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REVIEW

Nanotherapeutics targeting autophagy regulation for improved cancer therapy

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Abstract The clinical efficacy of current cancer therapies falls short, and there is a pressing demand to integrate new targets with conventional therapies. Autophagy, a highly conserved self-degradation process, has received considerable attention as an emerging therapeutic target for cancer. With the rapid development of nanomedicine, nanomaterials have been widely utilized in cancer therapy due to their unrivaled delivery performance. Hence, considering the potential benefits of integrating autophagy and nanotechnology in cancer therapy, we outline the latest advances in autophagy-based nanotherapeutics. Based on a brief background related to autophagy and nanotherapeutics and their impact on tumor progression, the feasibility of autophagy-based nanotherapeutics for cancer treatment is demonstrated. Further, emerging nanotherapeutics developed to modulate autophagy are reviewed from the perspective of cell signaling pathways, including modulation of the mammalian target of rapamycin (mTOR) pathway, autophagy-related (ATG) and its complex expression, reactive oxygen species (ROS) and mitophagy, interference with autophagosome-lysosome fusion, and inhibition of hypoxia-mediated autophagy. In addition, combination therapies in which nano-autophagy modulation is combined with chemotherapy, phototherapy, and immunotherapy are also described. Finally, the prospects and challenges of autophagy-based nanotherapeutics for efficient cancer treatment are envisioned.

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1. Introduction

Cancer is a major cause of death and a serious threat to human health[1-3]. For cancer treatment, the conventional clinical approaches include chemotherapy, surgery, and radiotherapy[4-6]. However, due to their inherent side effects and limitations, these therapies still fail to meet people's expectations[4-8]. In recent years, due to advances in molecular biotechnology, immunotherapy has emerged as the fourth method of tumor treatment following the three mentioned above[9]. However, the current clinical applications of immunotherapy are still limited by their narrow range of application, high cost, and individual rejection reactions[10,11]. As a result, there are still enormous challenges in cancer treatment, and we urgently need to find new therapies.

The rapid development of biomedicine provides new possibilities for cancer treatment. Among them, autophagy, a highly conserved cellular self-degradation process, has emerged as an emerging target for cancer therapy. Autophagy is an important process for maintaining cellular homeostasis and enabling cell survival under adverse conditions[12-14]. Importantly, there is growing evidence that autophagy significantly influences tumorigenesis and progression[15,16]. The effects of autophagy on tumors are complex and multifaceted. Generally, autophagy is considered a cytoprotective response that increases the tolerance of tumor cells to stress. However, autophagy also acts like a double-edged sword, inhibiting the growth and metastasis of tumors at different stages of their development and potentially inducing autophagic cell death (ACD)[17]. In addition, there is growing evidence that autophagy is closely associated with drug resistance and the immune escape of tumor cells, which also provides the possibility of combining autophagy modulation with other therapies[18]. Therefore, modulation of autophagy has been considered a promising strategy for cancer therapy[19-21].

Nanotechnology, which manipulates and comprehends matter on the scale of 1−100 nm[22], has greatly advanced the clinical treatments of cancer with its exceptional advantages in drug delivery[23,24]. Nanoparticles (NPs)-based drug delivery systems (nano-DDS) have emerged as amazing vehicles to overcome the limitations of poor pharmacokinetics and non-specific distribution for traditional drug formulations[25-27]. Besides, it can also be designed for smart triggered release in response to tumor-specific microenvironments (*e.g.*, glutathione, pH) to avoid indiscriminate release[28,29], thus diminishing side effects on normal tissues[30]. In terms of cellular uptake, nanocarriers can prolong the systemic circulation time of drugs, allowing them to enter cells *via* multiple endocytosis pathways[28]. In addition, autophagy-mediated nanotherapeutics generally require nanomaterials as carriers, and some of these have catalytic effects of their own and can be directly used as autophagy inducers[31], such as silica NPs, silver NPs, selenium NPs, polyethyleneimine NPs[32-36], iron oxide NPs[37], dendrimers[38] and quantum dots[39]. Therefore, it can be seen that bionanotechnology has distinct advantages in autophagy-mediated therapies to improve cancer treatment.

The combination of autophagy and bionanotechnology has received increasing attention and offers new alternatives for cancer treatment. As a burgeoning research focus, the mechanism of autophagy and its role in tumor therapy have been described in detail in several reviews[37-40]. Nevertheless, the combination of autophagy and nanotechnology has yet to be further elaborated. In particular, the modulation of autophagy by nanomaterials for cancer treatment has garnered escalating attention in the field of medicine[33,41]. Building upon these insights, this article reviews the latest advances in autophagy-mediated nanotherapeutics for cancer treatment and delves into the fundamental approaches of autophagy modulation as well as the combination of autophagy with other cancer therapies (Fig. 1).

2. Dual effects of autophagy on tumor progression

Autophagy, known as "self-eating," utilizes lysosomes to degrade dead or misfolded proteins to maintain normal cellular function under normal growth conditions[42]. Depending on the pathway of the substrate entry into the lysosome, autophagy can be categorized into three types, including macroautophagy, microautophagy, and chaperone-mediated autophagy[43,44]. Macroautophagy is the main pathway of autophagy and is most closely related to human health and disease. Therefore, in most cases, such as this review, the term "autophagy" specifically refers to macroautophagy. In this process, the endoplasmic reticulum (ER) and Golgi membranes elongate to form phagocytic masses, which wrap the surrounding cytoplasm or specific substances to form autophagosomes with a bilayer structure. Subsequently, autophagosomes fuse with lysosomes to form autolysosomes, and the substances contained therein are broken down by lysosomal hydrolases into small molecules (*e.g.*, amino acids and nucleotides) for reuse by the cell (Fig. 2).

Typically, this process is divided into three stages. The first is the initiation stage, in which the endoplasmic reticulum (ER) and Golgi membrane extend to form phagocytic vesicles, a process that involves the mammalian target of rapamycin (mTOR) and Unc-51-like kinase 1 (ULK1) complexes. Among these, mTOR serves as a central regulator of cell growth and proliferation that maintains the balance between anabolism and catabolism[45]. When cells are subjected to nutrient, oxidative, and ER stress, mTOR activity will be inhibited, leading to activation of the ULK1 complex and formation of detached membranes. Also, initial phagocytic membrane formation is dependent on the class III phosphatidylinositol 3-kinase (PI3K) complex, which binds to Vacuolar Protein Sorting 34 (VPS34) and Beclin-1 to form phosphatidylinositol 3-phosphate (PtdIns 3P). Autophagosomes form within the cup-shaped lumen of PtdIns 3P and are dynamically connected to the ER. When cells are in a subsequent state of stress, the cupular compartments and endoplasm rearrange in response to autophagy-associated proteins, resulting in the formation of phagocytic vesicles. Furthermore, AMP-activated protein kinase (AMPK) acts as an energy sensor that maintains cellular energy homeostasis in a dystrophic state by regulating autophagy[46]. Activated AMPK inhibits mTOR activity, which in turn activates the ULK complex or activates autophagy by phosphorylating the regulatory vacuolar protein-sorting 34 (VPS34) complex[47].

The second stage is the expansion of phagocytic vesicles and the formation of autophagosomes, a process that involves two complex systems composed of autophagy-related (ATG) proteins. One is the ATG5−ATG12−ATG16L complex, which acts on the outer membrane of extended phagocytic vesicles[48,49]; the other is the subcellular redistribution and lipidation of microtubule-associated proteins 1A/1B light chain 3B (LC3) precursor, which is converted to LC3-I in the presence of autophagy-related (ATG) proteins ATG4 and then binds to phosphatidylethanolamine (PE) in the membrane to form processed LC3-II in the presence of ATG7 and ATG3. The processed LC3-II is recruited to the growing phagocytic vesicles, facilitating autophagic membrane extension and closure to form autophagosomes[50].

The final stage is the fusion, degradation, and recirculation of autophagosomes and lysosomes. During this process, the autophagosomes merge with the lysosome to form the autolysosome,

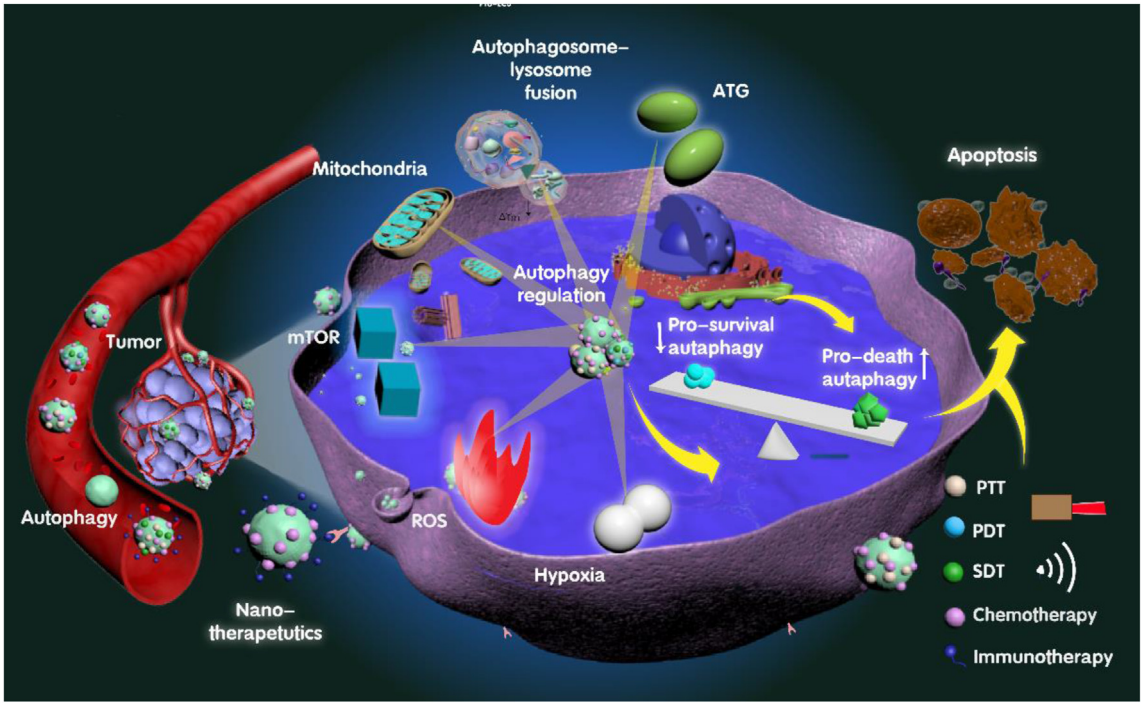

Figure 1 Schematic representation of nanotherapeutics targeting autophagy regulation for improved cancer therapy. Autophagy-based nanotherapeutics on modulation promote or inhibit autophagy by modulating mTOR, ATG, mitochondria, ROS, autophagosome-lysosome fusion, hypoxia, and other strategies, and are combined with other therapies (*e.g.*, chemotherapy, immunotherapy, PTT, PDT and SDT) to improve tumor treatment.

within which lysosomal hydrolases break down the enclosed substances into small molecules for cellular reuse[51].

In recent years, with the continuous exploration of new approaches to cancer therapy, the impact of autophagy on tumorigenesis and development has been gradually recognized. Autophagy is essential for maintaining cellular homeostasis under various stresses, and it plays a "double-edged sword" role in tumorigenesis, development, and metastasis[52,53]. On the one hand, in the early stage of tumorigenesis, autophagy maintains cellular homeostasis, inhibits the activation of oncogenes, and prevents tumorigenesis by removing damaged mitochondria, peroxisomes, and other cytotoxic substances from normal cells. However, on the

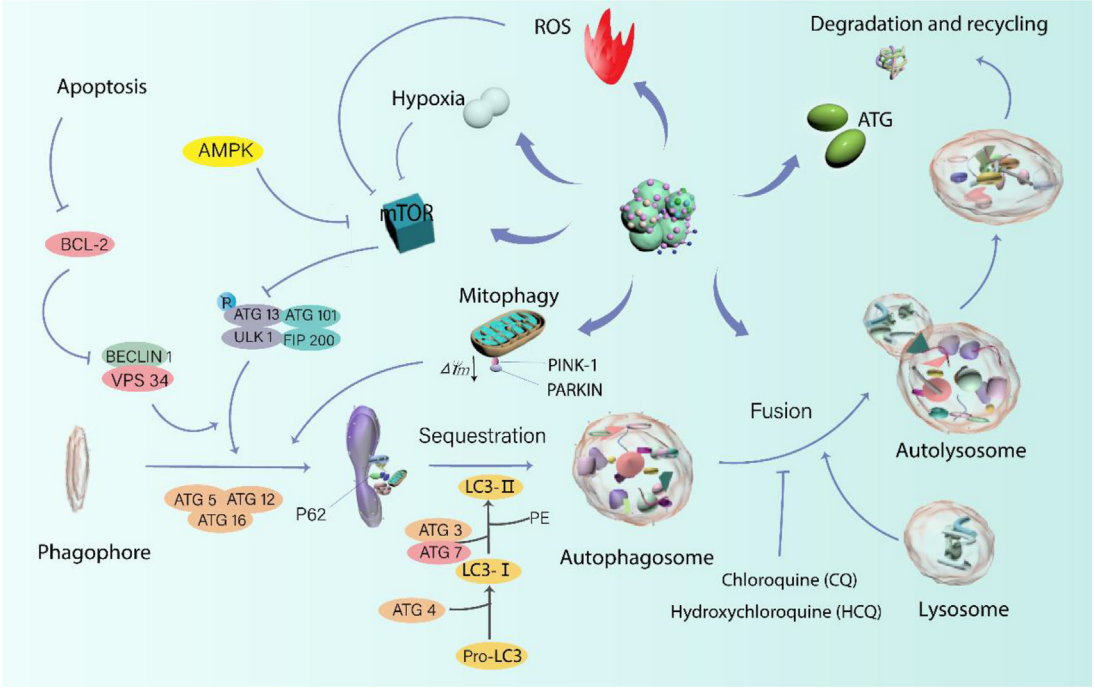

Figure 2 Schematic illustration of the mechanism of nanotherapeutics targeting autophagy regulation.

other hand, in cancer cells that have deteriorated and metastasized, autophagy provides nutrients for the survival of cancer cells, thus promoting the proliferation, invasion, and metastasis of malignant tumors.

2.1. *The promotion effect of autophagy on tumor*

Studies have shown that autophagy can contribute to tumor development by maintaining the stability of the tumor microenvironment (TME)[54], enhancing tumor drug resistance[55], and promoting the immune escape of tumor cells[56]. Autophagy enhances the tolerance of tumor cells to metabolic stress. Compared with normal cells, tumor cells exhibit elevated requirements for nutrients and energy, and demonstrate increased metabolic activity. When the microenvironment in which tumor cells live makes it difficult to maintain their metabolic homeostasis, the tumor cells will initiate autophagy to maintain their survival[54]. The study found that among patients treated with sorafenib for hepatocellular carcinoma (HCC), those with high expression of PSMD10 (Proteasome 26S subunit non-ATPase 10, an oncoprotein overexpressed in HCC) had a much shorter survival time than those with low PSMD10 expression[57]. Further studies have shown that PSMD10 promotes the expression of *ATG*7, which in turn induces the formation of LC3-II, thereby promoting autophagy, helping cancer cells fight against the adverse environment, and promoting the continuous growth of cancer cells[57]. In addition, the knockdown of *ATG* or the inhibition of the autophagy process with chloroquine (QC) leads to the accumulation of ROS and DNA damage, which can significantly shorten the survival time of pancreatic cancer cells[58].

Autophagy may also enhance drug resistance in tumors. Growing evidence suggests that unsatisfactory clinical outcomes in cancer therapy may be associated with high levels of autophagy induced by chemotherapy[55]. For instance, studies have shown that osteosarcoma cells can remove their damaged organelles and proteins through autophagy, thereby enhancing their survival during chemotherapy[59]. In addition, autophagy has also been proven to play an important role in the drug resistance of various tumor cells, such as laryngeal cancer[60,61], breast cancer[62], ovarian cancer[63], brain glioma[64], and melanoma[65]. Furthermore, the combination of chemotherapeutic agents and autophagy blockers has been shown to reduce the survival rate of tumor cells[66,67].

In addition, autophagy can also enhance the immune escape of cancer cells. Studies have revealed that autophagy helps cancer cells evade attacks of the immune system. One team found that autophagy in tumor cells appears to protect them from T cell-mediated death[56]. After knocking out three key autophagy-related genes (*RB1CC1*, *ATG9A*, and *ATG12*), the susceptibility of tumor cells to T-cell killing was significantly increased[56]. However, the study also found that pairwise deletion of specific autophagy genes made the cells resistant to killing by the immune system[68]. Knocking out both *ATG12* and *ATG5* could enhance tumor cells' resistance t T-cell killing, whereas knocking out only one of them did not[68]. Therefore, it was concluded that the effects of autophagy on cancer cell immunity may also be complex.

In addition to these effects, autophagy also plays a critical role in tumor cell metastasis and resistance to nest loss. Although autophagy can promote the growth of tumor cells, there is a limit. Once this mildly protective autophagy is inhibited or transformed into a hyperactivated phase by some methods, it is possible to induce ACD and achieve the purpose of anti-tumor directly[69]. Accordingly, it is feasible to treat cancer by modulating autophagy.

2.2. *The inhibition effect of autophagy on tumor*

Autophagy can prevent the occurrence of tumors in various ways, such as inhibiting inflammation[52], maintaining chromosome stability[70], and promoting immune response[71]. It is widely accepted that stimulations by pathogens and cytotoxic substances can cause chronic inflammatory damage to the organism, and the resulting inflammatory environment activates oncogenes and leads to tumorigenesis, while autophagy can interfere with this process[52]. For example, loss of the Beclin-1 allele often leads to accumulation of P62 and inhibition of NF-κB signaling, which induces macrophage aggregation and triggers an inflammatory response that ultimately leads to tumorigenesis[72]. Fortunately, intracellular autophagy can eliminate the excessive accumulation of sequestosome 1/p62 (P62), thus preventing tumorigenesis caused by the inflammatory responses.

Under stress conditions, cellular mitochondrial damage can lead to the accumulation of ROS, which in turn causes DNA damage and tumorigenesis. Autophagy can eliminate the mitochondria damaged by stress in the cell, thus preventing the accumulation of ROS and maintaining the stability of chromosomes[72]. In addition, it can also provide the necessary nucleotides for DNA repair *via* catabolism[52,70]. Therefore, autophagy can prevent oncogene activation and tumorigenesis by maintaining the stability of chromosomes in cells.

In addition, autophagy also can eliminate tumor cells by promoting the body's immune response. It has been shown that autophagy in antigen-presenting cells can promote the release of various cytokines, thereby activating immune responses. Meanwhile, autophagy can also activate bone marrow lymphocytes to maintain their survival. Therefore, autophagy plays an essential role in the innate immune response[71]. Besides, autophagy also elevates acquired immunity. It is well known that tumor cells usually evade immune surveillance by losing their antigenic identity or suppressing immune responses. Fortunately, autophagy in tumor cells can activate and enhance the antigen presentation of MHCI and MHCII molecules, thereby boosting the body's immune response and efficacy in eliminating tumor cells[73].

In summary, autophagy often plays a dual role in the process of tumor growth. Normally, autophagy inhibits tumor growth in the early stages of tumor development. With the continuous growth of tumors, cancer cells will use this survival pathway to maintain intracellular metabolic homeostasis and help them adapt to their survival environment. What's more, when chemotherapy, radiation, and other treatments are employed to kill cancer cells, tumors will also rely on this pathway to enhance their tolerance to these interventions. Due to the developmental characteristics of tumors, most patients' tumors are usually past the embryonic stage when discovered, and it is generally required to inhibit autophagy in combination with other therapies. Given the dual nature of autophagy characteristics, some studies have also focused on directly leading to cell death by autophagy through activation of autophagy in combination with other conventional therapies for cancer treatment. Accordingly, it is believed that inhibition of protective autophagy and induction of pro-death autophagy can achieve tumor suppression at different stages of cancer progression, respectively. Table 1[74-107] summarizes some of the small molecule drugs and NPs that fight tumors through autophagy regulation. However, further studies are needed to quantify and detect the

autophagy pathway to determine the best therapeutic options, as different patients require individualized treatment regimens.

3. Targeting autophagy regulation using nanotherapeutics

Considerable preclinical studies have demonstrated the feasibility of delaying tumor development through autophagy modulation[66,108]. As mentioned above, inhibition of autophagy in some cases can reduce the adaptability of tumor cells and improve their sensitivity to chemotherapy and radiotherapy[109]. Meanwhile, excessive induction of autophagy can also inhibit the growth and proliferation of tumor cells and even lead to cell death[110]. Given the advantages of nanotechnology in drug delivery, a variety of autophagy-based nanotherapeutic agents have been developed for cancer therapy, which mainly exerts antitumor efficacy by regulating the signaling pathways involved in autophagy and affecting the expression of autophagy-associated proteins in tumor cells[111], including (i) regulating of the mTOR signaling pathway; (ii) regulating the expression of ATG and its complexes; (iii) regulating the levels of ROS; (iv) regulating mitophagy; (v) interfering with the fusion of autophagosome and lysosomes; (vi) inhibiting the hypoxia-induced autophagy.

Table 1 A summary of autophagy agonists and inhibitors based on NPs and small molecules.

Drug	Mechanism	Ref.
Agonist		
Everolimus	Regulating ROS production	74
Retinoic acid	Unclear	75
Resveratrol	AKT−mTORC1↓	76
Apigenin	PI3K/AKT/mTOR pathway↓	77
Curcumin	mTOR↓	78
Kazinol C	ER stress-mediated signaling	79
SAHA	Regulation of autophagosome and lysosomal fusion	80
Rapamycin	mTOR↓	81
Everolimus	mTOR↓	82,83
FMK-9a	ATG4B↓	84
Fucoidan	mTOR/p70S6K/TFEB pathway	85
HMDB	AMPK-mTOR and AKT −mTOR pathways	86
Pyoluteorin	JNK/BCL-2 signal pathway	87
Ursolic acid	ATG5↑	88
AgNPs	ROS↑and p-mTOR↓	89
Au nanorods	ROS↑	90
AuNPs	Oxidative stress	91
Cd-based QDs	Oxidative stress	92
PdNPs	mTOR↓	93
Quantum dots (QDs)	ROS↑	94
ZONs	Regulating ROS production	95
Inhibitor		
3-MA	PI3K (VPS34)/Beclin-1↓	96,97
SBI-0206965	ULK1↓	98
LY294002	PI3K↓	99
Angelicin	ATG3/5/7/12↓	100
Bortezomib	ERK phosphorylation↑	101
Hydroxychloroquine	Autophagosome−lysosome fusion↓	102
Chloroquine	Autophagosome−lysosome fusion↓	102
Wortmannin	Autophagosome−lysosome fusion↓	103
SiNPs	Lysosome impairment	104
ZnO NPs	Mitochondria damage, lysosome dysfunction	105
AgNPs	Lysosome dysfunction	106,107

SAHA, suberoylanilide hydroxamic acid; FMK-9a, peptidomimetic; HMDB, 1-(2-hydroxy-5-methylphenyl)-3-phenyl-1,3-propanedione; ZONs, zinc oxide nanoparticles; 3-MA, 3-methyladenine; ER, endoplasmic reticulum.

3.1. Regulation of mTOR signaling pathway

The process of autophagy involves a variety of signaling pathways, including PI3K−AKT−mTOR and AMPK−mTOR, the best known of which is the signaling centered on the mTOR[110]. It is located upstream of the autophagy signaling pathway and has a negative regulatory effect on autophagy[112,113]. Under nutrient-rich conditions, mTOR is highly activated, highly phosphorylating ATG13, thereby reducing its affinity for ULK1 protein. In contrast, when nutrients are deficient, mTOR activity is inhibited, leading to the binding of dephosphorylated ATG13 to ULK1 kinase, which is then induced to form the initial autophagy vesicles with the help of the BECLIN 1−VPS34 complex[114]. This process is necessary for the formation of autophagosomes, and mTOR is, therefore, an essential target for nanotherapeutics to inhibit tumors through autophagy regulation.

A variety of nanotherapeutics have been developed to improve cancer therapy by inducing pro-death autophagy through overactivation of the AKT/mTOR signaling pathway in tumor cells. For example, a silymarin-based SeNPs (Si-SeNPs) was synthesized and preliminarily studied in four different cancer cell lines[115]. The results showed that Si-SeNPs could activate autophagic flux through inhibition of the PI3K/AKT/mTOR pathway in AGS cells, which in turn promotes apoptosis. In addition, Si-SeNPs had stronger inhibitory activity against AGS cancer cell proliferation compared to HepG2, A549, and Hela cell lines, without cytotoxic effects on normal cells. In addition, it has been reported that near-infrared photothermal therapy (NIR-PTT) employing anti-EGFR antibody-conjugated gold nanorods (anti-EGFR-GNs) could also induce high levels of autophagy by inhibiting the AKT−mTOR signaling pathway responsible for the autophagy induction, which was evidenced by a significant increase in accumulation of autophagosomes as well as autophagy-specific markers including LC3, P62, Beclin-1, and ATG5[116]. The *in vivo* experiments showed that anti-EGFR-GNs combined with NIR-PTT led to notable autophagic cell death in TNBC xenograft tumors, suggesting that autophagy elicited by the nanotherapeutics serves as an alternative cell death mechanism for effective cancer therapy.

It has been shown that nanotherapeutics can also be employed to activate the mTOR signaling pathway and thus inhibit autophagy in tumor cells to fight tumors. Recently, a new autophagy inhibitor, gold nanopyramid coated with titanium dioxide (NBP/TiO_2), has been prepared[117]. It was found that the NBP/TiO_2 nanostructures could eliminate the human glioblastoma U-87MG cells when their concentration exceeds 80 μg/mL (Au). The action mechanism of the nanostructures was explored, and it was clarified that they reduce autophagy *via* activating the AMPK/mTOR pathway, thereby blocking the autophagosome-lysosome fusion and inducing a large number of autophagosomes to accumulate and causing cell death. The study also demonstrated that the inhibition of autophagy by the NBP/TiO_2NPs in the combination therapy significantly improved the efficacy of bortezomib

and PTT, suggesting that the nanotherapeutics would be a potential autophagy modulator for the effective treatment of tumors.

3.2. Regulation of the expression of ATG and its complexes

The discovery of autophagy-related genes (*ATGs)* of yeast genetics in the 1990s has provided powerful genetic and molecular tools for the studies of human autophagy[118]. More than 35 ATG proteins, which can regulate and control different stages of autophagy formation, have been identified in yeast[119]. Among them, ATG 6 (Beclin-1) has been the most widely studied. As a positive regulator of autophagy, it has a crucial function in autophagy regulation[120]. BECLIN-1, mainly located in the ER, participates in the recruitment of proteins containing FYVE or PX motifs in the cytoplasm *via* forming a kinase complex with class III PI3K, promotes the formation of autophagosome membrane, and directs guiding other autophagy-related proteins to locate on it[121]. In this process, the formation of the core complex is regulated by various factors, thereby affecting the autophagy activity of cells[122,123]. Studies have confirmed that the BH3 domain of BECLIN-1 protein can interact with anti-apoptotic factors, including BCL-2, BCL-w, and BCL XL. Among them, BCL-2 inhibits the formation of the BECLIN 1−VPS34 complex by binding with the BH3 domain of BECLIN-1, thus weakening class III PI3K and inhibiting autophagy activity. Based on this, it is believed that autophagy can be affected by modulating BCL-2 expression in cells to achieve the purpose of cancer treatment[124,125].

Some nanomaterials have been verified to regulate the formation of autophagy-related complexes for cancer treatment[126]. Selenium nanoparticles (SeNPs) modified with laminate polysaccharide (LP) were prepared to improve their stability, cellular absorption, and permeability[127]. The results revealed that the cytotoxicity of LP-SeNPs on HepG2 cells was related to their regulation of autophagy and apoptosis. The treatment with LP-SeNPs inhibited the expression of the anti-apoptotic factor BCL-2 and attenuated the inhibitory effect of BCL-2 on BECLIN-1, thereby inducing apoptosis and early autophagy. Although this apoptosis-induced early autophagy favors surviving cells, LP-SeNPs can also block the later progression of this protective autophagy by inhibiting the fusion of autophagosomes with lysosomes, ultimately promoting apoptosis in tumor cells. Besides, zeolitic imidazolate backbone (ZIF-8) MOFs loaded with 3-methyladenine (3-MA) were designed to treat cancer[128]. In a cervical cancer xenograft tumor model, 3-MA@ZIF-8 MOFs showed higher antitumor efficacy compared with free 3-MA by inhibiting the expression of autophagy-related markers BECLIN1 and LC3, suggesting that MOFs serve as an efficient delivery vehicle to inhibit autophagy in cancer cells.

In addition to BECLIN-1, the expression of other ATGs also affects the autophagy process. There are different connection systems involved in the autophagy process, among which the ATG5−ATG12−ATG16 connection system functions to extend the isolation membrane to form autophagosomes. First, the ubiquitin-activating enzyme ATG7 activates ATG12 through the C-terminal glycine residue; then, the activated ATG12 is delivered to the ubiquitin transferase ATG10 and finally to ATG5 to form the ATG12−ATG5 complex. When autophagy occurs, ATG16 combines with ATG12−ATG5 to form the ATG16−ATG12−ATG5 complex, which is located on the isolation membrane and forms autophagosome by promoting the extension of the isolation membrane[129]. Therefore, autophagy can also be achieved by modulating other ATGs. For instance, treatment with polyethyleneimine-modified Fe_3O_4 magnetic nanoparticles (PEI-MNPs) resulted in an increase in ATG7 in tumor cells, which promoted the formation of autophagosomes and induced autophagy[130].

3.3. Regulation of ROS levels

Reactive oxygen species (ROS), mainly produced in the respiratory chain of the inner mitochondrial membrane, are the direct elicitor of oxidative stress[131]. When electron leakage occurs in the mitochondrial respiratory chain, superoxide radicals are generated to form ROS. ROS produced by oxidative stress have been shown to be essential regulators of autophagy[132]. As the second messenger, they can induce and regulate autophagy through various signaling pathways, including PI3K−AKT−mTOR and MAPK−ERK1/2. Besides, ROS can also directly oxidize the 81st cysteine residue near the active site of ATG4 to inactivate it, thereby preventing ATG4 from catalyzing LC3-II degradation. However, this does not affect the processing of the C-terminus of LC3-II by ATG4 but rather promotes the formation of autophagosomes. In addition to the effect on ATG4 activity, ROS can induce BECLIN-1 expression to promote autophagy[133]. Moreover, ROS can also promote the ubiquitination of degraded substances, which bind to LC3-II and anchor in autophagosomes for degradation[134,135].

On this basis, a variety of nanomaterials with the mechanism of inducing ROS to trigger autophagy have been reported. Among them, some nanomaterials have been modified to allow tumor cells to produce ROS, triggering autophagy modulation and thereby enhancing the effectiveness of cancer treatment. For example, Fe_3O_4 magnetic nanoparticles modified with polyethylenimine (PEI) were constructed into a nanotherapeutic system (PEI-MNPs) with good and high biocompatibility[130]. It was shown that PEI-MNPs facilitated the Fenton reaction in tumor cells, leading to excessive ROS production by intracellular mitochondria and NADPH oxidase. More importantly, it was demonstrated that cancer cells exposed to PEI-MNPs were induced to undergo autophagy through a series of cellular reactions. These reactions disappeared when ROS were inhibited, proving that ROS plays a critical role in the regulation of autophagy. Therefore, PEI-modified MNPs can exert anticancer effects by ROS-mediated autophagy in tumor cells. Besides, an iron oxide nanoparticle (Fe_2O_3@DMSA) that does not require chloroquine (CQ) or hydroxychloroquine (HCQ) has been constructed to treat cancer alone[33]. In hepatocellular carcinoma cells, Fe_2O_3@DMSA inhibited the fusion of autophagosomes and lysosomes, thereby enhancing pro-death autophagy by augmenting the production of sustained ROS. The results of *in vivo* experiments in the subcutaneous xenograft nude mouse model showed that Fe_2O_3@DMSA alone could effectively inhibit tumor growth without significant side effects.

In addition, the accumulation of ROS can also induce ferroptosis, so it is possible to combine autophagy modulation and ferroptosis to treat cancer[136,137]. For instance, a liposome nanotherapeutic system was constructed that encapsulates both copper peroxide nanodots (CPNs) and artemisinin (ART)[138] (Fig. 3). At the tumor site, the liposome nanotherapeutic system could be triggered to release CPNs and ART upon ultrasound stimulation. Among them, CPNs could release H_2O_2 and Cu^+ in an acidic tumor environment and then generate ·OH and Cu^{2+} through a Fenton-like reaction (catalytic reaction I). Then, Cu^{2+} could also catalyze the generation of ROS free radicals from ART components (catalytic reaction II), which further aggravated intracellular oxidative damage and the accumulation of lipid peroxidation,

leading to cancer cell death. Meanwhile, ART may act as a potent inducer of autophagy and promote iron death in cancer cells by degrading ferritin to increase intracellular iron levels, resulting in a potent antitumor effect.

3.4. *Regulation of mitophagy*

Mitophagy is a special kind of autophagy and self-protection of the body, which is closely related to the accumulation of ROS[139]. In the process of mitochondrial autophagy, depolarized mitochondria are wrapped in a double-layer membrane containing LC3 to form autophagosomes, which are then acidified and fused with lysosome precursors to form autophagolysosomes and degrade themselves[140,141]. The proteins of PARKIN and PINK-1 are involved in mitochondrial autophagy caused by a decrease in membrane potential. As a mitochondrial membrane protein, PINK-1 is rapidly degraded *via* mitochondrial membrane potential dependence under normal conditions. The decrease in mitochondrial membrane potential stabilizes the PINK-1 protein, allowing it to aggregate and recruit PARKIN with E3 ubiquitin ligase activity from the cytoplasm to the dysfunctional mitochondria. The mitochondrial substrate is then ubiquitinated and eventually recruited by P62 and sent to the autophagosomes for degradation[142,143]. In mammalian cells, autophagy of depolarized mitochondria can protect cells from damage caused by ROS. In contrast, in PARKIN-deficient cells, ROS will accumulate in the mitochondria, impairing the function of mitochondria and leading to cell death. This process is associated with tumorigenesis, tumor progression, and chemotherapy resistance. Therefore, regulation of mitophagy may be an effective strategy for cancer treatment.

In addition to inducing autophagy *via* the Ca^{2+}/CaMKKβ/AMPK/mTOR pathway, AgNPs can induce mitochondrial pathways to promote apoptosis in tumor cells[144,145]. For instance, the mechanism of mitophagy in A549 cells based on the cytotoxicity of AgNPs has been investigated[146]. AgNPs promoted the expression of PINK1 and PARKIN protein, causing the decrease in mitochondrial membrane potential, excessive ROS production, and the imbalance between oxidation and antioxidation in tumor cells[146]. Eventually, the mitophagy−lysosomal pathway was triggered, leading to the apoptosis of tumor cells. Besides, nanomaterials can also act as a transmitter of specific physical stresses to induce autophagy. For example, a magnetic nanosensor was developed by packing iron oxide into nanoparticles, which converted an external magnetic field into physical stress to induce

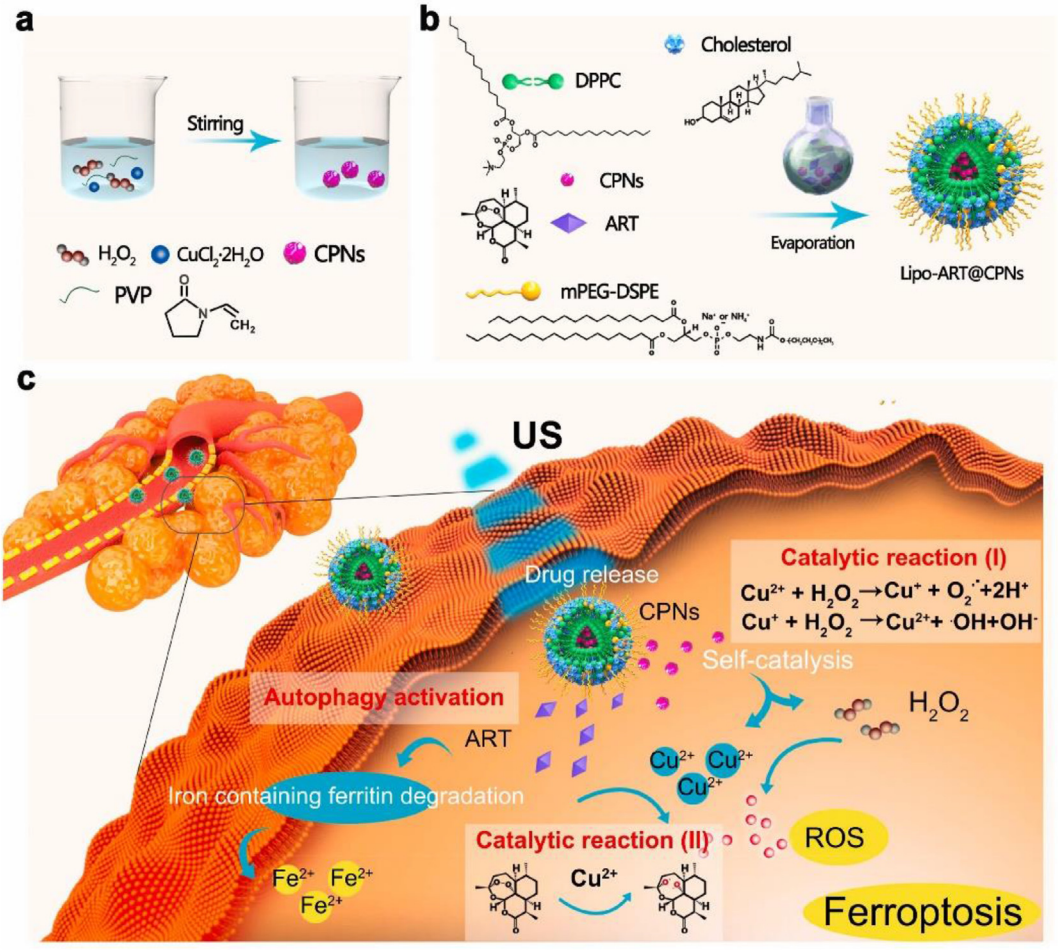

Figure 3 Schematic illustration of the synthesis and anticancer mechanisms of Lipo-ART@CPNs. (A) The synthesis process of CPNs. (B) Schematic diagram of the composition and structure of Lipo-ART@CPNs. (C) The anticancer mechanisms of Lipo-ART@CPNs including the self-catalytic process of CPNs and its further reactions generating ·OH and Cu^{2+}; Cu^{2+} catalyzing ART to generate large amounts of ROS to induce ferroptosis; ART-enhancing ferroptosis-involved cancer cell death through autophagy-induced degradation of ferritin. Reprinted with permission from Ref. 138.

mitophagy for killing cancer cells remotely[147]. The shape of nanoparticles also has a specific effect on their magnetic transduction ability, with spindle-shaped ones having the strongest magnetic transduction ability.

Notably, a manganese dioxide (MnO_2)-clad metal-organic skeleton (MOF) with a payload of carbonyl cyanide 3-chlorophenylhydrazone (CCCP) was constructed[148]. In tumor cells, the released CCCP served as a mitochondrial decoupler to induce mitochondrial autophagy, which could significantly enhance the autophagy triggered by the PDT process, thus transforming pro-survival autophagy into pro-death autophagy[148] (Fig. 4). In addition, *in vivo* experimental results showed that CCCP combined with PDT induced excessive immunostimulatory autophagy, generated long-term antitumor immunity, and prevented tumor recurrence and metastasis.

3.5. *Interference with autophagosome-lysosome fusion*

Autophagosome is a double-membrane structure formed by the extension of phagocytic carrier[149]. It can transport encapsulated cytoplasm or other specific substances to lysosomes and fuse with them to form autophagic lysosomes, which is an essential stage of autophagy[150-152]. Autophagy is a lysosomal-dependent degradation pathway, which can be interfered with by lysosomal dysfunction[153,154]. In general, the fusion of autophagosome membranes with lysosomal membranes is regulated by SNARE proteins (a superfamily of small proteins involved in membrane fusion). SNARE proteins include Syntaxinl7 (STX17), synaptic vesicle-associated membrane protein (VAMP8), and synaptosome-associated protein of 29kD (SNAP29). STX17 can be directed to the mature autophagosome membrane and initiate membrane fusion and form autophagosome *via* SNAP29 in the cytoplasm interacting with VAMP8 on lysosomal membranes[155].

In addition, the acidic environment of autophagosomes is also necessary for fusion. Some studies have utilized nanomaterials to alkalize lysosomes to affect autophagy. For instance, citrate-coated AgNPs were added to A549 cells, and the associated autophagy proteins were detected[106]. The results showed that AgNPs inhibited autophagy in cancer cells by inducing lysosomal alkalinization, leading to defective autophagy and autophagosome accumulation in the cancer cells[106]. Besides, increasing intracellular Ca^{2+} concentration can also inhibit the fusion of autophagosomes and lysosomes. For example, the prepared PAA/CaP NPs improved the therapeutic efficacy of transarterial chemoembolization (TACE) in an orthotopic rabbit hepatocellular carcinoma model by increasing the intracellular Ca^{2+} concentration, as well as inhibiting autophagosome-lysosome fusion to reduce autophagy[156].

In addition, studies have been conducted to inhibit protective autophagy by interfering with the binding of autophagosomes and lysosomes for the treatment of cancer[157,158]. The nanocatalysts of MOF(Fe) prepared by mimicking peroxidase catalyzed the production of highly oxidized ·OH in cancer cells (Fig. 5). At the same time, CQ alkalized lysosomes interfere with the binding of autophagy and lysosomes, thereby blocking self-protective autophagy under severe oxidative stress. So, cancer cells are unable to detoxify by decomposing their components and eventually succumb to ROS-induced oxidative damage[157]. Both *in vitro* and *in vivo* experiments have demonstrated the synergistic effect between nanocatalytic therapy and autophagy inhibition, and interfering with the fusion of autophagosomes and lysosomes is emerging as an effective strategy for cancer treatment.

3.6. *Inhibition of hypoxia-induced autophagy*

Given its crucial role in tumorigenesis and progression, TME has emerged as the most potential target for tumor therapy[159]. The primary obstacle that hinders the successful restructuring of the tumor microenvironment is the elevated levels of autophagy in hypoxic conditions, an adaptive mechanism that promotes the survival of cancer cells. To address this issue, researchers have employed nanodiamonds (NDs) as atypical autophagy inhibitors to assist cancer treatment. The combined application of nanodiamond and FDA-approved angiogenesis inhibitor sorafenib has been reported to cause severe death in Hela and MCF-7 cells. Intravenous administration of NDs and sorafenib significantly inhibited the growth of hepatocellular carcinoma in mice, resulting in a 76.5% reduction in average tumor volume. This is because NDs-mediated autophagy blockade can selectively trigger the death of hypoxic tumor cells, and this synergistic effect is effective in treating tumors when combined with anti-angiogenic agents[160].

Besides, solid tumors are often in a local hypoxic environment due to proliferation, which serves as a crucial factor for the development of drug resistance in tumors[161]. Hypoxia can induce autophagy in a variety of ways, such as HIF-1α, AMPK, and STAT4, which facilitates the survival of cancer cells under hypoxia conditions[162]. Therefore, provides a new alternative to overcome drug resistance in tumors.

For instance, a therapeutic system that promotes autophagy inhibition to enhance the sensitivity of tumor cells was studied based on the typical hypoxic microenvironment of a bladder cancer model[163]. MnO_2, a secure and valid nanomaterial, was deposited on human serum albumin (HSA) and served as a template. Subsequently, CQ was captured by MnO_2 under electrostatic force to form nanoparticles (HSA-MnO_2-CQNPs). Relying on the excellent biocompatibility of HSA, the nanoparticles entered tumor cells efficiently and gradually undergo decomposition. First, MnO_2 inhibited the formation of autophagosomes by reacting with H^+/H_2O_2 to generate O_2 and increasing the pH of the microenvironment. Then, CQ was released with the change of H^+/H_2O_2 concentration, which further inhibited the fusion of autophagosomes and lysosomes. These above effects all led to the inhibition of autophagy. *In vivo* studies in T24 xenograft mice showed that HSA-MnO_2-CQNPs effectively enhanced the sensitivity of bladder cancer to radiotherapy, with a tumor growth inhibition rate of 97.5%.

Additionally, alleviating hypoxia and down-regulating the expression of HIF-1α in tumor cells can effectively inhibit tumor metastasis, which is of great significance for tumor treatment[164-165]. For instance, a self-assembled nano platform was constructed to achieve synergistic treatment with the respiration inhibitor 3-bromopyruvate (3BP) and photodynamic therapy (PDT)[166]. After synthesizing the prodrugs of CD-3BP and CD-Ce6, as well as block copolymers (PEG-*b*-PMPC) containing polyethylene glycol (PEG), 3BP and Ce6 coated nanoparticles (CD-CE6-3BP NPs) were prepared by host-guest interaction. It is worth noting that 3BP enhanced PDT-induced autophagy, thus transforming pro-survival autophagy into pro-death autophagy and jointly playing the antitumor role with PDT, thereby completely inhibiting KB xenograft tumor growth in nude mice. More importantly, 3BP could reduce physiological oxygen consumption and downregulate the expression of HIF-1α to inhibit tumor metastasis effectively. According to the above descriptions, Table 2[167-210] and Table 3[211-258] summarize examples of nanotherapeutics that fight tumors by inhibiting or promoting autophagy.

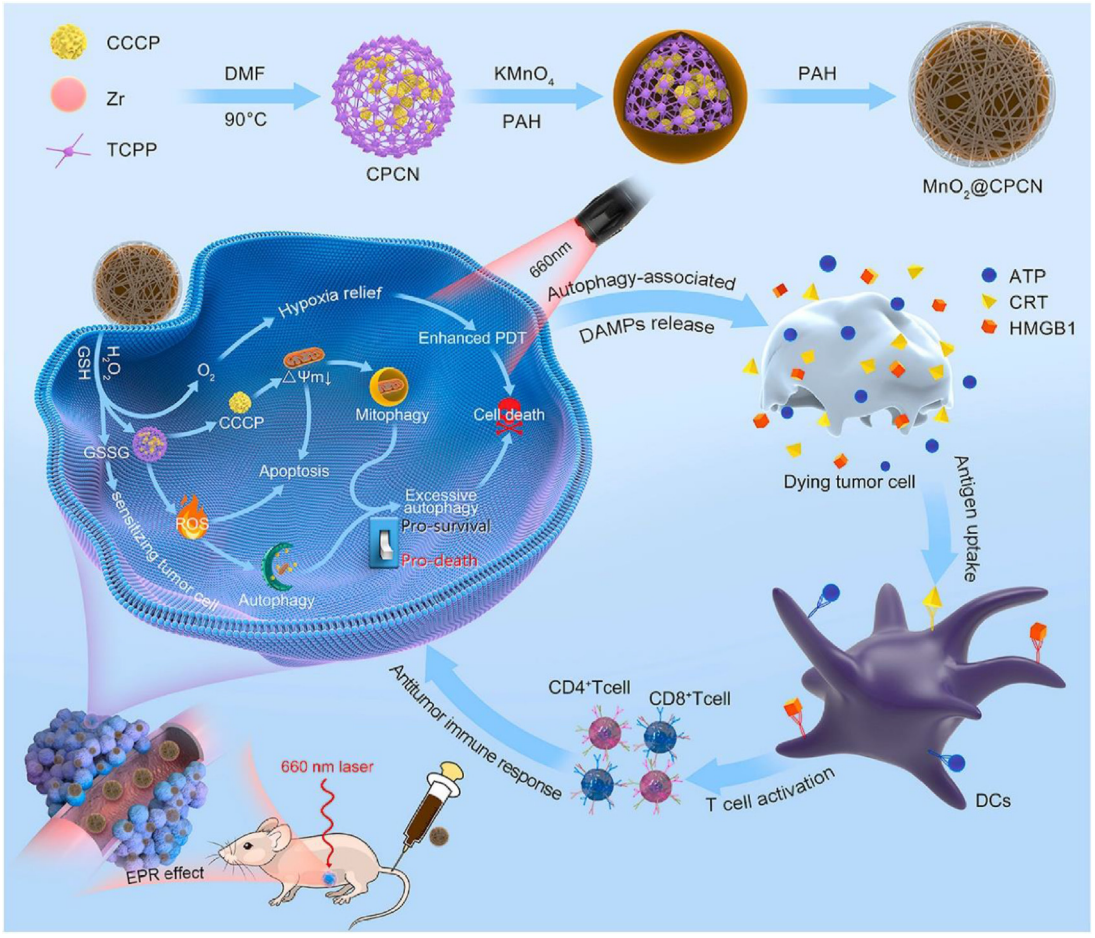

Figure 4 Schematic diagram of the synthetic process and anticancer mechanism of MnO2@CPCN. CCCP-induced mitochondrial autophagy transformed the ROS-induced pro-survival autophagy generated by CPCN into pro-death autophagy, which combined with the immune activation jointly induced by PDT and CCCP to produce significant anti-tumor effects. Reprinted with permission from Ref. 148. Copyright © 2022 Elsevier Ltd.

In summary, as a classical target of autophagy, mTOR mediates autophagy by responding to changes in the intracellular microenvironment and extracellular stress. Despite the dual nature of autophagy, most nanotherapeutics primarily overactivate autophagy by inhibiting mTOR to achieve the desired therapeutic purpose. In addition, the regulatory targets of autophagy are mainly focused on complexes with well-defined roles, such as BCL-2 and BECLIN1−VPS34 complex, to activate or inhibit autophagy. Excess ROS can lead to oxidative damage and interact with various other signaling pathways such as PI3K−AKT−mTOR and MAPK−ERK1/2. Most nanotherapeutics usually achieve therapeutic effects by stimulating cellular oxidative stress to generate large amounts of ROS and induce pro-death autophagy employing nanomaterials or other inducers. Mitochondrial autophagy is closely related to the production of ROS, and nanotherapeutics selected for mitochondrial autophagy modulate autophagy with the general aim of inducing pro-death autophagy as well. Interference with autophagosome-lysosome fusion can be achieved by inducing lysosomal alkalinization through nanomaterials and small molecule autophagy inhibitors or by increasing intracellular calcium ion influx. This strategy is chosen to inhibit the protective autophagy of the cell to achieve the desired therapeutic effect. Hypoxia causes cells to secrete cytokines that help tumor cells survive and metastasize. Therefore, increasing intracellular oxygen by various means is also a potentiating antitumor pathway. Given the dual nature of autophagy, appropriate methods to inhibit or promote autophagy should be selected based on a combination of the above strategies in order to obtain the desired therapeutic effect.

4. Combination therapy with nanotherapeutics targeting autophagy

A growing body of evidence from clinical trials suggests that monotherapies often fail to meet the efficacy of cancer treatment[259,260], which should be ascribed to their inherent limitations, such as the poor administration efficiency of chemotherapy[261], the low penetration of phototherapy[262], and the immunotoxicity of immunotherapy[263]. In addition, tumor resistance caused by various complex factors, such as pharmacokinetic properties or cell factors, is also one of the non-ignorable obstacles to cancer treatment by a single method or drug[264]. Studies have indicated that combination therapy can overcome the shortcomings of a single approach and significantly improve the efficacy of cancer treatment. Moreover, nanomaterials have been widely investigated in cancer therapy in recent years due to their high permeability, encapsulation properties, and controllable drug release, providing

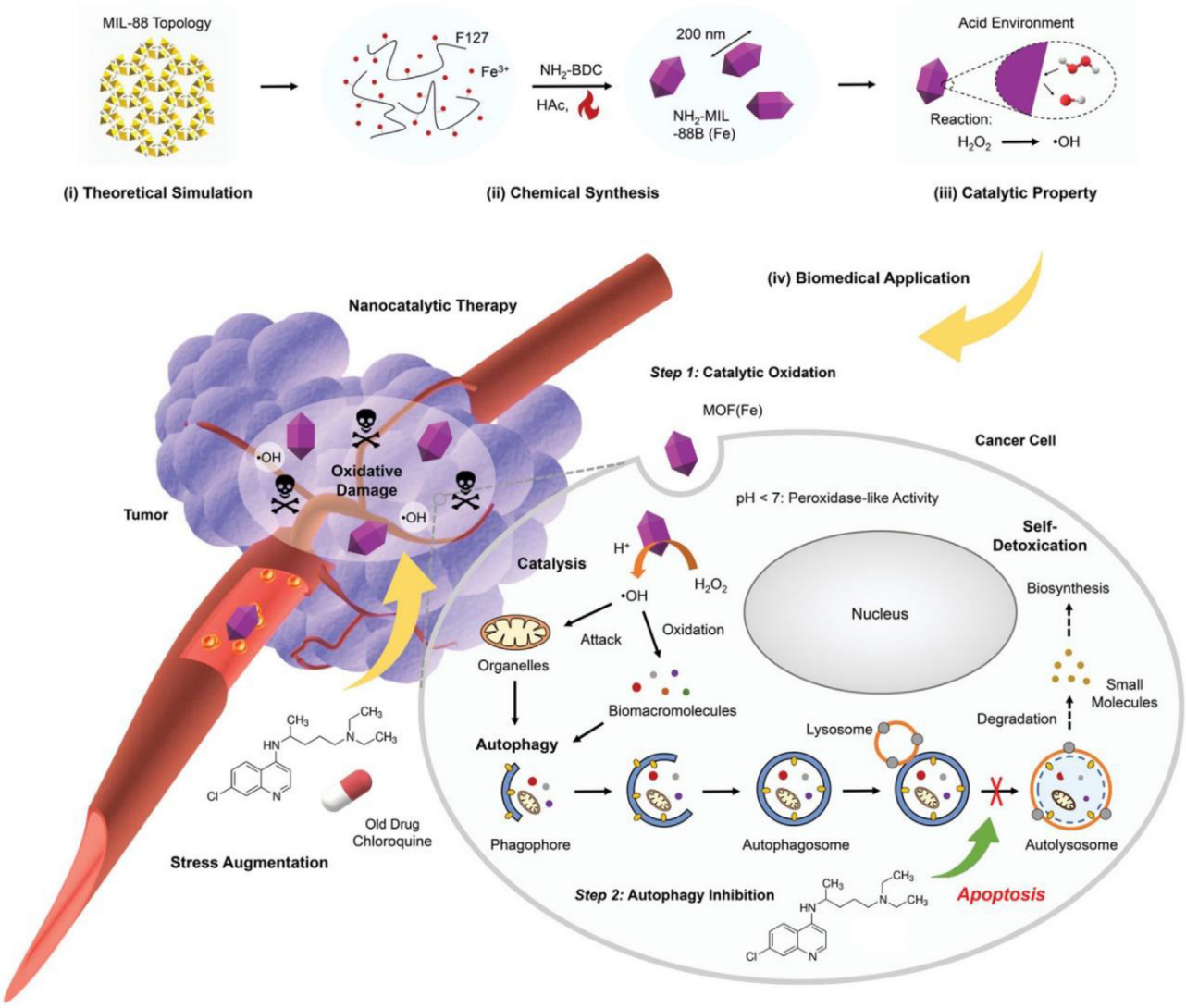

Figure 5 Schematic diagram of synthesis process and simplified anti-tumor mechanism. Step 1: MOF (Fe) catalyzes the production of large amounts of highly oxidized ·OH in cancer cells to attack and oxidize proteins and organelles in cancer cells to treat cancer. At the same time, protective autophagy reactions are activated, promoting the degradation of damaged proteins and organelles to keep the cells functioning properly. Step 2: CQ alkalizes lysosomes, thus interfering with the binding of autophagy and lysosome, cutting off self-protective autophagy under severe oxidative stress, and ultimately promoting apoptosis. Reprinted with permission from Ref. 157. Copyright © 2020 Wiley-VCH.

a versatile platform for combined drug delivery[265]. Therefore, the combination therapy based on nanotherapeutics targeting autophagy regulation is worth discussing.

4.1. Combination of autophagy and chemotherapy

Chemotherapy is currently the most widely utilized form of cancer treatment in clinical practice[266-268], and it is usually the foremost option for cancers such as leukemia and lymphoma that are difficult to undergo surgery and radiation[269-271]. However, it is well known that acquired drug resistance is a clinically unavoidable disadvantage of chemotherapy, which contributes largely to the mortality rate of cancer patients worldwide[272,273]. Therefore, overcoming the drug resistance of tumor cells has become the key to improving the anticancer activity of chemical drugs. Current studies have shown that autophagy is closely related to the drug resistance of tumor cells and is impacted by the modulators taken up by cells[274-277]. Therefore, typical strategies have focused on the modulation of autophagy employing nanomaterials or their payload to improve the sensitivity of tumor cells to chemotherapeutic agents[278,279].

Autophagy may reflect a typical cellular response to the exposure of nanomaterials. Zinc oxide nanoparticles (ZONs) have been reported to induce autophagy by accelerating intracellular lysis and the production of ROS to overcome drug resistance and thus enhance tumor chemotherapy. The results showed that the combination of ZONs with Dox addition could overstimulate autophagy by accelerating the release of zinc ions and ROS, thereby significantly increasing the mortality of tumors. In particular, the treatment of MCF-7/ADR cells showed that ZONs-induced P-gp protein expression level, as well as Dox uptake, were not significantly altered, which proved that ZONs-mediated autophagy modulation is responsible for overcoming drug resistance. More importantly, the 4T1 tumor cell models showed that

Table 2 Nanotherapeutics against cancer cells by inhibiting autophagy.

Mechanism	Nanotherapeutic	Cancer cell	Ref.
Regulation of the expression of ATG and complexes			
Beclin 1↓	HBPO/OEI600-PBA@siBec1	HeLa	167
	siBec1@PPN	HepG2/A549/HeLa	168
	CC-AuNP	AGS	169
ATG5↓	Chitosan NPs	A549	170
ATG7↓	miR-375/SF-LCC-NPs	HCC	171
LC3↓	FA-BSA-CM-β-CD NPS	HeLa	172
LC3-II↓	(O + B)@Trp NPs	HCT116/SW480	173
Class III PI3K↓	Dox/Wtmn micelle	B16F10	174
VPS35 complex↓	FL NPs	EC 9706	175
Interference with autophagosome-lysosome fusion			
Autophagosome−lysosome fusion↓	PDA NPs	HeLa	176
	Cu_2O NPs	C918	177
	PEG-AuNPs	Hepa1-6	178
	ACFe NPs	Huh-7	179
	PDGL-GEM@CAP/CQ	PDAC	180
	CCP@HP@M	HeLa	181
	Gefitinib/CQ-NPs	QGY	182
	PDA-PEG/CQ	HeLa	183
	CQ@HMPBs	HeLa	184
	MOF NPs	HeLa	185
	DOX/CQ NPs	MDA-MB-231	186
	HA-Mn_2O_3/HCQ	4T1	187
	CQ@ $CuFe_2O_4$ NPs	4T1	188
	PCNPs	MDA-MB-231	189
	mCG@ZIF	4T1	190
	ICGCQ@RCm NPs	4T1	191
	TF-CQ@mPdPt	4T1	192
	Au(I)⊂NPs	MCF-7	193
	CQ/CuZ@M_{4T1}-G	MDA-MB-231	194
	FeAC-DOX@PC-FITC-HCQ	MCF-7/MDA-MB-231	195
	Combo NP	4T1/MDA-MB-231	196
	mPDA@CMs NPs-CQ	RM-1	197
	PTX/HCQ-R8-dGR-Lip	B16F10	198
	HCQ/LIP-TR	B16F11	199
	VNP20009/HCQ Lip	B16F12	200
	PAA/CaP NPs	HepG2	201
	TiO_2 NPs	AGS	202
	LDH NPs	B16F10/CT26	203
	2D CVT PDT	4T1	204
Inhibition of hypoxia-induced autophagy			
Hypoxic mediation	NDs&Sorafenib	HeLa	161
	NDs&Arsenic trioxide	HepG2	205
Regulation of mitophagy			
Mitochondria autophagy↓	m-MCS@LA	4T1	206
Damaging mitochondria	HAL/3 MA@X-MP	4T1	207
Other mechanisms			
N/A	ZnO-NPs	SGC7901/BGC823	208
N/A	ZIF-82-PVP NPs	HL-7702/RM-1	209
N/A	CONs/pTRPM1	PC-2	210

NA, not applicable.

HBPO, 1,3-diol-rich hyperbranched polyglycerol; OEI600-PBA, oligo ethylenimine-phenylboronic acid; DOX, doxorubicin; siBec1, beclin-1 siRNA; CC, curtobacterium-cumin; Sf-LCC, sorafenib-lipid calcium carbonate; FA-BSA-CM-β-CD, folic acid-bovine serum albumin-carboxymethyl-β-cyclodextrin; (O + B), wxaliplatin + Berbamine; Wtmn, wortmannin; FL, 5-FU and LY294002; PDA, polydopamine; ACFe, amorphous-core@crystalline-shell Fe@Fe_3O_4; PDGL, 6PA-modified dendrigraft poly-L-lysine; GEM, gemcitabine; CQ, chloroquine; CCP@HP@M, chlorine e6-chloroquine@ hollow polydopamine@membrane; HMPBs, hollow mesoporous prussian blue nanoparticles; MOFs, metal-organic frameworks; HA, hyaluronic acid; HCQ, hydroxychloroquine; PC, polydopamine-calcium phosphate; mCG@ZIF, membrane-chloroquine-glucose oxidase@zeolitic imidazolate framework; ICG, indocyanine green; RCm, red blood cell and cancer cell hybrid membrane; TF-CQ@mPdPt, tannic acid−Fe metal organic framework-chloroquine@mesoporous PdPt; CQ/CuZ@M_{4T1}-G, chloroquine/Cu^{2+}-zeolitic imidazolate framework@tumor cell membrane-glucose oxidase; mPDA@CMs, mesoporous polydopamine@cancer cell membranes; PTX/HCQ-R8-dGR-Lip, paclitaxel/hydroxychloroquine-acta arginine-RGD peptide-liposome; Lip-TR, liposome TH-RGD peptide; PAA, polyacrylic acid; LDH, layered double hydroxide; CVT, $CaAl_2O_4$:Eu,Nd-verteporfin-triphenylphosphine; NDs, nanodiamonds; m-MCS@LA, mesoporous Mo-doped Cu9S5@L-Arginine; HAL/3MA@X-MP, hexyl 5-aminolevulinate hydrochloride/3-methyladenine@tumor cell-derived microparticle; ZIF-82-PVP; zeolitic imidazole framework-82-polyvinylpyrrolidone; CONs/pTRPM1, conjugated oligomer nanoparticles/plasmid transient potential receptor melastatin-2.

Table 3 Nanotherapeutics against cancer cells by activating autophagy.

Mechanism	Nanotherapeutic	Cancer cell	Ref.
Regulation of mTOR pathway			
mTOR↓	Rap@mFe3O4−DOX−HA	4T1/HBL-100	211
	RTLZ-NPs	Caco-2	212
PI3K/Akt/mTOR	PEI-GA/DOX/shAkt1	HepG2	213
	Si-Se NPs	HepG2/Hela/A549	214
	CS NPs/BET	MDA-MB-231	215
Akt/TSC2/mTOR↓	PAMAM NPs	A549	216
Akt/TSC3/mTOR↓	Carbon nanotube	A549	217
Akt/mTOR↓	Upconversion NPs	OPM2/K562	218
	CO NPs	HeLa	219
	Tmab-Au NPs	NCI-N87	220
	Anti-EGFR-GNs	MDA-MB-231	221
p38 MAPK; Akt/mTOR↓	FA-BSA NPs/BA	MCF-7	222
Akt/AMPK/mTOR↓	IO NPs	A549	223
	MMSNs@αCT1@AbCD133	GSCs	224
	CX-5461-MSNs	HeLa	225
Regulation the expression of ATG and complexes			
Beclin 1↑	Ovalbumin@$CaCO_3$ NPs	CD8T	226
	PTR-Se NPs	HCT 116	227
	P-Bec1 NPs	MCF-7	228
	Melanin-like NPs	HeLa	229
	Fe_3O_4 NPs	K562/OCI-AML2	127
ATG5↑	C_{60} nanocrystal	MCF-8	230
ATG6↑	Si NPs	LBC3	231
P53↑	Au-Ag@PDA NPs	TPC-1	232
Regulation of ROS levels			
	GQD	U251	233
	CST/DOX NPs	MCF-7	234
	CS NPs	SMMC-7721	235
	FePt/GO nanosheets	H460	236
	Au NPs	SKOV-3	237
	PTX/TMZ@CaP NPs	C6	238
	GONs	A549/NH1299	239
ROS mediation	Au NPs	MCF-7	240
	Zn-CuO NPs	HepG2	241
	Aft-Cu NPs	L02/HeLa	242
	CuPd NPs	MCF7	243
	(TP + A)@TkPEG NPs	4T1	244
	Fe_3O_4 NPs	HeLa	245
	Ag NPs	HeLa	246
Regulation of mitophagy			
	Fe@Au NPs	OECM1	247
	ZnO NPs	CAL27	248
	GCMSNs	A549	249
	Ag NPs	A549	147
Mitophagy	MnO_2@CPCN	4T1	149
	PLGA-PEG-AEAA NP	Hepa1−6/Huh7 HCC	250
	DSPE-PEG-Glucose/CaP	4T1	251
Other mechanisms			
Cell membrane damage	FePd nanocrystal	4T1	252
Autophagosome↑	PEG-PCL NPs	MCF-7/MDA-MB-1	253
Stability of SQSTM1↓; LC↑	Sur@T7-AIE-Gd NPs.	LM3; 3T3	254
Golgi-associated protein	AFMMB	LSC	255
N/A	BTP-4F-DMO NPs	4T1	256
N/A	5-Fu/MNPs-Fa	CT26	257
N/A	ASN	CT26	258

NA, Not applicable.

Rap, rapamycin; RTLZ, lecithins-Zein; PEI-GA, poly(ethylenimine)-glycyrrhetinic acid; CS, chitosan; BET, betanin; PAMAM, polyamidoamine dendrimerz; CO, cuprous oxide; Tmab, trastuzumab; GNs, gold nanorods; BA, baicalin; IO, iron oxide; MMSNs, magnetic mesoporous silica nanoparticles; PTR, pleurotus tuber-regium; P-Bec1, polymer-Beclin-1; GQD, graphene quantum dots; CST, celastrol; GO, graphene oxide; TMZ, temozolomide; GONs, gadolinium oxide nanocrystals; Aft, apoferritin; (TP + A)@TkPEG, (triptolide + AIE)@thioacetal ketone bond PEG; GCMSNs, gold-mesoporous silica nanoparticles; PLGA-PEG-AEAA, poly lactic-*co*-glycolic acid-polyethylene glycol-aminoethyl anisamide; DSPE, 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine; PCL, poly-caprolactone; Sur@T7-AIE-Gd, survivin siRNA@seven-peptide-aggregation-induced emission-Gadolinium; AFMMB, azacitidine-MOF-membrane; BTP-4F-DMO, an acceptor-donor-acceptor-structured dye; 5-Fu/MNPs-Fa, 5-fluorouracil/magnetic nanoparticles-folic acid; ASN, autophagy cascade amplification nanoparticle.

the antitumor efficacy of the combination was significantly superior to the same dose of ZONs or Dox alone. The results indicated that the regulation of autophagy has great potential in improving the efficacy of tumor chemotherapy. Even though various nanomaterials can alleviate chemoresistance through autophagy modulation, their mechanisms of action are slightly different. Unlike ZONs, TiO_2 NPs mediate autophagy primarily by promoting ROS production and disrupting the normal function of lysosomes[202]. It has been evidenced that TiO2 NPs increase the sensitivity of AGS gastric cancer cells to 5-fluorouracil (5-FU) and minimize its potential toxicity.

In addition to the employment of nanomaterials alone, the combination of autophagy inhibitors and nanotherapeutics represents an essential way to overcome drug resistance. A glutathione (GSH)-responsive self-assembled nanoparticle (Combo NP) for the treatment of triple-negative breast cancer (TNBC) was constructed with a combination of autophagy inhibitor (HCQ) and 7-ethyl-10-hydroxythectothecin (SN38) (Fig. 6). In tumor cells, intracellular GSH cleaved disulfide bonds (−S−S−), leading to the rapid release of SN38 and HCQ from Combo NP. HCQ-mediated autophagy inhibition disrupted the DNA repair process, thereby making tumor cells more sensitive to SN38-induced DNA damage and apoptosis[196]. The results showed that Combo NP achieved better therapeutic benefits in the metastatic triple negative breast cancer (TNBC) model, whether compared with free drug combination or mono nanotherapeutics. It was also found that Combo NP maintained the molar ratio of HCQ and SN38 in mice's blood circulation and tumor tissues within the synergistic range, providing a new method for combined proportional drug administration. Recently, furin-triggered aggregated

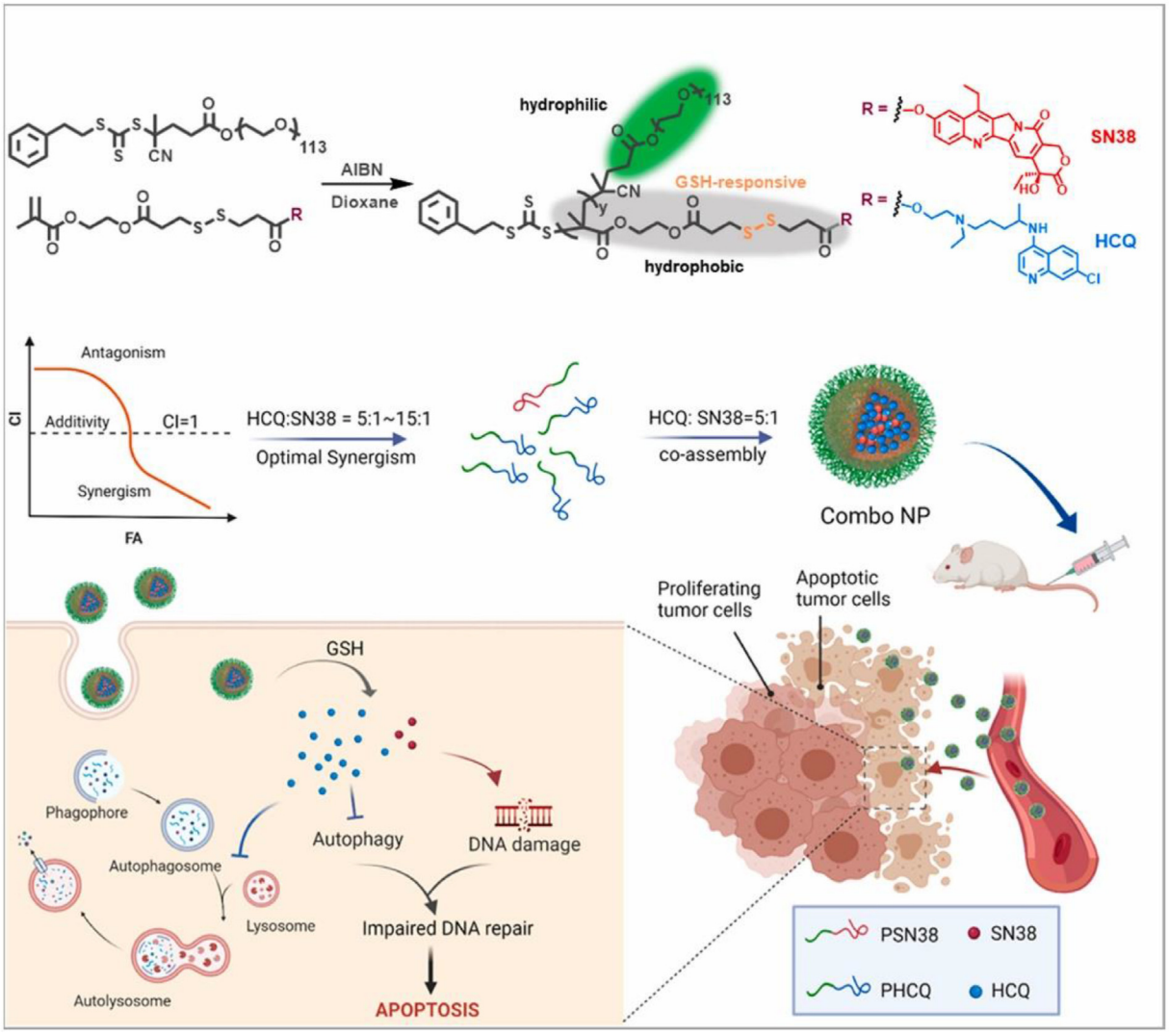

Figure 6 Schematic diagram of the preparation and simplified anticancer mechanism of Combo NP. The hydroxyl groups contained in HCQ and SN38 are used to form prodrug, and then the single SN38 and HC38 prodrug are self-assembled into prodrug nanoparticles through hydrophilic and hydrophobic interaction under the optimal synergistic molar ratio (5:1). Thus, GSH sensing self-assembled Combo NP nanoparticles were constructed. After Combo NP is absorbed by cancer cells, the intracellular GSH cleavage disulfide bonds (−S−S−), and SN38 and HCQ are rapidly released from Combo NP. HCQ-mediated autophagy blocking disrupted the DNA repair process, further sensitizing tumor cells to SN38-induced DNA damage and apoptosis, showing significant therapeutic advantages against metastatic TNBC. Reprinted with permission from Ref. 196.

AuNPs have been reported to overcome tumor cell resistance to DOX where HCQ was combined[158]. It was found that HCQ-induced autophagy inhibition can reprogram tumor-promoting M2-like TAMs to anti-tumor M1 phenotypes, thereby synergistically overcoming DOX resistance.

Interestingly, nanotherapies that combine autophagy inducers with chemotherapeutic drugs can also yield enhanced chemotherapy results. The contributing mechanism is primarily that autophagy inducers convert pro-survival autophagy into pro-death autophagy. A novel transferrin receptor (TfR)-targeted nanotherapeutic agents reported that induces excessive autophagy of tumor cells by delivering high-dose autophagy inducer rapamycin (RAP), rendering the cells unable to maintain homeostasis, thereby aggravating the damage to tumor organelles caused by the combined cytotoxic paclitaxel (PTX)[280].

The mentioned reports confirmed the effectiveness of autophagy inhibitors in combination with chemotherapeutic agent, but only combinations involving CQ/HCQ have been tested in clinical trials. Unfortunately, their toxicity led to the termination of the clinical trials, probably because it not only inhibits autophagy-related signaling pathways but may also affect other cellular functions. Accordingly, the mechanism of autophagy regulation needs to be further investigated, and the safety of nanomaterials, as well as other autophagy modulators, should be fully considered.

4.2. *Combination of autophagy and phototherapy*

As an emerging cancer therapy, phototherapy has a unique tumor-killing mechanism and does not induce drug resistance. In addition, it can localize the irradiation of cancerous areas, thus effectively avoiding damage to the healthy ones[281]. According to the mechanism of action, it mainly consists of photodynamic therapy (PDT) and photothermal therapy (PTT)[282].

4.2.1. *Combination of autophagy and PDT*

As a non-invasive therapy, the effectiveness of PDT in cancer treatment is well recognized[283,284]. One of the action mechanisms of PDT relies on the production of ROS by photosensitizers upon light irradiation to kill tumor cells[285,286]. However, concomitantly, the generated ROS also activates protective autophagy that favors tumor survival[287-288]. Several studies in recent years have attempted to turn pro-survival autophagy into pro-death autophagy by excessive autophagy, achieving the desired therapeutic effects[289]. The results imply that transforming autophagy that acts antagonistically to PDT into synergistically acting one is expected to greatly enhance the efficacy of multimodal cancer therapies[290].

In light of the above, nanotherapeutics that combine autophagy modulation with PDT to synergistically treat cancers have been extensively studied[291]. An autophagy agonist of rapamycin (Rapa) and photosensitizer of phthalocyanine (Pc) has been reported to co-encapsulate into a combo dendrimer nanoparticle delivery system[164]. Given the interaction of charges, Pc was modified with multicarboxyl to bind to the macromolecular polyamide. Rapa was then packed into the core of the carrier, taking advantage of the thioacetyl group's sensitivity to ROS. In response to light stimulation, Pc in tumor cells triggered the PDT and generated ROS. Concomitantly, the thioacetyl group in the center of the carrier was destroyed by ROS to release Rapa, which initiated autophagy and significantly enhanced the efficacy of PDT.

It has been shown that inhibition of PDT-induced autophagy could also achieve tumor suppression. In line with the supramolecular self-assembly characteristics of ultrapure silicon nanodots (OSiNDs), a unique supramolecular nano gel loaded with photosensitizer of tetraphenylporphinesulfonate (TPPS) was synthesized, which was composed of OSiNDs and copolymer methoxy-poly (ethylene glycol)$_{113}$-block−poly (L-glutamic acid sodium salt)$_{200}$ (PEG-PLE)[292]. The negative charge characteristics of TPPS and PEG-PLE, as well as the aggregation properties of OSiNDs in an acidic environment, enabled the nanogels to gather in lysosomes with a pH of 4−5 range. Upon light irradiation, lysosomes containing nanogels suffered damage, which facilitates TPPS-initiated PDT while impairing the autophagy process. The results of *in vivo* experiments demonstrated that the nanogels could reduce drug efflux and enhance drug inflow by avoiding the drug efflux pump on the plasma membrane, thus prolonging the retention time of the photosensitizer in the tumor cells, realizing multiple PDT treatments with a single administration in A549/DDP-resistant tumor model mice, and showing dramatically improved anticancer effects.

In addition, to address the critical problem of traditional PDT that requires long-term external light exposure, a unique nanotherapeutic based on irradiation-free PDT was developed, which consists of two-dimensional $CaAl_2O_4$:Eu, $Nd3^+$ persistent luminescence nanosheets (CAO PLNSs) and photosensitizer of verteporfin with mitochondrial-targeting function (Fig. 7)[204]. The results of *in vivo* tumor suppression experiments showed that the two-dimensional PDT nanotherapeutic-mediated autophagy inhibition amplified the apoptosis-mediated therapeutic effect, with tumor inhibition rates of up to 96.0% in nude mice bearing 4T1 tumors.

4.2.2. *Combination of autophagy and PTT*

In addition to combining with PDT for cancer treatment, the synergistic effect of autophagy and PTT has also received increasing attention[293]. Different from PDT, the mechanism of PTT is based on the photothermal effect of photothermal conversion agents, which triggers cellular necrosis at the site of the lesion by converting the applied external light energy into heat to cause localized warming[294]. Compared with traditional therapies, PTT offers the benefit of more rapid tumor elimination[295]. However, it also shares the same limitation with PDT, in that PTT also favors the survival of cancer cells' protective autophagy[296]. In addition, PTT often causes damage to normal tissues while killing tumors due to the effect of uneven heat distribution. Therefore, regulating autophagy can not only reduce tumor resistance to PTT but also enable it to kill tumor cells at relatively low temperatures, thereby reducing side effects[297,298].

A polydopamine nanoparticle (PDA)-based nanotherapeutic agent capable of mediating PTT has been reported to be assembled, which was able to heighten the lethality of PTT in cancer cells by inhibiting autophagy[201]. The PDA was first modified with PEG to obtain longer blood circulation capacity. Subsequently, the nanoparticle was prepared by loading CQ onto PDA-PEG through $\pi-\pi$ stacking interaction according to its electronic structure. Under near-infrared (NIR) light irradiation, PDA acted as a photothermal conversion agent to mediate the occurrence of PTT. At the same time, the nanotherapeutic selectively released CQ in the acidic microenvironment of tumors, which subsequently inhibited the autophagy−lysosomal degradation pathway of tumor cells and blocked the pro-survival autophagy induced by PTT. The results of *in vivo* experiments showed that under NIR light irradiation,

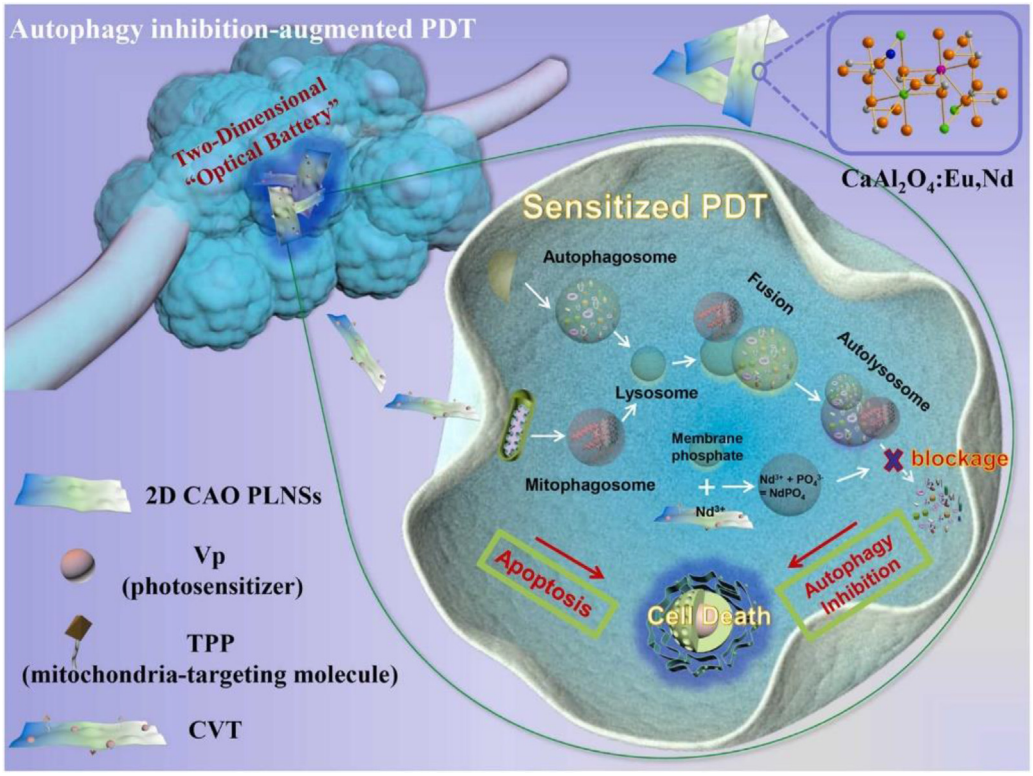

Figure 7 Schematic diagram of a simplified mechanism of 2D PDT nano-systems that enhance PDT by inhibiting autophagy. Mitochondrial-targeted CVT nanodrugs inhibit autophagy by disrupting lysosomal function. Nd3+ induces lysosomal membrane damage and promotes apoptosis to anti-tumor, and autophagy inhibition amplifies the therapeutic effect caused by apoptosis. Reprinted with permission from Ref. 204. Copyright © 2021 Elsevier Ltd.

administration of PDA-PEG/CQ led to complete inhibition of tumor growth in mice inoculated with MDA-MB-231 cancer cells.

Notably, as with PDT, despite the therapeutic benefits of inhibiting protective autophagy activated by PTT, over-activating this pro-survival autophagy to transform it into a pro-apoptotic one is also another feasible approach to improve the efficacy of PTT. To this end, a multifunctional nanotherapeutic agent based on autophagy induced by BECLIN1-derived peptides was constructed, which initiated the autophagic cell death pathway by over-activating autophagy[229]. In addition, nanoliposomes composed of NIR light-sensitive dye, IR780, and the chlorophyll-rich fraction of Anthocephalus cadamba (CfAc) could also cause the autophagic cell death, thereby exerting the antitumor activity of PTT along with autophagy[294]. The above studies suggest that the combination of autophagy modulation involved as a novel means to improve the efficacy of PTT has become a promising cancer treatment modality.

In summary, even though autophagy has been shown to significantly improve the efficacy of phototherapy, there are still unresolved potential issues that need to be addressed. Due to the dynamic characteristics of autophagy, the type of autophagy induced by different irradiation conditions, administered doses as well as tumor types during phototherapy may also vary. Whether the induced autophagy is more favorable for cytoprotection or apoptosis depends on the choice of autophagy modulation strategy and the possible side effects. One should start with the type of autophagy before the intervention and choose a more appropriate strategy to achieve the desired effect.

4.3. Combination of autophagy and immunotherapy

Immunotherapy has now been proven to be a promising strategy for cancer treatment. Recent studies have suggested a more complex interrelationship between autophagy and the immune system. On the one hand, autophagy can promote antigen presentation and immune response by regulating homeostasis, proliferation, and differentiation of immune cells (*e.g.*, macrophages, natural killer cells, plasma cells)[299]. It has been found that autophagy can promote the differentiation of T cells into cytotoxic T lymphocytes (CTLs) and Th cells and drive plasma cell differentiation as well as the production of specific antibodies (IgM and IgG)[300]. However, some studies have found that autophagy can also suppress T cell-mediated antitumor immunity and contribute to the immune escape of tumors[301,302]. Even though autophagy embodies a dual role in the immune response, it provides a new direction for improving immunotherapy[303,304]. In addition, the choice of appropriate means of immunomodulation is also a key component to improve the response rate of immunotherapy, in which the demonstrated ability of nanotherapeutics for effective drug delivery has attracted attention[305-307].

A kind of weakly alkaline layered double hydroxide nanoparticles (LDH NPs) has been designed to remodel the tumor immune microenvironment (TIME) and enhance tumor immunotherapy[203]. By neutralizing excess acid, LDH NPs can not only block the lysosomal-mediated autophagy pathway in tumor cells but also reshape TIME and increase the level of tumor-associated macrophages with M1 phenotype and T cells. *In vivo* experimental

results showed that LDH NPs administered intravenously into mice could inhibit colon tumors and melanomas by 81% and 91%, respectively, suggesting that LDH NPs can effectively boost the innate and adaptive immune responses of the organism, showing broad potential in the immunotherapy of solid tumors (Fig. 8).

In addition, triggering immunogenic cell death (ICD) is also a way for autophagy modulation to enhance immunotherapy. An on-demand autophagy cascade amplification nanoparticle (ASN), which relied on autophagy to boost antitumor immunotherapy, was designed[261]. The autophagy inducer STF-62247 was encapsulated into C-TFG micelles *via* self-assembly and was electrostatically surface coated with negatively charged oxaliplatin prodrug (HA-OXA) form autophagy-responsive nanoparticles. Upon absorption by tumor cells, OXA was released from HA-OXA in response to the reductive TIEM, leading to the triggering of ICD[258]. Due to the absence of HA-OXA coating, C-TFG micelles released STF-62247 in response to autophagy, stimulating autophagy into an "excessive" state[261,310]. Excessive activated autophagy induced the apoptosis of tumor cells and increased the release of relevant immune cytokines. In the Balb/c mouse model bearing CT26 cells, the tumor weight of the ASN group was only 0.48 times that of the OXA group, confirming the superiority of ASN in tumor suppression. Thereupon, autophagy with timely cascade amplification boosts the antitumor immune response. In addition, a polylactic-*co*-glycolic acid (PLGA)-PEG-aminoethyl anisamide (AEAA) nanoparticle that combines autophagy with immunotherapy to potentiate cancer treatment has also been designed and developed[250]. The nanoparticles loaded with icaritin and Dox replaced over-activated autophagy with selective mitophagy to stimulate the antitumor immune response, thus achieving a fantastic therapeutic effect with the overall survival of mice bearing HCC tumors in the combination group being almost twice as long as that of the control group.

The impact of autophagy modulation on the maturation of dendritic cells (DCs) has been attracting attention in recent years. A nanotherapeutic activator targeting immune cells was designed to induce autophagy, ultimately improving cancer treatment[165]. In the constructed nanotherapeutic activator, the autophagy-inducing peptide BECLIN1 and the antigen peptide OVA257−264 were each coupled to poly (β-amino ester) *via* thio-end click chemistry method to obtain an amphiphilic polymer that could self-assemble into nanoparticles. In the tumor tissues, the nanoparticles stimulate the maturation of more DCs through modulating autophagy, thereby promoting both antigen presentation and T cell activation, two key steps in the antitumor immune process. In the B16F10-OVA mouse model, both subcutaneous and intravenous administration of nanotherapeutic activators showed satisfactory

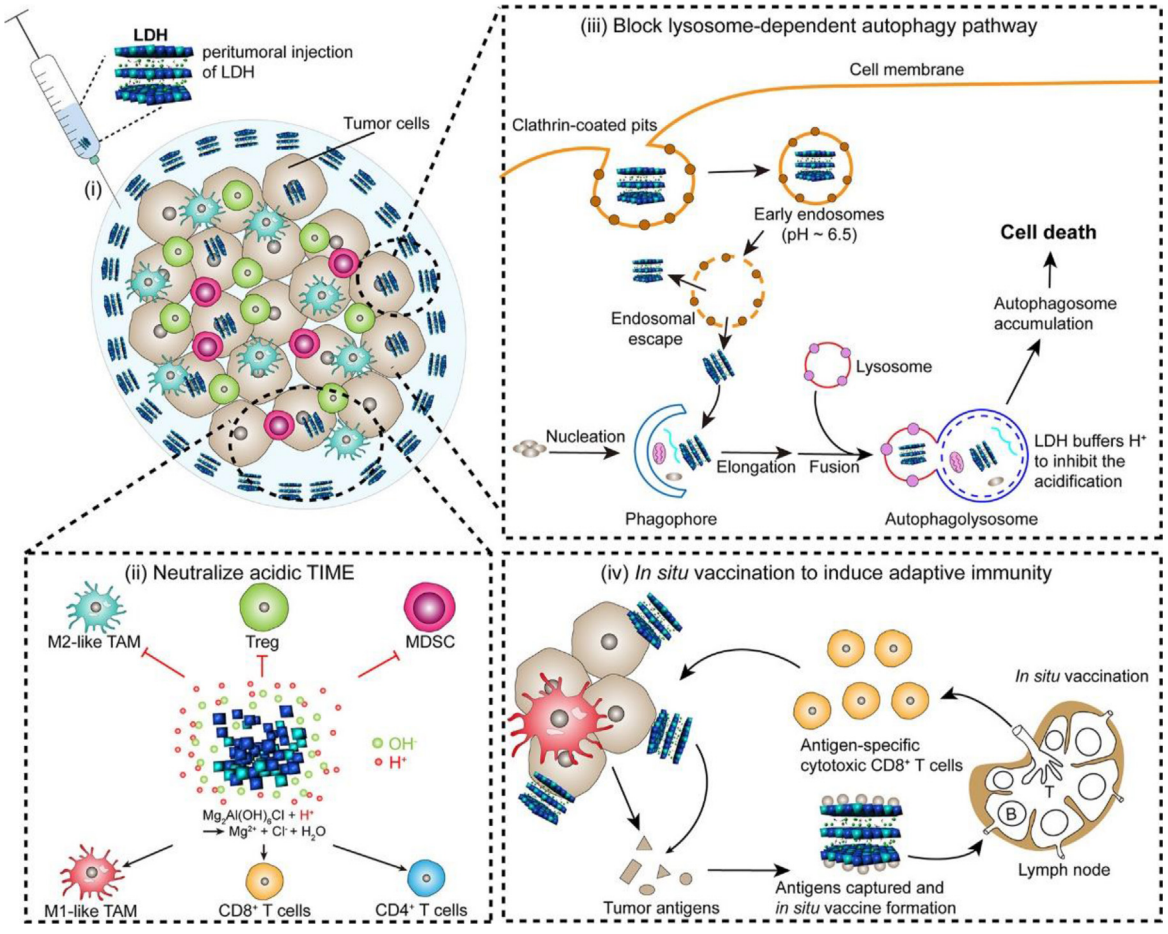

Figure 8 Schematic diagram of anti-tumor mechanism of LDH NPs. (i) LDH NPs were injected into the tumor, and LDH NPs gradually infiltrated around the cells from the inner zone to the outside. (ii) OH− released by hydrolysis of LDH NPs neutralized H+ extracellular at TIME and reshaped the immune microenvironment. (iii) LDH NPs further interfered with the fusion of autophagy and lysosomes by hindering the acidification of lysosomes in tumor cells, thus destroying autophagy and promoting tumor cell death. (iv) Tumor antigens released from dead tumor cells were captured by LDH NPs to form an *in situ* vaccine, which then induced an anti-tumor immune response. Reprinted with permission from Ref. 203.

therapeutic effects. Therefore, relying on autophagy to regulate immune cells could inhibit tumor cells and prolong the survival time of cancer patients. In addition, a nanotherapeutic agent composed of cyanic acid and solid calcium carbonate, which is equivalent to a calcium ion nano-generator, was constructed[308]. These nanotherapeutics enhanced antigen cross-presentation to augment immunotherapy in various ways, one of which was the inhibition of autophagy in DCs *via* calcium ions-mediated direct destruction of lysosomes[309]. Therefore, the combination of autophagy modulation and immunotherapy is a prospective therapy for cancer treatment.

As a non-negligible modulator of the immune system, autophagy is involved in maintaining the homeostasis, activation, and physiological functions of immune cells. Preclinical studies suggest that the combination of autophagy modulation and immunotherapy has great potential for future tumor treatment. However, due to the dual nature of autophagy, modulating autophagy may also diminish the effectiveness of immunotherapy, which depends not only on the cancer type but also on the individual's constitution and tumor progression. Therefore, the mechanism of the interaction between autophagy and the immune system still needs to be further explored, and more immunological indicators should be included in the monitoring of autophagy modulation in combination with immunotherapy to provide a research basis for the selection of appropriate autophagy modulation strategies.

4.4. *Combination of autophagy and sonodynamic therapy (SDT)*

As an emerging non-invasive therapeutic approach, SDT is characterized by precise targeting, safety, and high efficiency[310,311]. This therapeutic modality achieves precise and thorough tumor killing through localized focused ultrasound to the focal area, which activates the acoustic sensitizers ingested into the tumor cells, leading to the generation of ROS and calcium overload, and then destroys the tumor cells as well as the microvasculature[312,313]. The treatment modality is also known for its ability to induce macromolecular damage in the tumor cells, which may lead to the activation of protective autophagy. Unfortunately, this induced damage may activate the protective autophagy of tumor cells, rendering SDT much less effective. Therefore, combining autophagy inhibitors and SDT provides a solution for tumor resensitization and improves the efficacy of SDT.

A liposome containing the sonosensitizers protoporphyrin IX (PpIX) and the early autophagy inhibitor 3-MA was constructed, in which 3-MA effectively inhibited cellular pro-survival autophagy induced by sonosensitizers-augmented SDT[314]. It was shown that 3-MA significantly reduced the resistance of cancer cells to oxidative stress of SDT. On the other hand, autophagy-induced apoptosis in cancer cells had a significant synergistic effect on SDT-induced apoptosis. In addition, the PpIX/3-MA@Lip group inhibited MCF-7 tumors *in vivo* by 89.32% under ultrasound exposure, which was significantly higher than that of the other control groups. Similarly, hollow polydopamine-based nanotherapeutics loaded with acoustic sensitizers Ce6 and autophagy inhibitor CQ with homologous tumor cell membrane modification (CCP@HP@M) were constructed, where CQ inhibited SDT-induced protective autophagy while enhancing its induced apoptosis[181]. *In vivo*, results demonstrated that CCP@HP@M significantly inhibited the growth of colon tumors under ultrasound exposure.

Due to the dual effects of autophagy on tumors, the efficacy can also be improved by converting therapeutic agent exposure-induced protective autophagy into death-promoting one. An oxygen economizer (HMME@HMONs-3BP-PEG, HHBP) was constructed by coupling the respiratory inhibitor 3BP with hollow mesoporous organosilicon nanoparticles (HMONs) and then loading an organic acoustic sensitizer hematoporphyrin monomethyl ether (HMME), and finally by surface modifying with PEG, wherein HHBP could induce quenching of autophagy and thus enhance the antitumor effect of SDT. The results of *in vivo* experiments showed that HHBP and under ultrasound exposure resulted in 89.1% tumor inhibition in a 4T1 xenograft breast cancer model[315].

Studies involving SDT combined with autophagy have shown its potential for future clinical applications. However, the low biosafety and ROS generation rate of most acoustic sensitizers, their efficacy is not sufficient to replace conventional antitumor therapies. As a result, SDT has not been widely implemented in clinical practice. Given that the ROS generation rate is largely limited by the hypoxic microenvironment at the tumor site, the development of novel acoustic sensitizers with higher ROS generation capacity and the ability to synergize with autophagy to generate oxygen is the way forward.

4.5. *Combination of autophagy and other therapies*

Tumor starvation therapy (TST) is proposed based on the fact that tumor cells require more energy compared to normal cells due to their abnormal growth and proliferation[316]. When the supply of nutrients required by tumor cells is cut off, their metabolism becomes defective to the extent that they are unable to grow and proliferate properly, which ultimately leads to cell death. However, to compensate for nutrients to maintain normal metabolism, cancer cells will trigger protective autophagy in an attempt to reestablish homeostasis and weaken such treatment[317]. The combination of autophagy inhibitors with TST is, therefore, expected to address this issue. For example, autophagy inhibitor black phosphorus (BP) nanosheets loaded with glycolysis inhibitor 2-deoxy-D-glucose (2DG) blocked the protective autophagic flux and compensatory energy supplies, causing tumor cells to fail to extract their nutrient to feed themselves, finally succumbing to therapeutic interventions and starving to death[318]. A nanoenzyme (Cur@MOF-GOx/HA) was constructed *via* curcumin-supported MOF and surface modification with glucose oxidase (GOx) and hyaluronic acid (HA), which led to tumor starvation through GOx that catalyzed the conversion of glucose to H_2O_2 and gluconic acid. Importantly, the protective autophagy induced by TST can be hyperactivated with the loaded curcumin, thereby shifting it from survival promotion to growth inhibition[319]. *In vivo* experimental results showed that Cur@MOF-GOx/HA led to a 75.3% tumor inhibition rate in the 4T1 xenograft breast cancer model, much higher than that of the free GOx and Cur group.

Gas therapy (GT) is a novel "green" anticancer treatment strategy. It has been found that gas transmitters, as endogenous biomessengers, can regulate various physiological functions of the body and maintain homeostasis without adversely affecting normal organs and tissues[320,321]. In addition, they can exert specific anticancer effects when their concentration exceeds a certain threshold. Currently, a range of gas molecules have been used in GT, including oxygen (O_2)[322,323], nitric oxide (NO)[324,325], carbon monoxide (CO)[326,327], sulfur dioxide (SO_2)[328,329], and hydrogen sulfide (H_2S)[330,331]. Due to the diffusive properties of gas molecules, researchers have also attempted to combine GT with various therapeutic approaches, such as autophagy, to enhance the effectiveness of the treatment. For example, a dual light-activatable

perylenediimide derivative (P-NO) was developed for NO-enhanced PTT[332]. In an aqueous solution, it self-assembles into nanoparticles that release NO and photothermal molecules (P-NH) under green light irradiation, which activates the photothermal effect and inhibits protective autophagy of the cell, thus enhancing the therapeutic effect of PTT in the NIR light. *In vivo* experiments, P-NO inhibited tumors in the 4T1 xenograft model by up to 87.2%.

4.6. Combination of autophagy and multiple therapeutics

The combination of autophagy modulation with single therapies is usually unsatisfactory. Therefore, an emerging number of studies have been carried out to combine autophagy with multiple therapies simultaneously[333]. A novel mesoporous magnetic copper ferrite nanoparticle ($CuFe_2O_4$NP) loaded with CQ has been developed, which concurrently integrates magnetic hyperthermia therapy (MHT), chemodynamic therapy (CDT), and autophagy modulation to synergize cancer treatment[188]. In tumor cells, the system promoted the mass production of ROS *via* the Fenton redox process in which Cu^{2+} and Fe^{3+} ions participate (Fig. 9). In addition, the autophagy inhibitor CQ could weaken the resistance of cancer cells to oxidative stress, contributing to the mild MHT performed at 45 °C. Furthermore, the increase in temperature promoted the generation of hydroxyl radicals, which contributed to the synergy between CDT and MHT. The results of *in vivo* experiments showed that the inhibition rate of the nanotherapeutic group ($CuFe_2O_4$NP) under the effect of alternating magnetic field (AMF) was as high as 67.63% in mice inoculated with a 4T1 tumor model.

Hierarchical nanocomposites combining autophagy with multiple therapies provide another alternative to improve the antitumor effects. A layered assemblage of biomineralized nanocomposite (PCNP) was constructed to realize the synergistic antitumor effect of PTT, chemotherapy, and autophagy inhibition[189]. After loading the hydrophobic chemotherapeutic agent of docetaxel (DTX) into the calcium phosphate (CaP) nanoparticles, PDA was allowed to be distributed onto the surface of the CaP by self-assembly. Subsequently, the autophagy inhibitor of CQ was absorbed onto the PDA surface through non-covalent interaction to form PCNPs/DC. The acid-sensitive CaP core of PCNP and the photothermal effect of PDA coating make it dual pH/thermal responsive. Through blocking lysosomes and impairing autolysosomal degradation with PCNP/DC, effective autophagy inhibition in MDA-MB-780 breast cancer cells was achieved.

In addition to these combination regimens, some studies have combined chemotherapy, autophagy, and immunization to achieve significant antitumor effects[334]. For example, an immunochemotherapy regimen-based redox-responsive nanoassembly was developed (R-mPDV/PDV/DOX/siL), wherein LDHA siRNA inhibited cytokine-mediated MDSCs recruitment and DOX elicited ICD[335]. Interestingly, it was also found that R-mPDV/PDV/siL reduced the production of G-CSF and GM-CSF recruited by myeloid-derived suppressor cells (MDSCs) *via* autophagy-associated pathways. *In vivo*, experimental results demonstrated that the nano assemblies inhibited the 4T1 orthotopic tumors by up to 85.41%.

As mentioned above, the integration of multiple therapeutic agents into a combo nanotherapeutic system is superior to monotherapy. However, some potential drawbacks may hinder its further clinical application. First, it is not easy to demonstrate the synergies between multiple therapeutic agents and to identify the contribution of each. Second, the mechanism of multiple approaches is more complex than that of a single therapeutic agent, which may lead to more toxicity and adverse effects. Third, ensuring the consistency of each component is a great challenge for future industrial production and quality control. Therefore, manifold issues need to be addressed for the rational design of nanotherapeutic systems that combine autophagy with multiple therapies.

Studies have identified that autophagy is closely associated with tumorigenesis[336], drug resistance[337,338], and tumor migration[339]. Unfortunately, there are few clinical applications of autophagy for tumor treatment currently. It is known that only two small molecule drugs, CQ and HCQ, have been used as autophagy inhibitors in clinical studies for antitumor therapy[340]. In addition, the use of autophagy inhibitors alone often fails to meet clinical therapeutic requirements. For example, it was found that HCQ alone did not significantly improve the efficacy of tumor therapy in patients with previously treated metastatic pancreatic cancer[341,342]. Encouragingly, several successful phase I/II clinical trials have confirmed the efficacy of autophagy inhibitors in combination with chemotherapeutic agents. In a phase I/II trial of gemcitabine in combination with HCQ in patients with pancreatic adenocarcinoma, administration of gemcitabine and HCQ at 1200 mg q.d. was found to be safe and well tolerated, and overall survival was improved in patients with a 51% increase in the autophagy marker LC3-II[343]. Besides, a phase I clinical trial of HCQ in combination with temozolomide (TMZ) in patients with advanced solid tumors and melanoma demonstrated that HCQ and TMZ were effective in combining HCQ with chemotherapy. In addition, a phase I trial of HCQ in combination with temozolomide (TMZ) in patients with advanced solid tumors and melanoma demonstrated that the combination was safe and well tolerated and that inhibition of autophagy in patients showed significant antitumor activity.

In addition, there are some clinical trials combining autophagy inhibitors with radiotherapy, but the results are not satisfactory. The Phase I clinical trial of CQ combined with radiotherapy and TMZ for glioblastoma was terminated due to the adverse reaction caused by CQ[344]. The available clinical trials indicate that the use of autophagy inhibitors alone has little efficacy in the treatment of tumors, and the combination of autophagy inhibitors with other therapies should be emphasized. Moreover, there are some limitations in the clinical application of autophagy inhibitors in cancer therapy. First, when administered systemically, the level of autophagy inhibitors in the patient's tumor should be sufficient to inhibit autophagy[345]. Second, due to the complexity of autophagy, it should be ensured that autophagy does not interfere with normal tissues, especially in patients with chronic diseases. Finally, due to the specificity of patients, the characteristics of autophagy may change, which is not conducive to achieving the desired therapeutic outcome, so it is necessary to strengthen the research on autophagy detection methods.

5. Conclusions and outlooks

As a unique cell survival pathway, autophagy has dynamic degradation and quality control mechanisms. Generally, autophagy is dynamic in the process of tumorigenesis and development, acting as a tumor suppressor in the early stage and a tumor promoter in the process of tumor maintenance. From the existing basic research and clinical trials, the effect of cancer treatment by autophagy modulation alone is not satisfactory, and its combination with other therapeutic methods is the current trend of application. Nanotherapeutics-based autophagy modulation is expected to be a

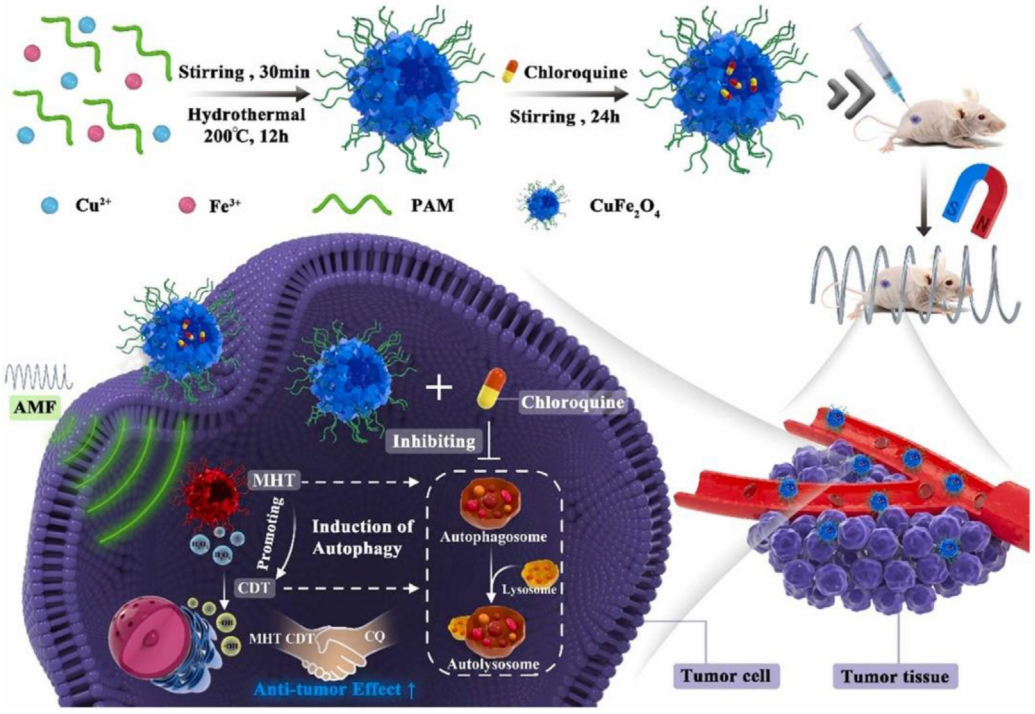

Figure 9 Schematic diagram of the preparation process and simplified action mechanism of CQ@CuFe2O4NP, which treats cancer through the synergistic action of CDT, MHT and autophagy inhibitor. Reprinted with permission from Ref. 188. Copyright © 2022 Elsevier Ltd.

novel cancer treatment strategy. So far, although the effectiveness of this treatment still has some potential limitations and is not satisfactory, the emergence of the new approach has brought hope and offers an alternative strategy with unlimited potential for improving patient survival. Therefore, it is necessary to summarize the latest advances in nanotherapeutics targeting autophagy to provide a timely reference for cancer clinical therapies.

Even though autophagy-based nanotherapies are on the rise, there are still some problems that need to be addressed. First, the signaling pathways involved in autophagy are usually not single and independent but rather intertwined. As mentioned previously, the mechanisms described in Sections 3 (i, ii, and iii) of this article all depend on the involvement of mTOR and ATG. Besides, due to the dual role of autophagy, it may have opposite effects on various cancer cells as well as distinct development stages of the same cancer cell, which is a great challenge to its clinical application. Second, since CQ and its derivative HCQ are the only autophagy inhibitors approved for clinical use so far, most of the existing clinical trials are based on their combination with conventional anticancer therapies. However, the unavoidable toxic side effects of these compounds also contribute to the failure of such clinical trials. Therefore, it is urgent to further investigate the interaction mechanisms between autophagy and tumor pathology and to develop autophagy inhibitors with better performance. Third, the impact of autophagy on normal tissue function remains to be explored. Treatment-induced autophagy inhibition or autophagy promotion may also lead to nonspecific cytotoxicity. Inhibition of autophagy may also amplify the side effects of therapeutic agents on normal tissues. These suggest the need to improve drug targeting to focal tissues, which is a difficult task for pharmaceutics.

In terms of reported studies on the subject, autophagy usually serves as an adjunct to other adjunct to other therapeutic approaches, including chemotherapy, phototherapy, and immunotherapy. For the assessment of autophagy modulation levels, most studies have been performed only by detecting typical markers such as BECLIN1, LC3, and P62 proteins. Although the therapeutic efficacy of autophagy-based combination nanotherapeutics is acceptable, their potential side effects may be difficult to predict, explain, and overcome due to the lack of detailed studies on the mechanisms of autophagy signaling pathways, which may hinder their clinical applications in the future. Therefore, research on the basic mechanisms of autophagy should be strengthened.

It is also worth noting that reported preclinical trials have shown that combining autophagy inhibitors with other nanotherapeutics indicates broad clinical application prospects. However, autophagy-based cancer nanotherapeutics are not yet fully mature. Close attention must be paid to its potential related issues, including nanobiological interactions, systemic transport of NPs to tumor cells, and targeting of NPs to tumor tissue or premetastatic niches, which will affect the safety and efficacy of nanotherapeutics *in vivo*[257]. In addition, successful clinical applications of nanotherapeutics must consider how to find suitable animal disease models, as well as address the issue of their controllable and reproducible production. In conclusion, although the application of nanotherapeutics targeting autophagy modulation is far from satisfactory or on-demand in improving cancer treatment, it is expected to provide a new alternative pathway to improve the clinical benefit of cancer patients once the issues mentioned are overcome before its clinical translation.

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Author contributions

Yunmeng Liu wrote the manuscript. Yaxin Wang was responsible for reviewing relevant researches. Jincheng Zhang, Taoyuan Yan, and Xiyue Xiao provided manuscript polishing. Kai Shi provided guidance and improved the content of the article. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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