Chapter 20

Autophagy in Multidrug-Resistant Cancers

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Additional information is available at the end of the chapter

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Abstract

Multidrug resistance (MDR) in cancers is the major challenge in cancer therapy, thus the development of sensitizing agents or small molecules with new mechanisms of action to kill the resistant cancers is highly desired. Autophagy is a cellular process responsible for the turnover of misfolded proteins or damaged organelles and recycling of nutrients to maintain cellular homeostasis. Recently, autophagy has been shown to regulate MDR in cancers. In this chapter, both intrinsic and acquired drug resistance affecting the efficiency of chemotherapy, and the MDR mechanisms including nonclassical MDR phenotype and classical transport-based MDR phenotype were discussed. In addition, the development of apoptosis-resistant cancer by the deregulation of apoptotic gene machinery, such as BCL-2, BAX, BAK, and TRAILR, was also covered. We then further discussed the controversial role of autophagy by illustrating how induction of autophagy could work as a tumor suppressor or promote tumor survival. The modulation of MDR in cancer by either induction or inhibition of autophagy was also discussed. We have further summarized the current compounds or drugs for modulating MDR cancers and how autophagy modulators could circumvent the MDR phenotypes in cancers. Finally, the new mechanisms participating in MDR phenotypes were proposed for future MDR drugs discovery.

Keywords: autophagy, multidrug-resistant cancers, apoptosis-resistant cancers, apoptosis, P-glycoprotein

1. Introduction

The efficiency of chemotherapy can be affected by both intrinsic and acquired drug resistance. Intrinsic resistance is caused by the existing resistance factors presented in the cancer cells before treatments, while acquired drug resistance is developed by mutations or adaptive responses arising during chemotherapy. Due to the high-molecular heterogeneity of cancer cells, drug

resistance can therefore be acquired through a minor population of resistant cancer cells presented in the initially drug-sensitive tumor. Using the genomic, proteomic, bioinformatics and systems biology approaches, a wide range of molecular mechanisms, genotypes and therapeutic targets have been identified in developing drug-resistance cancers. For example, alterations in drug transport or metabolism, local tumor microenvironment and drug targets all contribute to chemoresistance. Recently, autophagy has also been identified as an important mechanism in regulating multidrug resistance (MDR) in cancers [1].

Autophagy is constitutively active in its basal level for maintaining normal homeostasis, quality control of protein and organelle and working with the ubiquitin proteasomal system to degrade the polyubiquitinated and aggregated proteins. This catabolic process is triggered by cellular stressful conditions such as nutrient or energy deprivation, pathogen infection or misfolded protein accumulation, for the recycle of energy and nutrients to sustain cellular metabolism. While most evidence supports the prosurvival role of autophagy, unrestrained autophagy can contribute to cell death resulted from excessive cellular consumption [2] (**Figure 1**). Therefore, targeting autophagy for modulating MDR cancers has become an attractive approach in anticancer therapy.

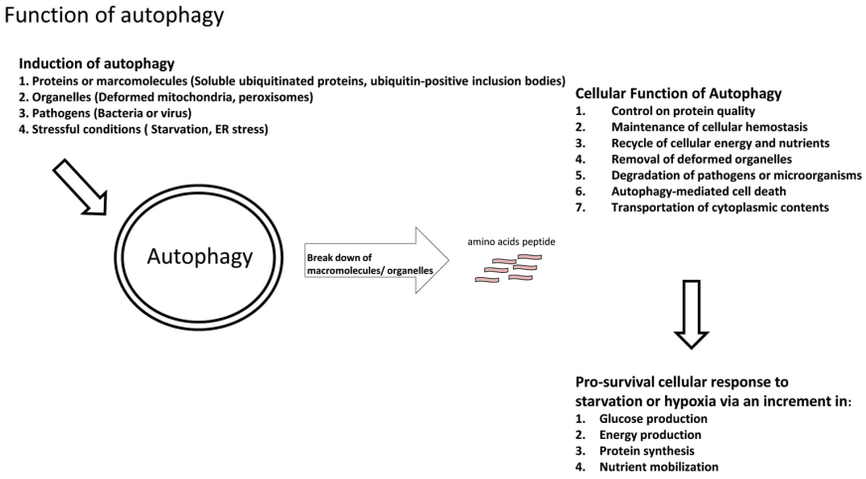

Figure 1. Cellular function and role of autophagy. Autophagy is a cellular-regulated degradation system for delivering unwanted cytoplasmic constituents to the lysosome for removal. Autophagy can be triggered by stressful conditions such as infection, nutrient deprivation or protein aggregates accumulation. Recent studies have depicted the physiological or pathological roles of autophagy in tumorgenesis, neurodegeneration, adaptation to starvation or development, clearance of misfolded proteins and organelles, antiaging, elimination of invading pathogens and regulation of cell death.

2. Autophagy and drug-/apoptosis-resistant cancers

2.1. Molecular mechanism of multidrug resistance in cancers

Drug-resistant mechanisms are classified into two major catergories: (1) nonclassical MDR phenotype and (2) classical transport-based MDR phenotype. Non-classical MDR refers to the

decreased sensitivity of tumor to certain anticancer drugs due to the activity of specific enzymes, including topoisomerase or glutathione S-transferase. Defective apoptotic proteins may also contribute to the development of drug resistant in tumors. Classical type of transport-based MDR involves the ATP-binding cassette (ABC) family of transporters, which 49 types of human ABC transporters were identified. Among them, three ABC transporters were reported to cause human MDR, including (1) multidrug resistance protein 1 (MDR1/P-glycoprotein/ABCB1); (2) MDR-associated protein 1 (MRP1/ABCC1); and (3) breast cancer resistance protein (BCRP/ABCG2), which are responsible for the efflux of several hydrophobic chemotherapeutic agents such as antimetabolites, taxanes or topoisomerase inhibitors across the plasma membrane [3].

MDR1, a membrane-bound glycoprotein, which is most abundant on the surface of excretory epithelial cells of colon, small intestine, pancreatic or bile ductules, and kidney proximal tubules, was found overexpressed and associated with drug resistance in kidney, liver and colon cancers. Recently, overexpression of MRP1 has also been found in chemoresistance breast, prostate and lung cancers. BCRP is a MDR drug efflux pump, which was associated with drug resistance in leukemia and breast cancer. Chemotherapeutic agents, such as imatinib, erlotinib, sunitinib and nilotinib, are known substrates and modulators of both MDR1 and BCRP [1].

2.2. "Apoptosis-resistance cancers"

Deregulation of apoptosis can cause drug resistance of cancer cells, and therefore, targeting the overamplifications, mutations and chromosomal translocations of antiapoptotic proteins, such as BCL-2 family members, caspase 8 inhibitor FLIP and inhibitor of apoptosis proteins (IAPs), are important in cancer therapies. Extensive studies suggested the overexpression of BCL-2 confers resistance of leukemia cells and mouse thymocytes to chemotherapies. Apoptosis involving the permeabilization of outer mitochondrial membrane (MOMP) can be blocked by BCL-2. Antiapoptotic BCL-2 family members, including BCL-XL and MCL1, and proapoptotic family members, including BAX, BAD, BAK and BH3-only proteins (BIM) which antagonize the antiapoptotic BCL-2 family members, are key regulators of apoptosis through the induction of MOMP. Increased expression of BIM is responsible for apoptosis induced by chemotherapeutic agents, including imatinib, gefitinib and erlotinib, in various cancer models. Besides, responsiveness to inhibitors of EGFR, HER2 or PI3K is correlated with the level of BIM. Deletion in the gene-encoding BIM is associated with intrinsic resistance to tyrosine kinase inhibitors (TKIs) therapies in lung cancer models [1].

Overexpression of prosurvival protein BCL-2 was found in malignant cells with defective apoptosis; therefore, drugs mimicking its antagonists, BH3-only proteins, may be effective in chemotherapy. Preclinical data confirmed that both ABT-737 (a BH3 mimetic) and its orally bioavailable form ABT-263, antagonized the antiapoptotic function of BCL-2, BCL-XL and BCL-W and exhibited cytotoxicity through Bax/Bak-mediated apoptosis. The weak-binding affinity of ABT-737 to the antiapoptotic BCL-2 family member (MCL1) can affect the effectiveness of ABT-737 and lead to drug resistance in cells. Therefore, targeting the enzymatic

degradation of antiapoptotic BCL-2 family members may be an alternative way to overcome the drug resistance in cancer cells [1].

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and agonistic antibodies targeting the TRAILR death receptors demonstrated antitumor properties in both *in vitro* and xenograft models. Currently, combinational use of TRAIL receptor agonists with chemotherapeutics, including carboplatin, paclitaxel, BCL-2 antagonists, bevacizumab, or histone deacetylase (HDAC) inhibitors showed prominent effect in clinical evaluations. Several drugs that are able to improve sensitivity to TRAIL can also decrease the level of the caspase 8 inhibitor (FLIP) and induce apoptosis. Therefore, inhibition of FLIP may work as an attractive therapeutic strategy for apoptosis-resistance cancers [1, 4].

The small molecule obatoclax (GX15-070) has been reported to antagonize antiapoptotic BCL-2 proteins, such as BCL-2, BCL-XL, BCL-W and MCL-1, and induce both apoptosis and autophagic cell death. Although the molecular mechanisms underlying the effect of obatoclax remain unclear, both single and combinational therapeutic uses of GX15-070 are under clinical evaluation, suggesting the role of apoptosis and autophagy in cancer therapy [5].

2.3. Autophagy in tumor suppression

In fact, the role of autophagy in cancer is controversial as it can work as a tumor suppressor, which inhibits tumor initiation or facilitates the survival of cancer cells during metabolic stresses induced by anticancer agents. Although autophagy may play a prosurvival role in tumor cells, loss of function mutations in the autophagy pathways were associated with tumorgenesis. For example, defects in apoptosis and autophagy may lead to tumorgenesis through chronic wound-healing response triggered by necrosis and inflammation. Malfunction of autophagy lead to the mismanagement of metabolic stress, which contributes to damage of cellular proteins, organelles or DNAs; insufficient ATP levels that are essential for maintaining normal DNA replication and genomic integrity, all these finally lead to genomic damage and tumor progression in autophagy-deficient tumor cells. This conception is supported by evidence of increased DNA breaks or damage response and aneuploidy in autophagy-defective cancer cells [6] (**Figure 2**).

Beclin 1 is a haploinsufficient tumor suppressor gene responsible for the induction of autophagy. Overexpression of beclin 1 can inhibit tumorgenesis. Accumulation of the autophagic substrate, p62/SQSTM 1 protein aggregates, could lead to the damage of mitochondria, accumulation of misfolded proteins, and overproduction of reactive oxygen species (ROS) that lead to DNA damage and genomic instability, suggesting the tumor suppressive role of autophagy [6]. Genetic instability and mutation are causes for increased cancer cells evolution and resistance to chemotherapy. While autophagy is associated with the promotion of longevity, DNA damage facilitates both cancer and ageing. Therefore, it is proposed that autophagy may play a protective role in maintaining cellular and genome stabilities, which can eventually prevent cancer and extend lifespan [7].

Furthermore, the induction of autophagic cell death has been observed in cancer cells triggered by excessive activation of autophagy, which causes irreversible damage to cells through

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redundant degradation of regulatory organelles, such as endoplasmic reticulum, mitochondria and golgi apparatus. Although evidence supporting the anticancer properties of autophagic death is limited and controversial, induction of autophagic cell death by novel small molecule activator of autophagy (e.g., STF-62247) was shown in renal cell carcinoma cells [6]. Proteins identified to be related to the autophagic cell death included steroid receptor coactivator, foxo1, histone deacetylases, ras or e4F1. Compound such as dasatinib, an inhibitor of Src/Abl family kinases, triggers autophagic cell death in ovarian cancer xenograft model; knockdown of

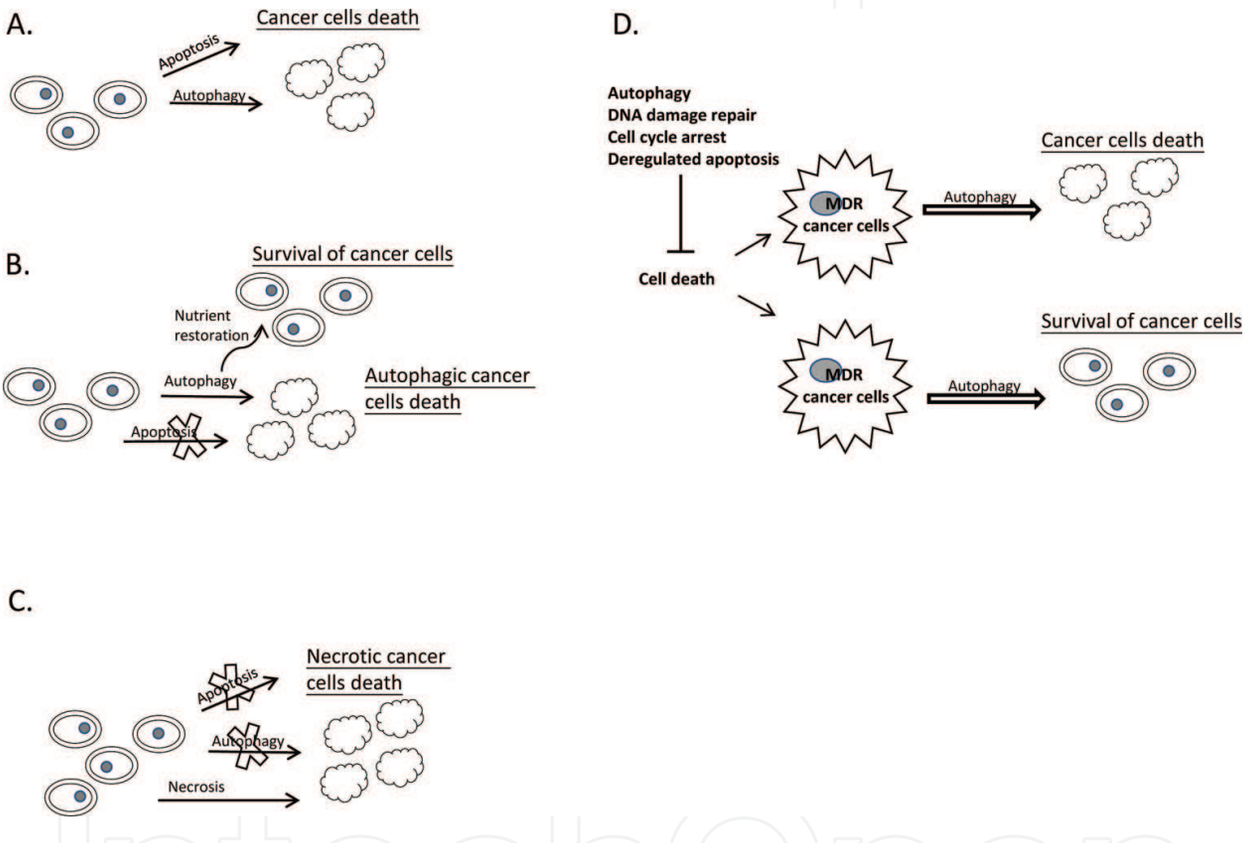

Figure 2. The interplay between autophagy, apoptosis and necrosis in the survival and death mechanisms of cancer cells. (A) Apoptosis and autophagy are programmed cell death mechanisms involved in various physiological and pathological conditions such as cancers. Failure in the induction of apoptosis or autophagy could result in malignant transformation of cells. Despite the basic physiological role of apoptosis and autophagy, targeting both apoptosis and autophagy pathways has been a popular strategy in chemotherapies. (B) Malfunction of autophagy is frequently found in human cancers. When apoptosis is inhibited, autophagy is promoted for inducing autophagic cancer cells death. However, evidence also indicated the induction of autophagy could confer stress tolerance to cancer cells and facilitates the survival of cancer cells under stressful condition, such as starvation, suggesting the controversial role of autophagy in cancer therapies. (C) The induction of necrotic cell death when both autophagy and apoptosis are inhibited. Necrosis is referred to the unprogrammed type of cell death characterized by an increase in cell volume and swelling, which finally lead to the rupture of the cell membrane and burst of cellular contents. (D) Inhibition of cell death is attributed to DNA damage induced by agents such as cisplatin, which can cause cell cycle arrest and allow the repairment of damaged cells, and finally lead to multidrug resistance (MDR). Besides, malfunction of apoptosis or induction of autophagy can also decrease drug-induced damage of DNA and cell death. All these mechanisms limit the effectiveness of chemotherapies via inhibition of specific enzymes or receptors in cells, leading to MDR in cancer cells.

beclin1 lead to reduction of autophagy and tumor growth. Interestingly, while oncogenic proteins, such as BCL-2, PI3K or AKT1, could inhibit autophagy, tumor suppressor proteins, such as beclin1, BIF-1, LKB1 or UVRAG, could induce autophagy. It was reported that autophagy may inhibit tumors growth by working with apoptosis and/or necrosis to cause cell death. For example, caffeine induces apoptosis through p70S6K-dependent activation of autophagy. A novel survivin suppressant, YM155, could induce autophagy-dependent apoptosis in prostate cancer cells. All these evidence suggested the potential role of autophagy in cancer therapy [3].

2.4. Inhibition of autophagy in cancer therapy

Increasing preclinical evidence supported the argument that pharmacological inhibition of autophagy or genetic knockdown of autophagy-related genes (ATGs) can increase sensitization of tumor cells to drug-induced cell death. Mechanistic pathways depicting the protective mechanisms of autophagy in cancers include the E3 ubiquitin ligase c-Cbl cascade that targets the active Src to promote survival of cancer cells via autophagy. Mutation of oncogene, *H-Ras* or *K-Ras*, upregulates basal autophagy for promoting the survival of cancer cells under nutrient deprivation conditions. Overexpression of inflammatory receptor, receptor for advanced glycation end products (RAGE), activated interleukin 6 (IL-6)-mediated mitochondrial pathway and transcription 3 (STAT3) signaling, induced autophagy and inhibited apoptosis to promote survival of pancreatic cancer cells. Lymphocyte-induced autophagy triggered tumorigenesis, suggesting a positive correlation between inflammation and cancer. An anticancer agent, suberoylanilide hydroxamic acid (SAHA), activated prosurvival autophagic pathway to attenuate both apoptotic and nonapoptotic cell death, suggesting the inhibition of autophagy may enhance the efficacy of SAHA [8].

With the prosurvival role of autophagy in cancer treatment, genetic or pharmacological inhibition on autophagy may therefore enhance the efficacy of cancer therapies. Pharmacological inhibition of autophagy can be induced by early phrase inhibitors such as 3-methyadenine (3-MA), wortmannin and LY294002. Late-phrase autophagy inhibitors include chloroquine (CQ), hydroxychloroquine (HCQ), bafilomycin A1 and monensin. CQ increased cyclophosphamide-induced cell death of tumor; reduced tumor size and enhanced apoptosis with the presence of anticancer drug vorinostat in colon cancer xenograft model. Besides, the treatment of saracatinib (Src inhibitor) with CQ in a prostate cancer mouse model demonstrated a higher percentage of tumor growth inhibition when compared with saracatinib alone [6].

Another autophagy inhibitor, 3-MA, enhanced 5-fluorouracil (5-FU)-induced apoptosis with increased regression of tumor in colon cancer models, suggesting the anticancer properties of autophagy inhibition in chemotherapy. While combinational use of bortezomib with CQ suppressed growth of tumor to a greater extent than bortezomib alone in colon cancer models, evaluation of phase I/II clinical trials is ongoing in patients with myeloma, suggesting the potential therapeutic use of autophagic inhibitor in cancer therapy [6].

2.5. Role of autophagy in MDR

2.5.1. Inhibition of autophagy in MDR

Overexpression of p-glycoproteins can efflux anticancer drugs and resulted in drug resistance and failure of anticancer therapies. It has been reported that the induction of autophagy may contribute to the survival of MDR cells during chemotherapy; defective autophagy contributes to MDR cells growth inhibition. In contrast, clinical trials have been performed to evaluate the beneficial role of autophagy enhancer in anticancer therapy, suggesting the double-edged sword of autophagy which its effect may highly dependent on the stage of tumor. The potent anticancer and apoptotic properties of gossypol, a BH3-mimetic small molecule isolated from cottonseeds, have been demonstrated in Ras-NIH 3T3-Mdr cells with overexpression of p-glycoproteins. However, results indicated that defective autophagy in the Ras-NIH 3T3-Mdr cells may enhance necrotic and apoptotic cell death induced by gossypol, suggesting the prosurvival role of autophagy in the MDR cells [9].

Further studies suggested that autophagy may contribute to resistance to chemotherapy drugs, such as tamoxifen, herceptin, paclitaxel (PTX) and epirubicin (EPI), in breast cancer. It was demonstrated that PTX- and vinorelbine (NVB)-induced autophagy facilitated the development of resistance to PTX and NVB in both MCF-7er and SK-BR-3er cells with overexpression of p-glycoproteins. The finding suggested that the use of autophagy inhibitors may be an attractive way for overcoming MDR in cancer therapy [10]. Further evidence suggested that the combinational use of autophagy and Src tyrosine kinase inhibitor was able to sensitize MDR cells to anticancer therapy. To increase the therapeutic efficacy of 5-fluorouracil (5-FU) to MDR colon cancer cells, many reports have confirmed the use of autophagy inhibitors, such as 3-MA or chloroquine, can increase the sensitivity of cancer cells toward treatment of 5-FU.

2.5.2. Activation of autophagy in MDR

Although mitigating MDR through inhibition of ABC transporter-mediated drug efflux or autophagy may be an effective approach in anticancer therapy, the induction of autophagy may also attenuate MDR. For example, vocamine (alkaloid) isolated from *Peschiera fuchsiaefolia* can mitigate drug resistance of osteosarcoma cells by inhibiting p-glycoproteins and inducing autophagic cell death when used with chemotherapeutic agent doxorubicin. Autophagy increases the efficacy of radiation therapy in both apoptosis-deficient lung cancer cells and xenograft model. Evidence demonstrating the potential anticancer efficacy of mTOR inhibitors was abundant. For example, combinational treatment by beclin1 expression and autophagic induction inhibited the growth of MDR (Ras-NIH 3T3) cells. Interestingly, constitutive expression of p-glycoproteins in hepatocellular cancer cells can lead to overexpression of BCL2 and mTOR, which contributed to resistance of cells to both apoptosis and autophagy [3].

In fact, autophagic cell death was observed in a p-glycoproteins overexpressing breast cancer cells that are resistant to paclitaxel. Further report demonstrated that long-term exposure to cisplatin leads to MDR and finally inhibition of both cisplatin-mediated apoptotic cell death and autophagy. Consistently, the presence of autophagic inducer can mitigate the resistance of cancer cells toward cisplatin-mediated apoptotic cell death, suggesting the anticancer

property of autophagy induction. p53, a well-known tumor suppressor gene, can lead to cancer cell death. Mutations in p53 were highly correlated with failure of chemotherapy or radiotherapy. However, while p53 mutant utilizes autophagy to kill the ovarian MDR cancer cells, wild-type p53 reverses the MDR phenotype by autophagy inhibition. The observation has further suggested the dual role of autophagy in MDR cancer therapy, and special cautions are required when applying autophagy modulators in cancer therapies [3].

3. Current approaches, challenges and compounds in targeting MDR

3.1. Current compounds/drugs in modulating MDR cancers

Malfunction of the apoptosis contributed to the survival of cancer cells under oxidative stress and hypoxia conditions. These lead to the accumulation of genetic defects in cells, which resulted in the deregulation of cell proliferation or promotion of angiogenesis during tumorgenesis. Therapeutic strategies targeting apoptosis through inhibition of antiapoptotic proteins or stimulation of expression of proapoptotic proteins have been used in anti-MDR cancer treatments. In fact, mutation or alteration in the level of drug targets may also confer resistance to therapeutic agents in cancer cells. For example, fluoropyrimidine 5-fluorouracil (5-FU), a common chemotherapeutic agent for breast and colorectal cancers, triggers cancer cell death via inhibition of thymidylate synthase (TS) [11]. Consistently, many evidences suggest that high expression of TS contributed to the increase resistance of cancer cells to 5-FU. Another type of chemotherapeutic agents, including paclitaxel, docetaxel, vinblastine and vincristine (vinca alkaloids), inhibited tumor growth via suppressing the polymerization of microtubules, and eventually lead to apoptotic cell death. However, cancer cells can acquire resistance to paclitaxel or vinca alkaloids by alternating the levels of tubulin isotypes, since a reduction in tubulin levels was found in paclitaxel-resistant cells. Platinum-induced DNA damage by cisplatin can trigger apoptosis. While an increase in the BAX to BCL-2 ratio by cisplatin could induce apoptosis, overexpression of BCL-2 was reported in tumors that were resistance to cisplatin. Therefore, functional defects in the apoptotic pathway or inactivation of apoptosis may contribute to the development of drug resistance in cancers and revealed the current challenges of using chemotherapeutic agents in MDR cancer therapies [12].

New therapeutics against specific antiapoptotic targets has been applied to enhance apoptosis and sensitize MDR cancer cells to anticancer agents. For example, antiestrogens, such as tamoxifen, can inhibit estrogen-dependent BCL-2 expression and increase the sensitivity of cancer cells to anticancer agent doxorubicin. Expression of BCL-2 or BCL-XL can be downregulated by small molecule compounds regulating retinoic acid receptors (RAR), PPAR or retinoid receptors. For example, RAR and RXR ligands are used to treat leukemia and lymphoma in clinical trials; PPAR agonist troglitazone, decreased serum prostate-specific antigen (PSA) in patients with prostate cancer; inhibitors of histone deactylases (HDACs) can suppress the expression of antiapoptotic BCL-2-family genes in cancers and enhance sensitivity of cancer cells to conventional cytotoxic agents in xenograft models or clinical trials. Moreover, antisense oligonucleotides targeting the BCL-2 mRNA are in phase III clinical trials.

BH3-only proteins, endogenous antagonists targeting BCL-2 and MCL-1, have been revealed for their therapeutic potency to induce apoptosis. The anticancer effect of synthetic BH3 peptides occupying the BH3-binding site of BCL-2 or BCL-XL, and BH3-mimicking compounds have already been validated for their anticancer properties. Small molecule BCL-2 inhibitors (HA14-1), BH3 peptidomimetics and BCL-2 antagonists (ABT-737 and ABT-263) have been shown in the preclinical studies to enhance the sensitivity of cancer cells to ionizing radiation or chemotherapeutic agents, providing us an overview on current approach of targeting apoptosis in MDR cancer therapies [12].

Overcoming intrinsic apoptosis failure during anticancer therapies could be achieved by triggering extrinsic apoptosis. For example, TNF treatment by cytokines FasL and TRAIL can activate caspases without the proinflammatory activation of the NF-KappaB pathways. TRAIL and its agonistic antibodies that bind TRAIL receptors have been proved to possess potent antitumor effect in mouse xenograft models. Moreover, clinical trials evaluating the efficacy of agonistic antibodies were completed, suggesting the potential of applying these biological agents to circumvent the defective intrinsic mitochondrial apoptotic pathway. CDDO and CDDOm are synthetic triterpenoids that sensitize cells to TRAIL-induced apoptosis in chemoresistant leukemia cells. Byrostatin, a protein kinase C (PKC) modulator, triggers the production of TNF and apoptosis in myeloid leukemia cells. All-trans-retinoic acid (ATRA) induces the production of cytokine TRAIL and apoptosis in acute leukemia cells, confirming the beneficial role of targeting TRAIL to kill cancer cells that are resistance to apoptosis. Heat-shock protein 90 (Hsp90) is a molecular chaperone ubiquitously expressed for the maturation of a set of substrate proteins called clients. Hsp90 promotes invasion, angiogenesis and metastasis which all contribute to tumorgenesis. Hsp90 stabilizes Raf-1, Akt and ErbB2 proteins and lead to the resistance of cancer cells to radiation therapy. Geldanamycin, inhibitor of Hsp90, enhances the sensitivity of cancer cells to radiation therapy. However, due to the poor solubility, high toxicity and problems of drug efflux by p-glycoprotein, modification on synthetic Hsp90 inhibitors has been made. For example, pyrazole resorcinol compound NVP-AUY922 has higher binding affinity to Hsp90, and NVP-BEP800, a 2-aminothieno pyrimidine class Hsp90 inhibitor, possess high antiproliferative activity in cancer cells. These inhibitors increase the sensitivity of tumor cells to apoptosis via depletion and destabilization of Hsp90 proteins and finally lead to increased DNA damage and apoptosis [12].

3.2. Current compounds/drugs regulating MDR cancers through autophagy

Most, if not all, chemoresistant cancers have defects in apoptotic pathways. In addition, the mitochondrial/cytochrome c pathway of apoptosis is frequently perturbed in various types of human cancers [13]. For instance, gene deficiency of BAX or BAK is commonly found in many malignancies, and BAX-BAK double-knockout mouse embryonic fibroblasts (MEFs) are resistant to various apoptosis-inducing agents [14]. On the other hand, caspase-3 and caspase-7 are crucial mediators of mitochondrial-mediated apoptosis [15], whereas caspase-3, caspase-8 and caspase-9 contribute the signal transduction roles in apoptosis induced by anticancer agents. Deficiency of these caspases would ultimately develop apoptosis-resistance and drug resistance phenotypes [16]. Although autophagy is considered as a crucial player in drug

resistance because cancer cells can circumvent cellular stress via autophagy induction, it has been shown that autophagy facilitates resistance of cancer cells to chemotherapeutic agents, and inhibition of autophagy could be therapeutically beneficial in some cases [17]. Nevertheless, significant number of studies demonstrated that the use of small molecules to induce autophagy-dependent cell death in apoptosis-defective or apoptosis-resistant cancer cells is an effective therapeutic approach [18]. These evidences are fuelling novel approaches to treat cancer and impede multidrug resistant through the induction of autophagy (**Table 1**).

Compounds or drugs	**Sources**	**Target pathways**	**Autophagy inducer or inhibitor**	**Types of MDR**	**Origin of cancers**	**References**
Saikosaponin-d (Ssd)	*Bupleurum falcatum L*	SERCA	Inducer	Caspases 3, 7 or 8 deficient Bax-Bak DKO	MEFs	[19]
Liensinine, isoliensinine, dauricine, cepharanthine	*Nelumbo nucifera, Asiatic moonseed rhizome, Stephania cepharantha*	AMPK-mTOR	Inducer	Caspases 3, 7 or 8 deficient Bax-Bak DKO	MEFs	[20]
Hernandezine	Thalictrum glandulosissimum	AMPK	Inducer	Caspases 3, 7 or 8 deficient Bax-Bak DKO	MEFs, colon	[21]
Ursolic acid	Apple peels	JNK signaling	Inducer	p53 mutation	Colorectal cancer	[22]
Rottlerin	Kamala powder	unknown	Inducer	Caspase 3 deficient	Breast cancer	[23]
Coibamide A	Marine cyanobacterium	mTOR-independent	Inducer	Apaf-1-null	MEFs, glioblastoma	[24]
Chalcone-24	Synthetic	c-FLIPL and c-IAPs degradation	Inducer	TRAIL resistant	Lung cancer	[25]
PG545	Synthetic	Heparanase	Inhibitor	Heparanase-overexpressing cancer	Cancer cells	[27]
Nelfinavir	FDA drug	Unfolded protein response (UPR) and endoplasmic reticulum	Inducer	Doxorubicin resistant	Breast cancer	[28]

Compounds or drugs	Sources	Target pathways	Autophagy inducer or inhibitor	Types of MDR	Origin of cancers	References
		(ER) stress				
Rapamycin	FDA drug	mTOR, mdr1 expression	Inducer	Doxorubicin resistant	Colon cancer	[29]
Lansoprazole	Synthetic	Proton pump	Inhibitor	Doxorubicin resistant	Solid tumors	[30]
Oxaliplatin derivatives with axial DCA ligands	Synthetic	Mitochondria and glucose metabolism	Inducer	Cisplatin resistant	Colorectal cancer	[31]
LY294002 and rapamycin	Synthetic and FDA drug	Akt/mTOR signaling, miR-222	Inducer	Cisplatin resistant	Bladder cancer	[32]
Rapamycin	FDA drug	mTOR	Inducer	Cisplatin resistant	Cervical cancer	[33]
Ursodeoxycholic acid	Synthetic	CD95/Fas	Inducer	Cisplatin resistant	Gastric cancer	[34]
Monanchocidin A	Marine sponge Monanchora pulchra	Lysosomal membrane permeabilization	Inducer	Cisplatin resistant	Germ cell tumor, prostate and bladder cancer	[35]
Resveratrol derivative, TMS	Synthetic	SERCA	Inducer	Gefitinb resistant	NSCLC cells	[36]
Chloroquine	FDA drug	Autophagy	Inhibitor	Gefitinb resistant	Liver cancer	[37]
Leu-Leu-O-methyl	Synthetic	Lysosome membranes	Inhibitor	Sunitinib resistant	Renal carcinoma	[39]
Metformin	FDA drug	GRP78	Inhibitor	Bortezomib resistant	Multiple myeloma	[40]

Table 1. Current compounds or drugs targeting MDR through modulation of autophagy.

In fact, the active components isolated from natural products have been found effective in inducing autophagic cell death or autophagy-dependent cell death in apoptosis resistance cells or cancers. For example, saikosaponin-d (Ssd), extracted from Chinese medicinal herb *Bupleurum falcatum L.*, is capable of inducing autophagic cell death in a panel of apoptosis-resistant cells [19]. Ssd increases cytosolic calcium via direct suppression of sarcoplasmic/endoplasmic reticulum Ca^2+ ATPase Pump (SERCA), leading to autophagy induction through

the activation of the Ca^2+/calmodulin-dependent kinase kinase (CaMKK)—AMP-activated protein kinase (AMPK)—mammalian target of rapamycin (mTOR) pathway. Importantly, Ssd-disrupted calcium homeostasis stimulates endoplasmic reticulum (ER) stress as well as the unfolded protein responses (UPR) and eventually contributes to autophagic cell death in apoptosis-defective or apoptosis-resistant mouse embryonic fibroblasts (MEFs), which either lack caspases 3, 7 or 8 or had the BAX-BAK double knockout [19]. Concomitantly, a group of natural alkaloids, including liensinine (*Nelumbo nucifera*), isoliensinine (*Nelumbo nucifera*), dauricine (*Asiatic Moonseed Rhizome*) and cepharanthine (*Stephania cepharantha*), were identified to stimulate AMPK-mTOR-dependent induction of autophagy and autophagic cell death in the same panel of apoptosis-resistant cell [20]. These alkaloids were later confirmed as novel and direct AMPK activators [21]. Furthermore, hernandezine, an alkaloid isolated from Chinese medicinal herb *Thalictrum glandulosissimum,* sharing structural similarity with the above isoquinoline alkaloids, exhibits specific cytotoxicity and induces autophagy in a panel of cancer cells. Hernandezine is a new class of AMPK activator, which induces autophagy and autophagic cell death in a panel of caspases-deficient apoptosis-resistant MEF. Those studies further indicated that the MEFs with genes deficiency of BAX and BAK demonstrated drug-resistant phenotypes in various chemotherapeutic agents, such as cisplatin, adriamycin, taxol, etoposide and staurosporine, but not in hernandezine. And hernandezine also shows similar cytotoxicity toward both wild type and double knockout of BAX/BAK in human DLD-1 colon cancer cells, suggesting the cross sensitivity of hernandezine toward this apoptosis-deficient cancer [21].

Apart from AMPK-mTOR signaling, mutations of tumor suppressor p53 have been shown to confer cellular resistant to various chemotherapeutic agents. For instance, colorectal carcinomas (CRCs) with p53 mutations have developed resistance to widely used chemotherapeutic agent, 5-fluorouracil (5-FU) [22]. A natural triterpenoid, ursolic acid, was found to sensitize p53 mutant apoptosis-resistant colorectal cancer cells to 5-FU effects via activation of c-jun N-terminal kinase (JNK) [22]. In addition, rottlerin, a natural polyphenol purified from the kamala powder, induces autophagic death in caspase-$3^{-/-}$ apoptosis-resistant MCF-7 breast cancer cells [23]. Coibamide A, an N-methyl-stabilized depsipeptide isolated from a marine cyanobacterium, induces autophagy and cell death in apoptosis-resistant MEFs and glioblastoma cells [24]. Other synthetic compounds and derivatives can overcome chemoresistance by modulation of autophagy. For instance, a novel chalcone derivative, chalcone-24, potentiates the anticancer activity of TNF-related apoptosis-inducing ligand (TRAIL) through autophagy-mediated degradation of cellular FADD-like IL-1β-converting enzyme-inhibitory protein large (c-FLIPL) and cellular inhibitor of apoptosis proteins (c-IAPs), which could be an effective approach in alleviating drug resistance [25]. Besides, sepantronium bromide (YM155) is a selective survivin inhibitor that exhibits potent antitumor activities in head neck squamous cell carcinoma (HNSCC) *in vitro* and *in vivo* by inducing apoptosis and autophagic cell death [26]. On the other hand, heparanase is a mammalian enzyme capable of cleaving heparan sulfate, whose enzymatic activity contributed to tumor inflammation, angiogenesis and metastasis. Recent studies indicated that heparanase-overexpressing cancers were more resistant to chemotherapy in a manner associated with increased autophagy, and therefore,

the suppression of heparanase and its mediated autophagy by heparanase inhibitor (PG545) is a promising strategy in treatment of these resistant cancers [27].

Several clinically approved drugs were found to be effective in treating doxorubicin-resistant cancer cells through modulation of autophagy. For example, nelfinavir, a clinically approved anti-HIV drug targets multidrug-resistant mechanism to enhance the efficacy of doxorubicin in doxorubicin-resistant MCF-7 breast cancer cells [28]. Rapamycin, a mTOR inhibitor, reverses drug resistance to doxorubicin in colon cancer through induction of autophagy and apoptosis, and suppression of multidrug resistance gene 1 (mdr1) expression [29]. Proton pump inhibitor lansoprazole potentiates the therapeutic effects of doxorubicin by improving its distribution and activity in solid tumors [30].

In cisplatin-resistant cancer, study reported that oxaliplatin derivatives with axial dichloroacetate (DCA) ligands induce autophagy and potentiate toxicity in cancer cells through modulation of mitochondria and glucose metabolism. These derivatives can also overcome inherent and acquired resistance to cisplatin and oxaliplatin [31]. Inhibition of Akt/mTOR signaling by LY294002 and rapamycin prevents miR-222-induced proliferation and restores the sensitivity of resistant bladder cancer cells to cisplatin. These findings indicated that miR-222 activates the protein phosphatase 2A subunit B/Akt/mTOR axis and thus plays a critical role in regulating proliferation and chemotherapeutic drug resistance [32]. Consistently, cisplatin cytotoxicity could be greatly enhanced in resistant cancer cells when mTOR had been inhibited prior to cisplatin treatment that was likely due to increased autophagy level [33]. Ursodeoxycholic acid effectively kills drug-resistant gastric cancer cell through induction of autophagic death [34]. Besides, a novel alkaloid, monanchocidin A isolated from the marine sponge *Monanchora pulchra*, overcomes drug resistance by induction of autophagy and lysosomal membrane permeabilization [35].

In other drugs-resistant cancers, a new analogue of resveratrol, (Z)3,4,5,4′-trans-tetramethoxystilbene (TMS), inhibits gefitinib-resistant non-small cell lung cancer (NSCLC) through inhibition of SERCA and induction of autophagy [36]. In contrast, co-delivery of gefitinib and chloroquine by chitosan nanoparticles overcomes gefitinb-resistant liver cancer by the inhibition of gefitinib-mediated autophagy [37]. Similarly, inhibition of lapatinib-mediated protective autophagy sensitizes HER2-positive breast resistance cancer cells to lapatinib, suggesting that autophagy is a promising target for circumventing lapatinib resistance of HER2-positive breast cancer cell [38]. Inhibition of sunitinib-mediated autophagy overcomes sunitinib resistance in metastatic renal cell carcinomas [39]. Similarly, metformin suppresses glucose-regulated protein 78 (GRP78), a key driver of bortezomib-induced autophagy and enhances the antimyeloma effect of bortezomib [40].

Collectively, MDR cancer cells defective in apoptosis signaling pathway are more sensitive to various types of autophagy inducers, which eventually induce autophagy-associated cell death or autophagic cell death. It is suggested that autophagy and its associated cell death provide an alternative promising approach for inducing cell death in MDR cancers. However, both autophagy inducers and inhibitors are commonly involved in the suppression of many other drugs-specific MDR cancer cells. Understanding the role of autophagy in particular

chemotherapeutic treatment is crucial for establishing an effective treatment of MDR via modulation of autophagy.

4. New mechanisms participating in MDR phenotypes for future drug discovery

Heme oxygenase-1 (HO-1) contributes to imatinib resistance by promoting autophagy in chronic myeloid leukemia through disrupting the mTOR-signaling pathway [41], whereas Src/STAT3-dependent HO-1 induction contributes to doxorubicin resistance in breast cancer cells by promoting autophagy [42]. Thus, HO-1 may be a novel target for improving MDR phenotypes in leukemia and breast cancer therapy. Galectin-1 is a beta-galactoside-binding lectin, and its mediated autophagy facilitates cisplatin resistance of hepatocellular carcinoma (HCC). Thus, galectin-1 may be a potential target to improve the efficacy of cisplatin in the treatment of patients with HCC [43]. Other studies showed that activation of autophagy in tumor associated macrophages (TAMs) inhibits proliferation and induces apoptosis in colon cancer cells and alters the expression of radiosensitivity associated proteins. Therefore, stimulating TAM autophagy may increase the radiosensitivity of colorectal cancer cells [44]. BRAF is an oncogenic protein, which promotes protective autophagy in colorectal tumor cells. BRAFV600E is the mutant protein of BRAF, which contributes to the drug-resistant phenotype of colorectal tumors. Study showed that pretreatment of autophagy inhibitor 3-MA followed by combinational treatment with drug PLX4720 targeting BRAFV600E can synergistically sensitize resistant colorectal tumors and provide novel efficient approaches for the treatment of resistant colorectal tumors bearing BRAFV600E [45]. The CD44 isoform-containing variant exon v6 (CD44v6) exhibits a crucial role in the progression, metastasis and prognosis of colorectal cancer. Overexpression of CD44v6 contributes to acquired chemoresistance via upregulation of autophagy in colon cancer SW480 cells, indicating that CD44v6 may be the new therapeutic target for resistant colorectal cancer [46].

Early growth response gene-1 (Egr-1) enhances hypoxia-induced autophagy to contribute chemoresistance of HCC. Dominant negative Egr-1 inhibits autophagy and thus enhances the sensitivity of HCC cells to chemotherapeutic agents, indicating that hypoxia/Egr-1/autophagy axis might be a novel therapeutic target for improving drug resistance in HCC [47]. Urothelial carcinoma is characterized by therapeutic resistance and frequent tumor relapse. Study indicated that the synergistic cytotoxic effect of gemcitabine/mitomycin with autophagy inhibitor (chloroquine) or with glycolytic inhibitor (2-deoxyglucose) may be of help in improving the treatment outcome in patients with urothelial carcinoma [48]. Blockage of prosurvival autophagy by TGF-β inhibition in bone marrow fibroblasts circumvents bortezomib resistance in patients with multiple myeloma. Therefore, a combinational treatment of bortezomib and TGF-β inhibitor may provide the basis for a novel targeted therapeutic approach [49]. Metabolic reprogramming by activation of glutaminolysis induces resistance to anti-NOTCH1 therapies in T-cell acute lymphoblastic leukemia (T-ALL). Suppression of both glutaminolysis and autophagy synergistically potentiate the antileukemic effects of anti-

NOTCH1 therapy in mice harboring T-ALL, suggesting glutaminolysis as a novel therapeutic target for the treatment of T-ALL [50].

5. Conclusion

This chapter, with the main focus on the role of autophagy in multidrug-resistant cancers, has demonstrated the controversial role of autophagy in cellular mechanisms of defense against cancers and immunochemical homeostasis. Autophagy, a cellular process responsible for the turnover of misfolded proteins or damaged organelles, is important key mechanism for recycling of nutrients to maintain normal cellular homeostasis, DNA replication and genomic integrity. This prevents the overproduction of metabolic stress that contributes to damage of cellular proteins, organelles or DNAs, which finally lead to genomic damage and tumor progression in cells. This conception is supported by our listed evidence of increasing number of novel autophagic small molecules that could circumvent the MDR phenotypes in cancers via cellular regulation of autophagy. This chapter has therefore given a comprehensive summary on the role of autophagy or autophagic enhancers/ inhibitors in the cellular mechanisms of defence and homeostasis in cancers.

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