baf A1 inhibit gefitinib-induced autophagy at late-stage significantly increased cell death in gefitinib-sensitive and -insensitive breast cancer cells (Dragowska et al., 2013). 3-MA or Baf A1 also improved the sensitivity of gefitinib to MDA-MB-231 and MDA-MB-468 triple-negative breast cancer cells (TNBCs) (Liu et al., 2017). In addition, the autophagy flux inhibitor clarithromycin (CAM), a macrolide antibiotic can enhances the cytotoxic effect of gefitinib in nonsmall cell lung cancer cells (NSCLC), as well as EGCG can overcomes NSCLC resistance to gefitinib by inhibiting autophagy and augmenting cell death through targeting ERK pathway (Sugita et al., 2015; Meng et al., 2019). The antagonistic activity on cell proliferation has been found when coadministration of gefitinib and cisplatin to EGFR-TKI-sensitive human lung cancer PC9 cells. After combination with CQ, resulted in a synergistic effect *via* inhibiting autophagy, further suggesting a potential strategy to reverse the antagonistic effects between EGFR-TKIs and chemotherapeutic drugs (Liu et al., 2015). Another EGFR-TK inhibitor erlotinib has been demonstrated to trigger autophagy in wild-type EGFR NSCLC. Drug resistance caused by this autophagy can be overcame with CQ which represent a beneficial strategy to enlarge the application scope of erlotinib efficacy in cancer therapy (Zou et al., 2013). Cediranib is a potent inhibitor of VEGF receptor tyrosine kinases. Combined with the late-stage autophagy inhibitor quinacrine, the antiangiogenic efficacy of cediranib in intracranial glioma is synergistically enhanced (Lobo et al., 2013).

Proteasome Inhibitors

Proteasome inhibitors has been widely used as clinical anticancer drugs for the bone marrow cancer multiple myeloma (MM) and exhibited remarkable efficacy in solid tumor malignancies treatment, including the first-in-class proteasome inhibitor bortezomib and second-in-class proteasome inhibitors carfilzomib and oprozomib (Saavedra-García et al., 2020). However, increasing studies indicate that cancer cells show resistance to the proteasome inhibitors and autophagy contributes to the mechanisms associated with carfilzomib and bortezomib resistance (Zang et al., 2012; Zheng et al., 2017). CQ and HCQ can enhance carfilzomib induced cell apoptosis by inhibition of autophagy toward MM (Jarauta et al., 2016; Baranowska et al., 2016). The cytotoxicity of bortezomib on MM also can be augmented by Baf1, HCQ, or macrolide antibiotics *via* inhibiting prosurvival autophagy in cotreatment manner (Di Lernia et al., 2020; Miyazawa, 2011; Moriya et al., 2013). Moreover, 3-MA promoted sensitivity of glioblastoma cells to bortezomib by inhibition of bortezomib induced cytoprotective autophagy (Zhang et al., 2014). MLN9708, the active form is ixazomib which is an orally administered proteasome inhibitor. The cytotoxic effect of ixazomib on colorectal cancer cells has been proved enhanced with ABT-737 by autophagy inhibition *via* inhibiting Mcl-1 expression (Yang et al., 2016).

Other Specific Signaling Inhibitors

The PI3K/Akt/mTOR pathway plays a pivotal role in oncogenesis; consequently, it is an attractive pharmacologic target. Because mTOR inhibition is involved in the induction of autophagy that limits the therapeutic effects of PI3K/Akt/mTOR signaling inhibitors, autophagy inhibition can overcome antitumor therapeutic resistance to PI3K/Akt/mTOR signaling inhibitors. Rapamycin is an allosteric mTORC1 inhibitor that has been identified as a broad-spectrum autophagy inducer. Combination therapy of rapamycin with resveratrol by autophagy blockade showed enhanced cell apoptosis effects in breast cancer cells (Alayev et al., 2015). Everolimus, a mTOR inhibitor, has been approved for second-line therapy. Combination everolimus/CQ could strongly and synergistically induce renal cancer cell death (Grimaldi et al., 2015). In addition, WYE-354, a novel mTORC1/2 dual inhibitor, of which the potential anticolon cancer cell activity can be augmented by Baf A1 and 3-MA treatment (Wang et al., 2016). Baf A1, 3-MA and CQ can also enhance a novel mTOR kinase inhibitor, KU-0063794, which induces cytotoxicity against anti-HepG2 hepatocellular carcinoma cells (Yongxi et al., 2015). The hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase-

inhibiting drug simvastatin induces the activation of AMP-activated protein kinase (AMPK) and mTOR in glioma cell death. Inhibition of autophagy with Baf A1 and 3-MA, as well as AMPK inhibition with compound C, markedly increased simvastatin-induced apoptotic death (Misirkic et al., 2012). By inhibiting HMG-CoA reductase, statins can also mediate cytoprotective autophagy in human leukemic cells, and Baf A1 enhanced the apoptotic death induction (Vilimanovich et al., 2015). In aggressive prostate cancers, the efficacy of the AKT inhibitor AZD5363 is limited, and blocking autophagy using 3-MA, CQ, and Baf A1 enhanced cell death (Lamoureux et al., 2013). Pharmacological Notch1 signaling blockade by the γ-secretase inhibitor MRK003 is used to treat glioblastoma neurospheres, and combination treatment with CQ can abrogate chemoresistance caused by induction of protective autophagy (Natsumeda et al., 2016). The addition of CQ could also enhance the cytotoxic effects of flavopiridol, a cyclin-dependent kinase (CDK) inhibitor, in chronic lymphocytic leukemia (CLL) (Mahoney et al., 2012). Store-operated Ca^{2+} entry (SOCE) inhibitor SKF-96365 exhibits potent antineoplastic activity, but its antitumor capacity is often limited by cytoprotective autophagy that delays apoptosis. HCQ could significantly augment the anticancer effect of SFK-96365 in colorectal cancer (Jing et al., 2016). Dichloroacetate (DCA), an inhibitor of pyruvate dehydrogenase kinase (PDK), was demonstrated to be a promising nontoxic antineoplastic agent. DCA-induced protective autophagy can be inhibited by 3-MA and then restore DCA-induced apoptosis in LoVo colonic carcinoma cells (Gong et al., 2013) (**Table 3**).

CLINICAL TRIALS

Based on preclinical research, including ***in vitro*** and ***in vivo*** models, the researchers conducted several clinical trials, combining drugs that triggered protective autophagy with an autophagy inhibitor (Poklepovic and Gewirtz, 2014) (**Table 4**).

In patients with advanced solid tumors and melanoma, a phase I trial of HCQ with dose-intense temozolomide was conducted (Rangwala et al., 2014). Another phase I/II trial concerning the antitumor activity of HCQ with temozolomide and radiation for glioblastoma patients was performed, accompanied by pharmacodynamic and pharmacokinetic analyses for HCQ dose-dependent autophagy inhibition (Amaravadi et al., 2011; Rosenfeld et al., 2014). A phase I trial in patients with advanced solid tumors conducted based on preclinical models showed that a proton pump inhibitor, pantoprazole exerted enhanced antitumor activity of DOX by improving drug distribution and inhibiting autophagy (Brana et al., 2014). In addition, a phase I clinical trial was conducted along with pharmacodynamics evaluation of combination treatment with HCQ and DOX for spontaneously occurring lymphoma in pet dogs (Barnard et al., 2014). Using combined autophagy inhibitor HCQ and proteasome inhibitor bortezomib, a phase I trial in patients with relapsed/refractory myeloma was conducted (Vogl et al., 2014). Combination treatment with mTOR and autophagy inhibitor, a phase I trial of temsirolimus and HCQ in patients with advanced solid tumors and melanoma was conducted (Rangwala et al., 2014). Moreover, coadministration with HCQ and HDAC inhibitor vorinostat, a phase I trial in patients with advanced solid tumors was conducted

TABLE 3 | Autophagy inhibition of drugs targeting specific signaling in cancer treatment.

Drug name	Targeting signaling	Autophagy Inhibitor	Targeting Cancer cells	References
Rapamycin	mTORC1	Resveratrol	Breast cancer	(Alayev et al., 2015)
Everolimus	PI3K/AKT/mTOR	CQ	Renal cancer	(Grimaldi et al., 2015)
Simvastatin	AMPK	BafA1, 3-MA or AMPK Inhibitor	Glioblastoma	(Misirkic et al., 2012)
SKF-96365	Calcium/CaMKIIγ/AKT	HCQ	Colorectal cancer	(Jing et al., 2016)
AZD5363	AKT	BafA1, 3-MA or CQ	Prostate cancer	(Lamoureux et al., 2013)
AZ7328	AKT	CQ	Bladder cancer	(Dickstein et al., 2012)
MRK003	Notch1/γ-secretase	CQ	Glioblastoma	(Natsumeda et al., 2016)
Flavopiridol	CDK	CQ	Leukemia	(Mahoney et al., 2012)
SKF-96365	SOCE	HCQ	Colorectal cancer	(Jing et al., 2016)
Dichloroacetate	PDK	3-MA	Colorectal cancer	(Gong et al., 2013)

CQ, chloroquine; HCQ, hydroxychloroquine; 3-MA, 3-methyladenine; Baf A1, bafilomycin A1; PI3K, phosphatidylinositol 3 kinase; mTORC1, mammalian target of complex 1; Akt, protein kinase B; mTOR, mammalian target of rapamycin; AMPK, adenosine monophosphate activated protein kinase; CDK, cycling-dependent kinase; SOCE, store-operated Ca^{2+} entry; PDK, pyruvate dehydrogenase kinase.

TABLE 4 | Combination treatment by targeting drug-induced autophagy in clinical trials for cancer therapy.

Phase	Drug name	Targeting cancer cells	Autophagy inhibitor	References
I	Temozolomide	Melanoma and advanced solid tumors	HCQ	(Rangwala et al., 2014)
I/II	Temozolomide	Glioblastoma	HCQ	(Rosenfeld et al., 2014)
I	Doxorubicin	Advanced solid tumors	Pantoprazole	(Brana et al., 2014)
I	Doxorubicin	Lymphoma	HCQ	(Barnard et al., 2014)
I	Bortezomib	Myeloma	HCQ	(Vogl et al., 2014)
I	Temsirolimus	Melanoma	HCQ	(Rangwala et al., 2014)
I	Vorinostat	Advanced solid tumors	HCQ	(Mahalingam et al., 2014)

HCQ, hydroxychloroquine.

and researchers further analyzed the data from the effect of safety, tolerability, pharmacokinetics, and pharmacodynamics (Mahalingam et al., 2014).

THE CHALLENGE AND DEVELOPMENT OF TARGETING CYTOPROTECTIVE AUTOPHAGY AS A CANCER THERAPEUTIC APPROACH IN CLINICAL APPLICATION

Since autophagy was considered as a double-edged sword that might cooperate, aggravate, or antagonize apoptosis, current understanding of the role of autophagy in the response to some certain cancer therapy remains controversial, such as sorafenib- induced autophagy in HCC. The effect of sorafenib-triggered autophagy serves as a prosurvival response or promotes the lethality of sorafenib against HCC cells is indistinct (Liu et al., 2017). Therefore, targeting autophagy induced by antitumor agents by combination of these agents with autophagy inhibitors in clinical cancer therapy application to improve outcomes for patients remains a challenge. More preclinical research should be conducted to confirm that autophagy provides an adaptive mechanism of resistance to antitumor drugs in cancer cells and inhibition of autophagy could further enhance the cytotoxic effects of these drugs in a synergistic manner rather than attenuating the autophagy-dependent antitumor effect.

It is clear that using autophagy inhibitor to target antitumor agents-induced protective autophagy to augment cytotoxic effects *via* switching-off the autophagic mechanism, coadministration is the key procedure. Antitumor agents with cytoprotective autophagy and autophagy inhibitors are different in physicochemical properties, such as molecular weight and size. If given separately, may result in differences in bio-distribution and cancer cell accumulation between the two drugs, which means failure combination treatment. Thus, a drug delivery system needed to facilitate the combination strategy, especially for some agents cannot enter cells efficiently by itself. By taking advantage of nanoparticles, researchers successfully coloaded miR-375, an inhibitor of autophagy and sorafenib into calcium carbonate nanoparticles with lipid coating (miR-375/Sf-LCC NPs) followed by significant autophagy inhibition and enhanced antitumor effect of sorafenib in HCC (Pengxuan Zhao et al., 2018). Another group prepared R8-dGR peptide modified paclitaxel (PTX) and HCQ incorporating liposomes (PTX/HCQ - R8- dGR- Lip) for increasing drug delivery and confirmed that combined chemotherapeutic PTX with HCQ exhibited augmented efficiency on inhibiting malignant melanoma (Sheng Yin et al., 2018). In addition, researchers developed "a strategy based on Cu(I)-catalyzed click chemistry-triggered aggregation of azide/alkyne-modified micelles for the codelivery of the DOX and the autophagy inhibitor wortmannin." This Dox/wortmannin coloaded size-adjustable micelles exerted a significant antitumor effect in a synergistic manner in melanoma and breast cancer by inhibition of autophagy (Jingdong Rao et al., 2019).

Besides, autophagy also found as a survival pathway to induce therapy resistance in sonodynamic therapy (SDT) for several cancers. Therefore, targeting autophagy regulation is also a strategy to enhance SDT efficiency. For breast cancer, a biomimetic nanoplatform exhibited capability in restoring cells' sensitivity to SDT *via* autophagy inhibition. This design "based on hollow mesoporous titanium dioxide nanoparticles by HCQ loading and cancer cell membrane coating" (Qianhua Feng et al., 2019). For the chemotherapy of glioma, blood brain barrier and autophagy-induced chemo-resistance are two limitation factors. One group designed a smart "all-in-one" nanosensitizer platform to improve therapeutic efficiency by coloading the sonoactive chlorin e6 (Ce6) and HCQ into angiopep-2 peptide-modified liposomes (Fei Qu et al., 2019).

Clinically used antimalarial drugs CQ and its derivative HCQ, are well-known autophagy inhibitors function by preventing the acidification of the lysosomal compartment. Although CQ and HCQ showed an equipotent effect at autophagy inhibition *in vitro* studies, the toxicity of them showed different *in vivo*. High peak concentrations of CQ may result in infant deaths in case reports that associated with single-tablet ingestions indicated the significant toxicity of CQ. However, people survived suicide attempts taking HCQ, demonstrating HCQ is safely dose-escalated in cancer patients. Moreover, clinical trials showed that autophagy is unable to be completely inhibited by CQ *in vivo*. These warrant us that searching more potent autophagy inhibitors is critical for promoting an opportunity to apply the combination therapeutic strategy in clinical studies (Lalita Guntuku et al., 2019), especially agents that specifically inhibit autophagy-related (ATG) proteins (Pei-Feng Liu1 et al., 2018).

Targeting the autophagic process by coupling autophagy inhibitors with current cytotoxic chemotherapy or other available anticancer therapies are really considered promising therapeutic strategy for cancer. For further clinical application, more efforts should be made in identifying the role of autophagy induced by cancer therapy, developing beneficial coadministration system for drug delivery and discovering novel and efficient autophagy inhibitors (**Figure 1**).

DISCUSSION

Autophagy may act as one of the contributing factors in cellular mechanism of survival during cancer development and therapeutically triggered stress with basic biological importance. Thus, basic and clinical research will be imperatively needed to identify if autophagy is a cancer treatment-related resistance mechanism (Tan et al., 2015; Sannigrahi et al., 2015; Hu et al., 2016).

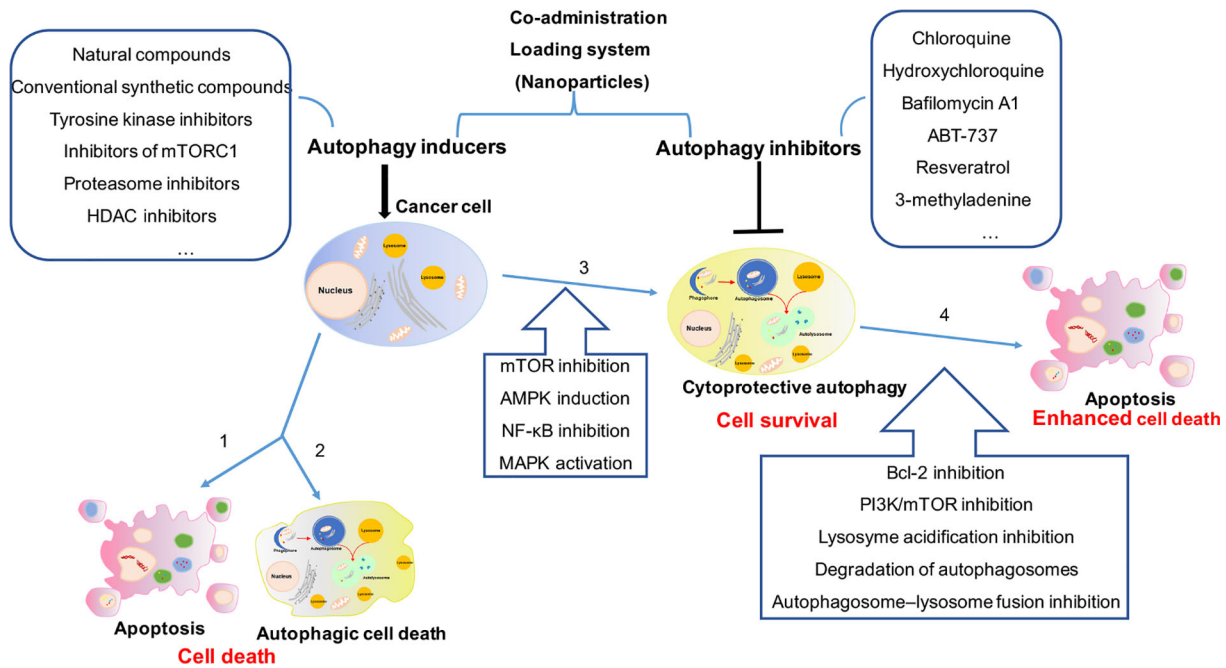

FIGURE 1 | The comprehensive mechanism of autophagy induction and inhibition in cancer therapy. (1) Cancer cells treated with autophagy inducers alone will trigger cell death as 1 apoptosis and/or 2 autophagic cell death, or will induce 3 cytoprotective autophagy result in drug resistance. (2) Combination treatment with autophagy inducers and inhibitors in cancer cells will 4 enhance cytotoxicity by cytoprotective autophagy inhibition. (3) More efforts should be made in identifying the role of autophagy induced by cancer therapy (2 or 3), developing beneficial coadministration system for drug delivery and discovering novel and efficient autophagy inhibitors.

Studies in preclinical models established autophagy as a therapeutic target, and inhibition of autophagy enhanced chemo-sensitivity and promoted tumor cell death.

Meanwhile, multiple early-phase clinical trials evaluated the effect of autophagy inhibition by using HCQ combined with therapeutic agents. These studies indicated that strategies targeting autophagy in cancer are potentially new opportunities for drug development, thus more potent autophagy inhibitors are needed to identify (Yang et al., 2011). CD133 on cancer stem cells is considered a potential therapeutic target. There has been a report that CD133 mAb can sensitize HCC cells to DOX and cisplatin attributed to inhibiting autophagy and facilitating necrotic cell death. Therefore, targeting CD133 with the autophagy inhibitor CD133 mAb is a potential therapeutic approach for hepatocellular carcinomas (Chen et al., 2013). It is easier for solid tumor cells to trigger cell autophagy against nutrient deprivation and oxygen stress conditions caused by antiangiogenic therapy. Thus, we could exploit combination treatment with autophagy inhibitors and antiangiogenic agents, such as bevacizumab (Guo et al., 2013).

For most antitumor agents, combination treatment with either autophagy initiation inhibitors or autophagy maturation inhibitors causes synergistic effects (Adiseshaiah et al., 2013). However, in some circumstances, combination treatment with different autophagy inhibitors at different stages of autophagy may lead to opposite effects. Using 3-MA or small interfering RNA against Atg5 (siRNA-ATG5) to suppress imatinib-induced autophagy at an early stage could decrease the cytotoxicity of imatinib. By contrast, inhibiting autophagy at a late stage by Baf A1 augmented imatinib-induced apoptosis mediated through mitochondrial disruption, indicating that the cytotoxic efficiency of imatinib for malignant glioma may only be enhanced by the appropriate autophagy inhibitor function at a late stage of autophagy (Shingu et al., 2009). Similarly, inhibition of the early stages of autophagy by 3-MA attenuated the cytotoxic effect of arsenic trioxide (ATO) in glioblastoma multiforme cells. By contrast, interfering autophagy flux at a late stage by CQ enhanced the ATO induced cell death (Li et al., 2015). Both pharmacological and molecular targeting of elements of the autophagic process need to occur under certain circumstances to apply to therapeutic approaches.

Autophagy also acts as an obstacle in radiotherapy (Ye et al., 2016). Based on this notion, a strategy was designed to block autophagy in tumor cells to augment radio-sensitization by the autophagy inhibitor 3-MA (Chen et al., 2011). Except for cancer cells, autophagy also plays a central role in the function of immune cells. Anticancer agents with metabolic modulating by autophagy induction can result in antitumor immune disorders (Townsend et al., 2012). It has been reported that inhibiting autophagy during interleukin 2 (IL-2) immunotherapy can

promote long-term tumor regression by tumor inhibition and enhance immune cell proliferation and infiltration (Liang et al., 2012). Thus, combination radiation or chemotherapy with an autophagy inhibitor can both selectively suppress tumor cells and restore the capability of the immune system by promoting the integrity of beneficial antitumor immune cells (Gewirtz, 2014).

This review was aimed to identify a potent strategy to enhance the sensitivity of cancer cells to therapeutic agents. All sections and tables are not meant to be completely presented because many compounds and agents have effect of autophagy regulation by autophagy induction or inhibition in cancer therapy, and new ones are being discovered routinely.

AUTHOR CONTRIBUTIONS

TL designed and wrote the manuscript. JZ revised the article KL and LD collected the material. HW supervised and directed all work.

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