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Targeted regulation of autophagy using nanoparticles: New insight into cancer therapy☆

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ABSTRACT

Normal cells depend on autophagy to maintain cellular homeostasis by recycling damaged organelles and misfolded proteins and degrading toxic agents. Similar to apoptosis, targeting autophagy has been under attention in cancer therapy. However, autophagy has both pro-survival and pro-death functions in tumors, and its targeting requires further elucidation. The current review focuses on using nanoparticles for targeting autophagy in cancer treatment. Nanocarriers can deliver autophagy regulators along with chemotherapeutic agents leading to intracellular accumulation in cancer cells and synergistic cancer therapy. Furthermore, genetic tools such as siRNA and shRNA can be used for targeting molecular components that regulate autophagy, such as the ATG12-ATG5-ATG16L1 complex. A number of nanostructures, such as gold and zinc oxide nanoparticles, can be used to enhance oxidative stress-mediated apoptosis and autophagy, reducing cancer progression. Further, using nanoparticles to modulate autophagy potentiates the anti-tumor effects of cisplatin and gefitinib during chemotherapy. Polymeric nanoparticles, lipid-based nanostructures and carbon-based nanomaterials are among other nanoparticles capable of regulating autophagy in cancer cells. Of note, various regulatory components of autophagy such as ATGs, Beclin-1 and LC3-II can be affected by nanomaterials. Based on the role of

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nanomaterial-induced autophagy as pro-survival or pro-death, further targeting can potentiate the fight against cancer cells.

1. Introduction

Cells are continuously exposed to various intracellular and extracellular stressors, requiring strategies or mechanisms to maintain homeostasis and prevent cell death [1]. Macroautophagy, referred to here as autophagy, is responsible for the degradation of damaged organelles and misfolded proteins, decomposition of macromolecules such as proteins and the response to intracellular and extracellular stimuli [2–6]. Eukaryotic cells rely on autophagy's housekeeping functions for regulating cellular homeostasis [7]. Hence, autophagy occurs constitutively at low levels in the cell [8]. However, autophagy can be further induced at higher levels to maintain normal cellular function in response to stressful stimuli such as oxidative or metabolic stress [9–12]. Autophagy is a highly-conserved eukaryotic process that functions to degrade and recycle cellular components [13]. This process involves the formation of double-membrane vesicles called autophagosomes which sequester pathogens, cytoplasmic organelles, proteins and macromolecules [14]. The formed autophagosome fuses with acidic lysosomes, which function to degrade and recycle the cargo into metabolites that can be used as biosynthetic precursors for the cell [15–17]. Autophagy is vital for normal cell function, and its dysfunction can lead to the development of various malignancies, including brain dysfunctions [18–20], diabetes [21,22], cardiovascular diseases [23–26], viral infection [27–30], and more importantly, cancer [31–35]. Therefore, targeting and regulating autophagy is essential in disease therapy [36–39]. To date, various strategies, with the help of gene therapy or compounds, have affected autophagy in disease therapy. Chloroquine [40,41], rapamycin [42] and naturally occurring compounds including berberine [20], curcumin [43] and resveratrol [44] are examples of agents that have been developed for autophagy regulation and disease therapy. Furthermore, autophagy can be regulated by targeting genes using technologies such as small interfering RNA (siRNA), short-hairpin RNA (shRNA) and CRISPR/Cas9 system [45–47]. However, there are biological barriers in cancer cells that pose a direct challenge in treatment, requiring targeted delivery systems to overcome them [48–50]. Moreover, compounds administered in autophagy regulation often suffer from poor bioavailability that can benefit from the use of nanoparticles for their delivery [51]. Nanoparticles have the capacity to regulate autophagy [52,53]. Hence, the role of nanoparticles in autophagy regulation and their ability as targeted delivery systems should be investigated. In the present review, we aim to focus on autophagy regulation by nanoparticles. First, we provide an overview of the autophagy machinery, related molecular pathways, and its role in oncology. Then, we describe how nanoparticles can be used to regulate autophagy for cancer treatment.

2. Autophagy machinery

There are three distinct types of autophagy in mammalian cells: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) [54–56]. All of which function to deliver cargo to the lysosome for degradation and recycling. Of the three types, macroautophagy (simply as autophagy) is the best studied and will be the focus of this review. Autophagy is a molecular mechanism for decomposition and involves several regulatory proteins [57,58]. Thus, their identification is vital for targeted therapeutic strategies aimed at perturbing autophagic mechanisms of the cell. Many cellular stressors such as starvation and metabolic stress can lead to autophagy activation via overexpression of 5′-AMP-activated protein kinase (AMPK) and the subsequent induction of unc-51-like autophagy-activating kinase (ULK1). The ULK1 is a complex containing ULK1, FIP200, autophagy-related gene 13 (ATG13) and ATG101. The ULK1 complex induces Beclin-1 expression, which leads to the formation of class III phosphoinositide 3-kinase (PI3K) VPS34 complex consisting of Beclin-1, VPS34, VPS15 and ATG14L [59–61]. This process is a requirement for the initiation of phagophore formation. It has been reported that AMPK can suppress the mammalian target of rapamycin (mTOR) pathway and induces autophagy [62]. Formation of the autophagosome is mediated by lipidation of light chain 3-I (LC3-I) to form LC3-II. ATG5 and ATG16L1 are directly involved in modifying LC3-I and the subsequent emergence of the autophagosome machinery [63–66]. Next, the autophagosome fuses with a lysosome. This fusion is induced by proteins such as lysosomal-associated membrane protein 2 (LAMP2), soluble NSF attachment protein receptors (SNAREs), as well as homotypic fusion and protein sorting/vacuolar protein sorting complex. A variety of enzymes are required to degrade autophagosome cargo, such as proteases, acid phosphatases, lipases and nucleases (Fig. 1) [67].

Autophagy's dual role as a tumor-promoting and a tumor-suppressing factor in cancer cells makes it a particularly complex issue, with its ultimate function being context-dependent. One experiment may highlight autophagy induction as a promising strategy in cancer treatment, while another experiment may suggest autophagy inhibition in cancer therapy. Hence, the exact role of autophagy in cancer should be determined before regulatory methods are explored [67–70]. Autophagy continuously interacts with other cell death types. For example, autophagy activation stimulates ferroptosis in pancreatic tumors [71]. It is worth mentioning that the type of autophagy taking place, either tumor-promoting or tumor-suppressing, determines the response of cancer cells to therapy and should be considered in further experiments [72]. The inhibition of the PI3K/Akt/mTOR axis by anti-tumor compound ziyuglycoside II induces both apoptosis and autophagy in colorectal cancer [73]. Another anti-tumor compound, known as dihydroartemisin can also stimulate tumor-suppressor autophagy in cervical and endometrial cancers [74]. There are interactions between autophagy genes and cell cycle regulators such as cyclin-dependent kinase 1 (CDK1) and cyclin B. In enhancing cell cycle progression of cancer cells, CDK1 can stimulate mitotic autophagy via phosphorylating ULK1/ATG13 complex [75]. Inhibition of tumor-promoting autophagy can be induced in hypoxic regions of tumor microenvironment, increasing radiation sensitivity of bladder cancer cells [76]. However, this complexity illustrates the “double-edged sword” nature of autophagy in tumors and autophagy regulation depends on its activity [43,77–83].

Based on the experiments, autophagy and apoptosis often occur during cancer progression or inhibition [84]. These mechanisms show interactions with each other in various tumor cells that need to be clarified due to dual function of autophagy and developing novel therapeutics in near future. According to new experiments, apoptosis induction and stimulating pro-death autophagy can significantly decrease survival of glioma cells, as one of the malignant brain tumors [85,86]. Autophagy with tumor-suppressor function can boost apoptosis in tumor cells. A recent experiment has shown that rapamycin enhances miRNA-26-5p expression to down-regulate DAPK1 that is of importance in triggering autophagy and subsequent decrease in cell proliferation and viability via apoptosis induction. In fact, autophagy induction boosts apoptosis in glioma cells [87]. However, pro-survival autophagy may prevent apoptosis in tumor cells. Matrine is an anti-tumor agent that induces apoptosis in reducing breast cancer progression. Notably, matrine simultaneously induces autophagy that functions as a pro-survival mechanism in breast cancer [88]. In this case, autophagy inhibition can be beneficial in promoting cytotoxicity of matrine against breast cancer cells [88]. Another experiment reveals role of autophagy in potentiating apoptosis in breast cancer [89]. The autophagy and apoptosis regulation and interaction can also be observed in lung cancer

[90]. Based on a new experiment, down-regulation of Akt and Hedgehog molecular pathways by Jervine leads to autophagy-dependent apoptosis in lung cancer cells [91]. In bladder cancer, autophagy and apoptosis interaction determines therapy response [92] and ROS overgeneration by artenusate can induce autophagy-mediated apoptosis in restricting bladder cancer progression [93]. A same phenomenon occurs in prostate cancer and therefore, autophagy and apoptosis interaction can affect proliferation and progression of various tumor cells [94–96]. The following sections focus on the use of nanoparticles in autophagy regulation and merge the evolving fields of bioengineering and medicine concerning cancer treatment.

3. Pre-clinical models of autophagy

Animal models have been developed for studying autophagy, an emerging target in cancer therapy, and its mechanisms in pre-clinical stages. Animal models broaden our understanding of the physiological and pathological roles of autophagy. Two kinds of mouse models have emerged for examining autophagy in vivo, including "autophagy-monitoring mice" and "autophagy-deficient mice". ATG4b-c KO, TNF-α Tg, SumF1 KO, Dram2 KO, Nlrp3 KO, PiK3c3 KO, 2045 and CIEA NOG mice have also been developed for investigating autophagy [97–105]. A relatively new type of autophagy, known as mitophagy, selectively targets mitochondria [106]. Notably, two kinds of mouse models are used to investigate mitophagy, including mt-Keima transgenic mice and *mito*-QC transgenic mice [107,108]. In addition to genetic modification to produce mouse models for studying autophagy, another method that has contributed to understanding the role of selective autophagy in vivo is to manipulate specific receptors such as SQSTM1/p62, OPTN and BCL2L13 [107,109–111]. However, there are challenges with using in vivo mouse models in evaluating autophagy. For instance, living organisms cannot be scrutinized in terms of alterations in organelles to monitor autophagy, and experimental manipulation in mammals is complex. Thus, zebrafish has emerged as a new model for evaluating autophagy, mitophagy and other types of autophagy in vivo [112]. Primate models are also of importance for studying autophagy and revealing its role in physiological and pathological events. For instance, monkey kidney MARC-145 cells have been applied as cell models for evaluating toxicity of fumonisin B1 and understanding autophagy function. Autophagy inhibition can reduce cell death in monkey kidney cells exposed to fumonisin B1 [113]. The primate models are also beneficial for evaluating autophagy role in neurological diseases. In cynomolgus monkey brains, autophagy level significantly diminishes before amyloid plaque formation, showing that autophagy inhibition is an important step for neurological disease development in primates [114]. A new experiment has used adult *Macaca mulatta* for autophagy activation status and its role in periodontits lesions [115]. Therefore, primate models (in vitro and in vivo) can be utilized along with other models to improve our understanding of autophagy function in diseases [116,117].

4. Nanomaterials and autophagy regulation

4.1. Polymeric nanoparticles

In recent decades, polymeric nanoparticles have demonstrated considerable potential in cancer therapy via the delivery of various therapeutics and their role in imaging [118]. Different polymers can be used to synthesize polymeric nanoparticles such as collagen, gelatin, PLGA and albumin [119,120]. These polymeric nanostructures can mediate the co-delivery of anti-tumor agents such as chrysin and 5-fluorouracil in combination cancer therapy [121]. The efficacy of polymeric nanoparticles in cancer treatment is highlighted by their photodynamic therapy potential [122]. Like other nanoparticles, polymeric nanoparticles can easily undergo surface modification in targeted cancer therapy [123]. Furthermore, stimuli-responsive polymeric nanoparticles add to their function of cancer suppression [124]. This section describes the role of polymers in the synthesis of nanocarriers and evaluates their potential for delivery of autophagy regulators in cancer treatment. Although chitosan (CS) and hyaluronic acid (HA) are polymers derived from natural sources, we allotted a separate section (3.5 section) to discuss their role in the synthesis and modification of nanoparticles in autophagy regulation.

In cases where autophagy possesses a tumor-suppressor role, the focus is on the induction of this molecular mechanism. For instance, Beclin-1 upregulation induces autophagy and can reduce the viability

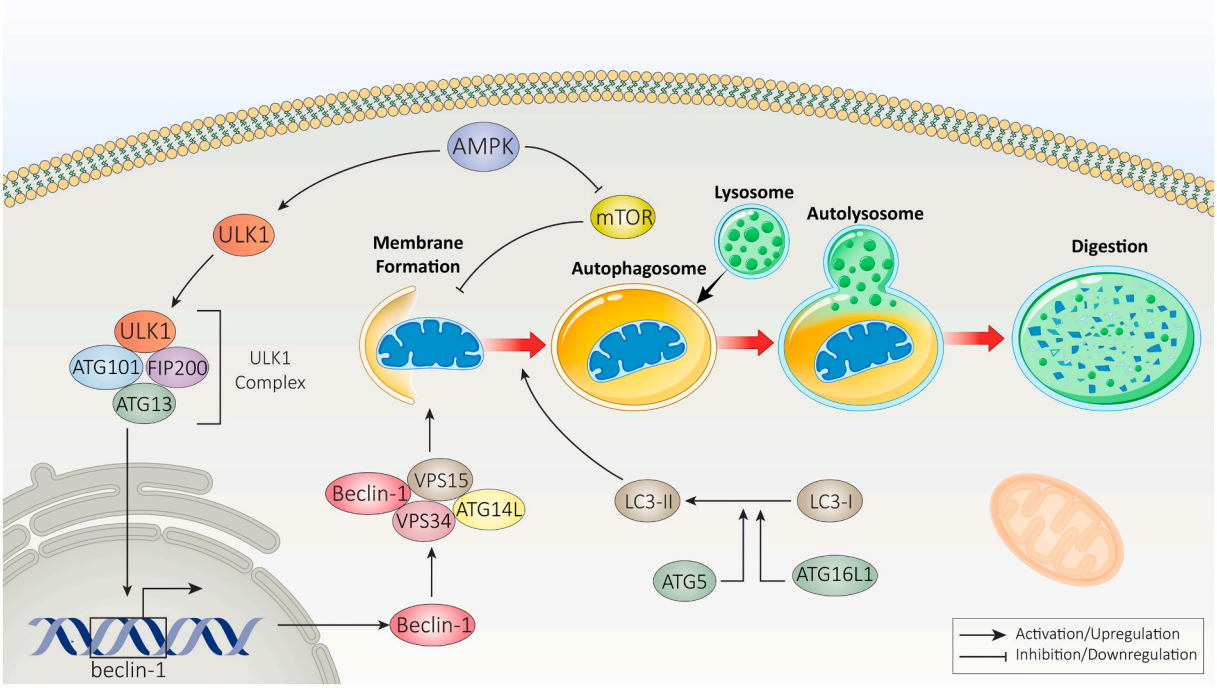

Fig. 1. Molecular pathways of autophagy.

and progression of breast cancer cells in vivo. Therefore, the delivery of Beclin-1 by polymeric nanoparticles is of importance in exerting high anti-tumor activity. In this way, peptide-modified polymeric nanoparticles were prepared using poly(β-amino ester) through supramolecular assembly. Autophagy stimulation by Beclin-1-loaded polymeric nanoparticles significantly diminishes breast cancer progression. The role of polymeric nanoparticles is to protect Beclin-1 against enzymatic degradation, preventing non-specific biodegradation and enhances targeted delivery [125]. In contrast, when autophagy has tumor-promoting role, its inhibition can sensitize cancer cells to chemotherapy. In an experiment, hyperbranched polyacylhydrazone (HPAH) was used to prepare hydrophilic polymeric nanoparticles that are pH-sensitive. Then, doxorubicin (DOX) as a chemotherapeutic agent and LY294002 (LY) as an autophagy inhibitor were encapsulated in these polymeric nanoparticles. Upon penetration into oral cancer cells, cargo (DOX and LY) release occurs in response to acidic pH. These DOX- and LY-loaded polymeric nanostructures synergistically suppressed cancer progression. This experiment demonstrated that autophagy down-regulation using LY is important in enhancing the potential of DOX in oral cancer suppression [126]. Another experiment also prepared polymeric nanoparticles using poly(β-amino ester)s that are pH-sensitive and can self-assemble into polymeric micelles capable of triggering autophagy. Gold (Au) compounds were loaded to these polymeric micelles to increase the potential for cancer suppression. These nanoparticles can penetrate breast cancer cells (MCF-7 cells) and accumulate inside acidic lysosomes. Au-loaded polymeric nanoparticles inhibit autophagosome-lysosome fusion upon protonation of tertiary amines of poly(β-amino ester)s, leading to the dissociation of micelles and subsequent damage of lysosomes. Further, Au inhibits thioredoxin reductase (TrxR) and subsequently elevates ROS generation, leading to autophagy and apoptosis induction in breast tumors. Autophagy suppression increases cellular stressors via excessive depletion of organelles and proteins and triggering cell death (Fig. 2) [127].

It is worth mentioning that the impact of polymeric nanoparticles on autophagy is concentration-dependent and should be considered in cancer therapy. Low concentrations of polymeric nanostructures stimulate autophagy by affecting mTOR signaling, while high concentrations of polymeric nanoparticles lead to autophagic cell death favouring cancer therapy (Fig. 3) [128]. Therefore, it is evident that polymeric nanoparticles are potential regulators of autophagy and apoptosis in cancer therapy, and they can also mediate the delivery of anti-tumor agents regulating autophagy [129].

4.2. Green-modified nanoparticles

Over recent decades, attention has been directed towards using polymers derived from natural sources to synthesize and modify nanoparticles since such nanostructures have high potential for cargo delivery and high biocompatibility [130]. CS is derived from chitin and has two functional groups, including hydroxyl and amine groups [131]. CS has a positive charge and can interact with negatively charged biomolecules [132,133]. This linear alkaline polysaccharide has several beneficial features such as biocompatibility, biodegradability and its ability to undergo changes by different methods using chemicals and enzymes [134–136]. Modification of nanoparticles with CS plays a vital role in potentiating the biocompatibility of these carriers. Furthermore, CS-based nanocarriers can effectively deliver cargo (drug or gene) in cancer therapy [137–139]. It has been reported that CS-based nanoparticles can regulate autophagy in cancer. Exposing Hela and SMMC-7721 cells to CS-based nanoparticles induces ROS overgeneration and stimulates autophagy. Furthermore, CS-based nanoparticles can enhance LC3 accumulation in triggering autophagy. However, it seems that autophagy in this context plays a tumor-promoting role and reduces doxorubicin-mediated apoptosis in cancer cells [140]. Therefore, autophagy inhibition can promote the sensitivity of cancer cells to chemotherapy. Noteworthy, CS-based nanoparticles have demonstrated high efficiency in delivering genetic tools such as siRNA and shRNA [141–145]. Hence, targeting autophagy genes can inhibit cytoprotective autophagy in cancer therapy. It has been reported that co-delivery of shRNA-ATG-5 and gefitinib by CS-based nanocarriers significantly suppresses the progression of lung cancer cells (A549 cells) and increases chemosensitivity. These nanoparticles inhibit autophagy and promote apoptosis [146]. This experiment reveals the interaction between apoptosis and autophagy in cancer cells and demonstrates how tumor-promoting autophagy can function as a shield against apoptosis induction in cancer. Additionally, CS-based nanoparticles have been shown to regulate p62 expression in ovarian cancer using siRNA and enhancing cisplatin (CP) sensitivity [147]. Nanocarriers are important for delivering genetic tools, such as siRNA, that would otherwise be rapidly degraded in the cell. In this way, nanocarriers offer protection against breakdown and optimize internalization into cancer cells [131,148–150]. In a recent experiment, the surface of gold nanoparticles was modified with CS. These nanostructures demonstrated high cytotoxicity against leukemia cells while preserving the state of bone marrow and normal cells. The CS-modified gold nanoparticles were able to increase ROS levels and trigger cell death in leukemia cells. However, increased ROS levels induce autophagy as a tumor-promoting factor [151]. Interestingly, a new experiment showed that the delivery of 5-fluorouracil (5-FU) by CS-based nanoparticles induces autophagy via LC3-II upregulation and is important in reducing the viability of head and neck cancer cells [152]. Nonetheless, future experiments will help to shed more light on autophagy regulation by CS-based nanoparticles in cancer treatment.

HA is a linear glycosaminoglycan that is negatively charged and hydrophilic in physiological conditions [153]. High biocompatibility, biodegradability and lack of immunogenicity are among the benefits of HA, making it an appropriate agent for application in drug delivery systems [154,155]. Further, surface modification of nanoparticles with HA promotes their selectivity towards cancer cells by binding to CD44 receptors [156]. An experiment has prepared PLGA core-shell nanoparticles for co-delivery of chloroquine and receptor-interacting protein kinase 3 (RIP3) in colon cancer therapy. The surface of these nanoparticles was modified with HA to enhance selectivity towards cancer cells. The investigation of molecular pathways revealed that RIP3- and chloroquine-loaded HA-modified PLGA nanostructures could increase the expression of p62 and LC3-II and trigger autophagy (Fig. 4) [157]. Alginate and starch are other types of natural polymers used to modify nanoparticles to deliver autophagy regulators and affect this molecular pathway favouring cancer treatment and enhancing chemosensitivity [158,159].

4.3. Lipid-based nanoparticles

4.3.1. Liposomes

Liposomes were first discovered in 1965 by Bangham. These nanostructures have a shell containing one or several phospholipid bilayers and an aqueous core [160]. Ease of synthesis, biocompatibility, biodegradability and capacity in loading hydrophilic and hydrophobic drugs are among the benefits of liposomes, making them appropriate choices in nanoscale delivery [161–163]. Recently, liposomes have been used in cancer therapy due to their ability to enhance intracellular accumulation of drugs and genes and overcome the blood-brain barrier (BBB) [164]. The selectivity of liposomes towards cancer cells can be improved using surface modification by ligands and aptamers [165,166]. Furthermore, liposome-based nanocarriers have been employed to treat cancer upon approval by the Food and Drug Administration (FDA), showing that innovations in this field can significantly improve the fight against cancer [167]. In this section, we focus on liposomal nanocarriers for delivery of autophagy modulators and subsequent cancer therapy.

The mTOR signaling pathway is an inhibitor of autophagy and consists of two complexes, including mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [168]. mTOR induces signal transducer

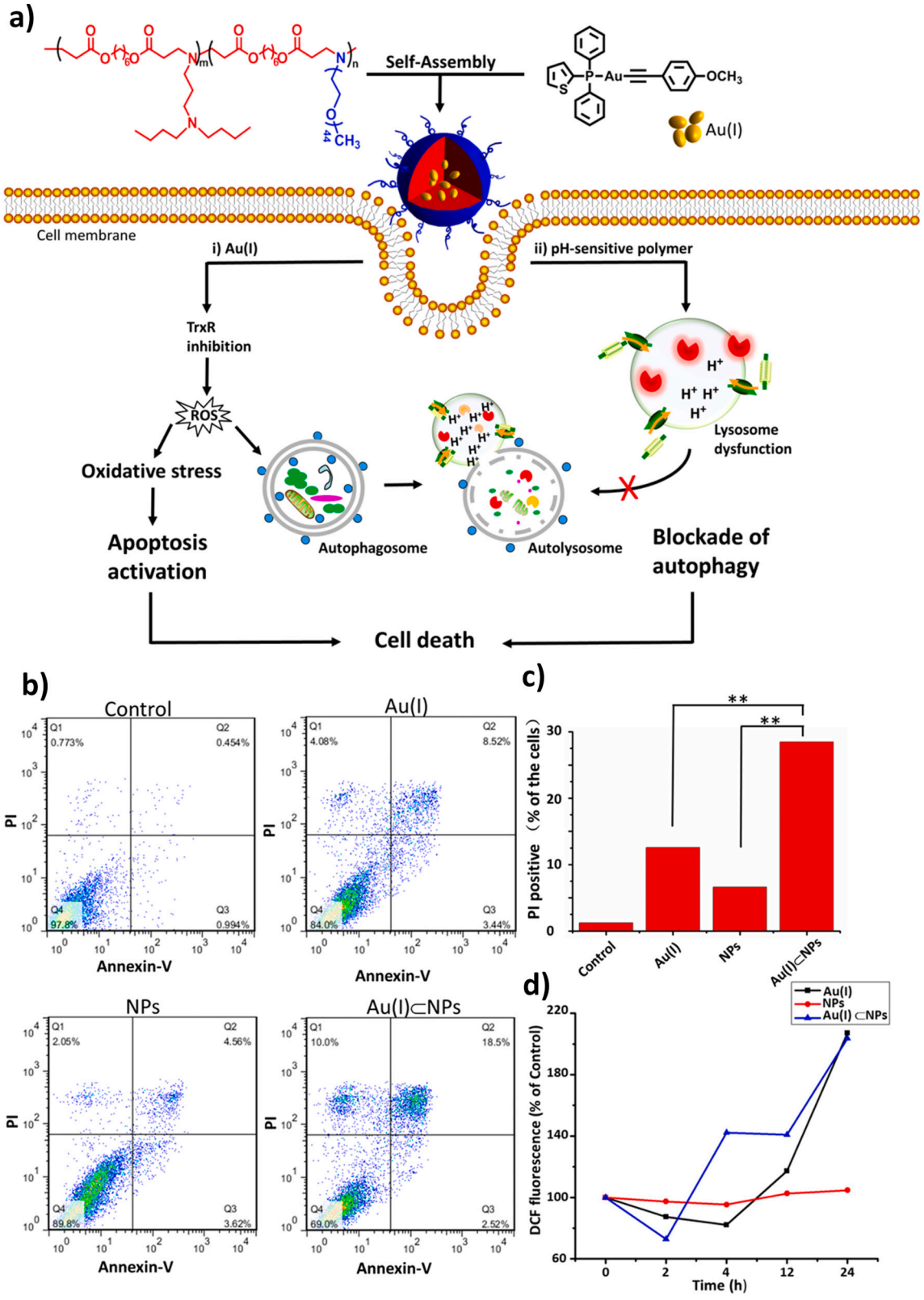

Fig. 2. A) The synthesis of nanostructures and their impact on cell death and providing synergistic cancer therapy; B) Apoptosis assay by Flow-cytometry; C) Quantitative clarification; D) Investigating the level of ROS production in MCF-7 cells after exposing to nanoparticles.
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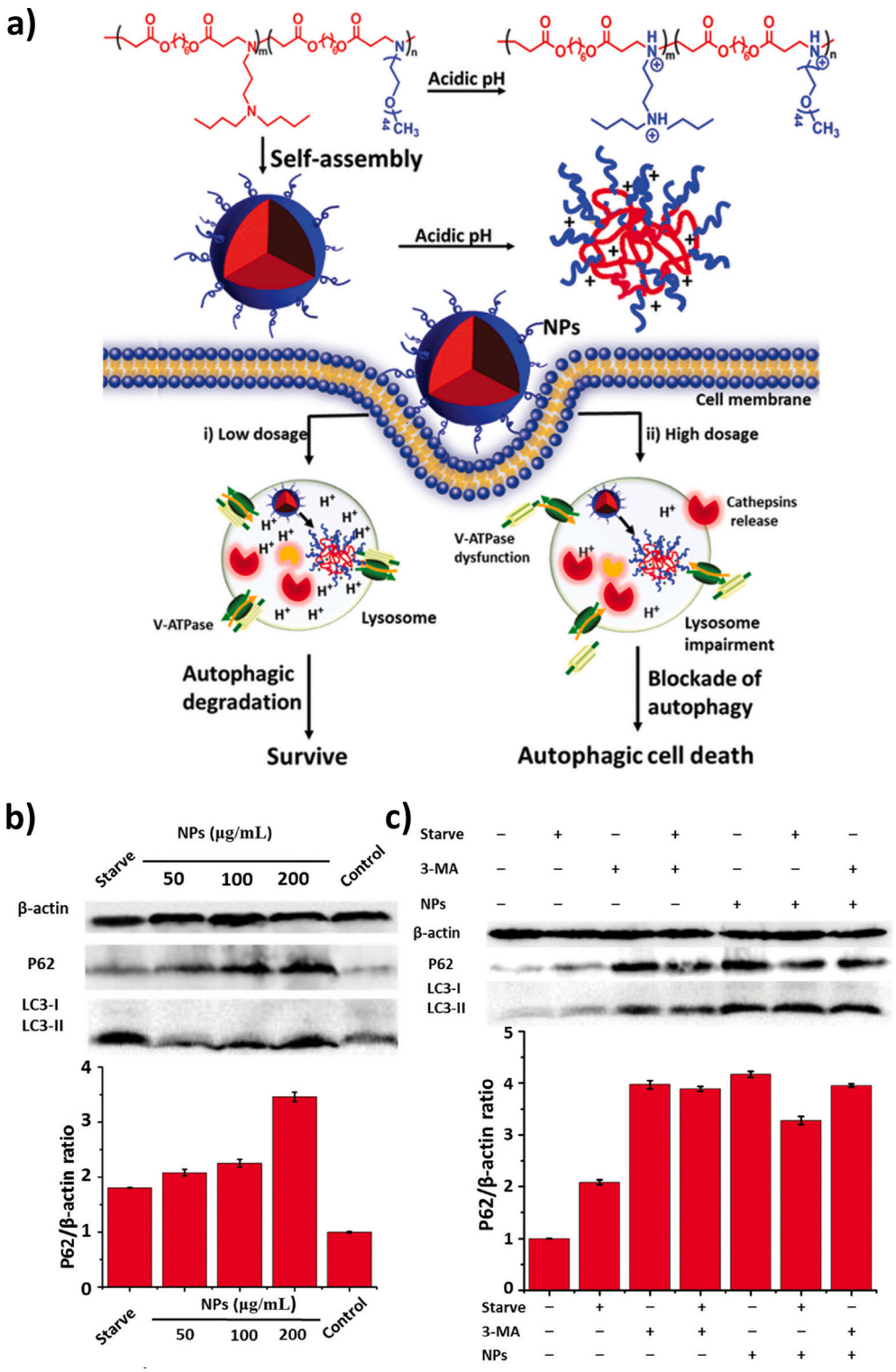

Fig. 3. A) The regulatory impact of prepared nanostructures on autophagy; B and C) The Western blot analysis and quantitative measurement. Reprinted with permission from Wiley [128].

and activator of transcription 3 (STAT3) via phosphorylation at serine 727. Furthermore, phosphorylation at tyrosine 705 can stimulate STAT3 signaling performed by cytokines and growth factors [169]. A recent experiment applied starvation and ropivacaine-loaded liposomes in the treatment of melanoma. JAK2 and mTORC1 stimulated STAT3 signaling following tyrosine 705 and serine 727 phosphorylation, respectively. Exposing melanoma cells to starvation inhibits mTOR signaling, and liposomal nanocarriers suppress JAK2 to disrupt autophagic degradation, enhancing cell death in melanoma cancer [170]. This experiment highlights the anti-tumor activity of autophagy and its role in potentiating cell death. Liposomes can also be used for the co-delivery of anti-tumor agents. For instance, dihydroartemisinin and epirubicin were loaded on liposomes to investigate the effect of apoptosis and autophagy in breast cancer. These nanoparticles enhanced the circulation time of

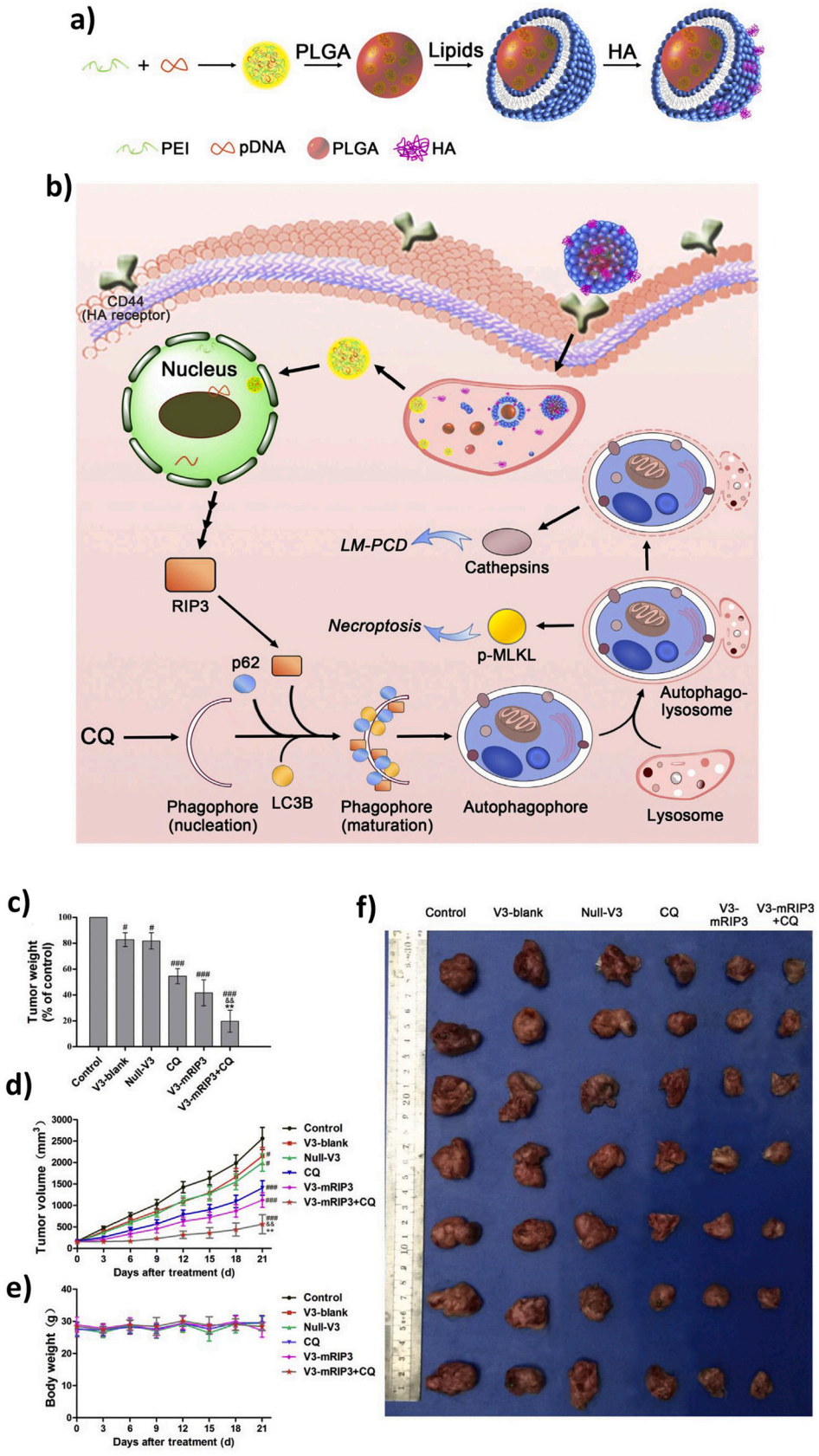

Fig. 4. A and B) Nanostructure synthesis and evaluating their impact on autophagy mechanism; C) Balb/c mouse tumor weight; D) Tumor volume; E) Body weight and F) tumor images.
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these drugs and promoted their accumulation at the tumor site. Furthermore, drug-loaded liposomes down-regulate Bcl-2 activity and accelerate its dissociation from Beclin-1, leading to Bax upregulation. Subsequently, Bax stimulates apoptosis, while Beclin-1 induces autophagy, leading to breast tumor therapy [171].

Furthermore, liposomal nanocarriers can modulate the therapy response of cancer cells by affecting autophagy [172]. Due to their aggressive behavior and high capacity in growth, colon cancer cells can become resistant to chemotherapy [173]. Liposomes are loaded with dihydroartemisin and DOX to suppress the drug-resistant trait in colon cancer cells. As cancer cells demonstrate overexpression of mannose receptors, the liposomal nanocarriers were mannosylated to enhance their selectivity towards colon cancer cells. This combination therapy and their delivery by liposomes effectively suppressed colon cancer progression in vivo by 88.59% and improved the accumulation of DOX in nuclei. The investigation of molecular pathways revealed apoptosis and autophagy induction as factors involved in anti-tumor activity of these liposomal nanoformulations [174]. Although this experiment has not evaluated the association between autophagy and apoptosis in increasing chemosensitivity of colorectal cancer cells, further investigation can show whether autophagy inhibition or induction, along with using the liposomes mentioned above, exert a synergistic impact or not.

Surface modification of liposomes is a promising strategy in the fight against cancer cells. The folate receptor (FR) is upregulated on the surface of cancer cells. Interaction between FR and its ligand folate leads to enhanced penetration into cells via receptor-mediated endocytosis [175–177]. Rapamycin-loaded folate-modified liposomes were prepared using film hydration and used to evaluate their cytotoxicity against bladder cancer cells. The prepared liposomes had a size less than 160 nm with an entrapment efficiency of 42%. The surface modification of liposomes by folate increased their penetration into bladder cancer cells two-fold compared to conventional liposomes. In vivo and in vitro experiments revealed the role of these nanostructures in suppressing cancer progression. Mechanistically, rapamycin-loaded folate-modified liposomes down-regulated mTOR expression to induce autophagy-mediated cancer suppression [178].

The surface modification of nanoparticles with peptides is another candidate for cancer therapy [179]. The role of autophagy in chemoresistance is highlighted by its involvement in forming a barrier for anti-tumor agents. Autophagy induction has been correlated with the production of cancer-associated fibroblasts (CAFs) from pancreatic stellate cells that further generate collagen, increasing stoma density [180–182]. This impediment can induce resistance of pancreatic cancer cells to paclitaxel (PTX) chemotherapy. PTX and the autophagy inhibitor hydroxychloroquine (HCQ) were loaded in peptide-modified liposomes to overcome this barrier. These nanostructures were able to bind to αvβ3 integrins and selectively target tumor microenvironment. HCQ delivery suppressed autophagy and prevented stroma formation, increasing PTX penetration and enhanced cytotoxicity against cancer cells [183]. This experiment highlights a new aspect of autophagy that is not related to cell death but is related to its role in forming a barrier against chemotherapeutic agents.

4.3.2. Micelles

Micelles are another ideal candidate in cancer therapy that belong to lipid-based nanocarriers. By enhancing the intracellular accumulation of anti-tumor compounds, micelles can effectively suppress cancer progression [184]. Furthermore, micelles can mediate the co-delivery of anti-tumor agents, suppressing neovasculature and invasion of cancer cells [185]. Micelles can undergo surface modification, and they induce anti-tumor immunity [186]. Therefore, it is of importance to use micelles in cancer treatment. Recent work has focused on using micelles for the delivery of autophagy regulators. These micelles were prepared using Cu (I)-catalyzed click chemistry-triggered aggregation of azide/alkyne and were loaded with DOX and wortmannin (Wtmn) as the autophagy inhibitor. These nanostructures exhibit an increase in size in a time-dependent manner, elevating cellular uptake by B16F10 and 4 T1 cells. Further, the preparation of micelles using click cycloaddition increases their ability to target the tumor site. DOX- and Wtmn-loaded micelles caused the down-regulation of LC3-II and p62 upregulation, leading to autophagy inhibition and chemosensitivity of cancer cells (Fig. 5) [187]. Inhibiting autophagy is important in protecting cargoes against degradation. For instance, delivery of miRNA-124 and obatoclax by cholesterol-penetratin micelles prevents degradation of miRNA-124 and p62 by autophagosomes, preserving their concentration in breast cancer, inducing apoptosis via Bax and caspase-9 overexpression [188].

Increasing evidence reveals that autophagy induction is associated with docetaxel resistance in cancer cells [189]. In an experiment, polymeric micelles were prepared using membrane dialysis by PEG-b-PLGA. They had a size of 40 nm with an entrapment efficiency of 72.8%. The docetaxel- and chloroquine (autophagy inhibitor)-loaded polymeric micelles inhibited autophagy in breast cancer cells (MCF-7 cells), potentiating the anti-tumor activity of docetaxel. This result showed that chloroquine increased the potential of breast cancer treatment 12-fold [190]. Another study uses micelles for co-delivery of docetaxel and chloroquine to suppress chemoresistance. This study also revealed that using an autophagy inhibitor along with PTX increased breast tumor chemotherapy. The role of micelles is to mediate cellular accumulation [191].

Based on the detection of molecular pathways involved in autophagy, genetic tools such as siRNA can affect the expression level of genes and inhibit or induce autophagy [192]. Nanostructures have been designed for siRNA delivery to improve the potential in gene silencing and cancer suppression, protect against degradation and increase intracellular accumulation [49,131,148,150,193]. The activation of autophagy protects hepatocellular carcinoma cells against apoptosis. Micelles loaded with siRNA-ULK1- and narciclasine-loaded suppress autophagy and enhance the intracellular accumulation of both the drug and siRNA. These nanostructures are pH sensitive and release cargo at the tumor microenvironment. Autophagy inhibition by these micelles sensitizes hepatocellular carcinoma cells to apoptosis [194]. Hence, similar to liposomes, micelles demonstrate high efficiency in delivery of autophagy modulators, and their surface modification enhances tumor targeting. Furthermore, stimuli-responsive micelles and liposomes promote potential in targeting autophagy.

4.4. Carbon-based nanomaterials

4.4.1. Carbon dots

As an abundant element, carbon has various allotropes, and to date, different kinds of agents such as fibers, nanotubes and carbon dots (CDs) have been synthesized from carbon [195]. The CDs belong to quantum dots, and these nanoparticles demonstrate great fluorescence capacity. High biocompatibility, safety, fluorescence activity and particle size less than 10 nm have made CDs appropriate nanocarriers [196]. Recently, attention has been directed towards using CDs in cancer therapy. CDs are essential in the treatment of brain tumors, as they can penetrate the BBB [197]. In cancer suppression, CDs can exert photothermal features to diminish the viability of cancer cells [198]. Furthermore, CDs can induce stress in mitochondria, leading to apoptosis [199]. These nanocarriers can be synthesized from natural sources such as the *Lawsonia inermis* (Henna) plant to increase the biocompatibility and safety profile of CDs [200].

Recently, nitrogen-phosphorous-doped carbon dots (NPCDs) were developed using thermal treatment and their potential for melanoma treatment (B16F10) was evaluated. NPCDs suppressed melanoma progress in a dose-dependent manner and induced apoptosis and cell cycle arrest via promoting ROS production, disrupting mitochondrial function and increasing p21 expression. Noteworthy, NPCDs increase ATG5 and LC3-II expression and diminish p62 expression and induce autophagy in melanoma cells. Hence, apoptosis, autophagy and cell cycle arrest are responsible for the anti-tumor activity of NPCDs against

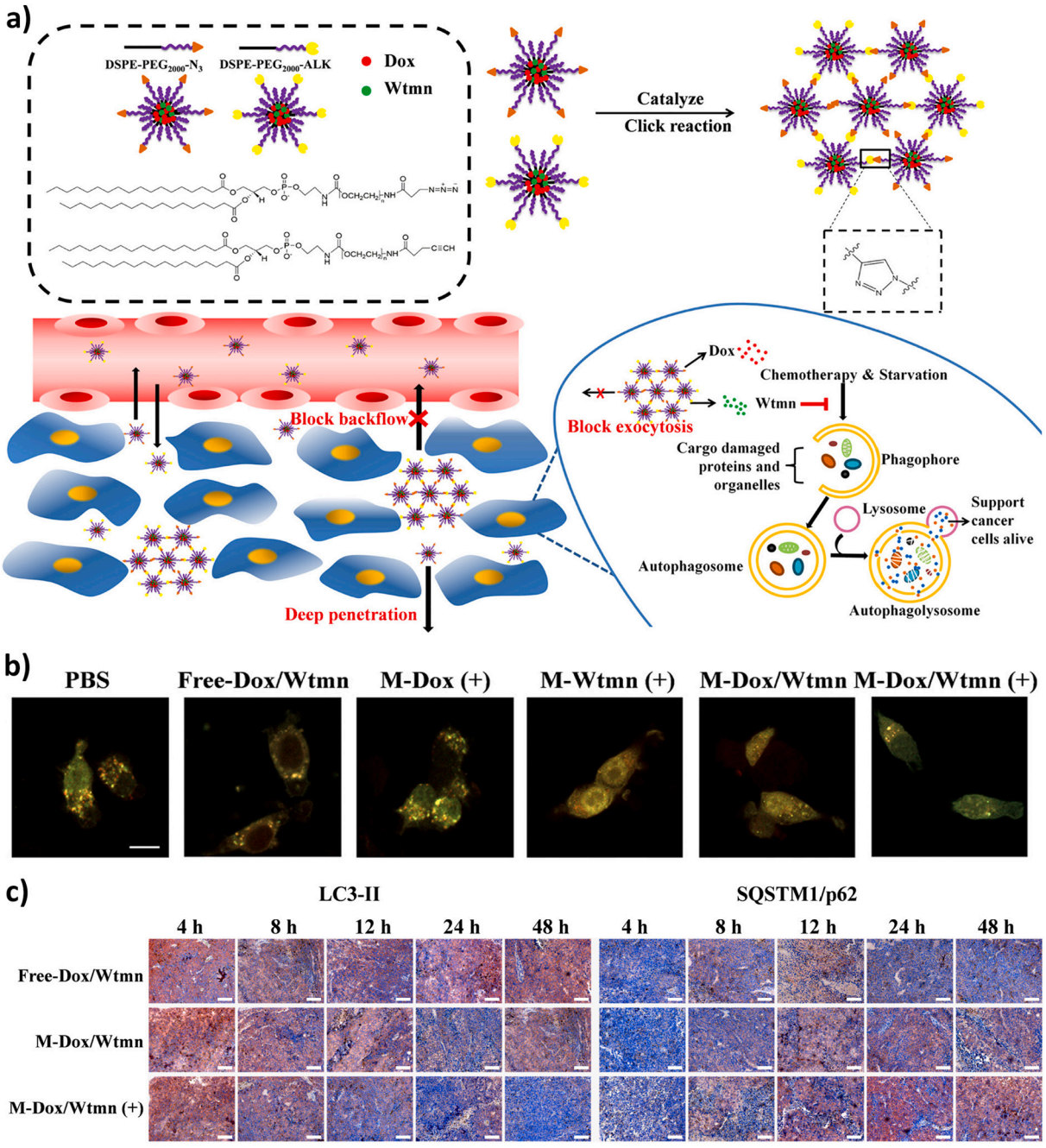

Fig. 5. A) Synthesized nanoparticles and their capacity in regulating autophagy mechanism for cancer therapy; B) CLSM images; C) Immunohistochemical images. Reprinted with permission from Elsevier [187].

melanoma [201]. Quantum dots follow different pathways to suppress cancer progression, and autophagy is among them. In addition to concentration, quantum dots can diminish cancer viability in a time-dependent manner. Notably, various molecular pathways regulating autophagy are affected by quantum dots. For instance, these nanoparticles can inhibit the progression of endometrial cancer by autophagy induction through upregulating ATG12, Beclin1 and LC3-II [202].

It has been reported that quantum dots can be utilized to deliver chemotherapeutic agents such as 5-FU and affect molecular pathways responsible for drug resistance. Increasing evidence demonstrates that autophagy induction significantly enhances 5-FU resistance and various molecular pathways, including long non-coding RNAs (lncRNAs), sirtuin-1 (SIRT1) and BAG3 play a remarkable role in this case [203,204]. Nanocarriers have been developed for co-delivery of 5-FU and autophagy inhibitors to suppress 5-FU resistance and elevate esophageal tumor chemosensitivity [205]. In preventing 5-FU resistance in lung cancer cells, near-infrared (NIR) emitting Ag_2S quantum dots (QDs) have been modified with PEG and their surface modified with Cetuximab (Cet) antibody to increase their selectivity towards cancer cells. The benefit of using Cet for functionalization of QDs is in targeting A549 lung cancer cells and inducing apoptotic cell death. An important aspect of A549 cells is that their treatment with free 5-FU results in autophagy as a cytoprotective mechanism and leads to chemoresistance. However, treatment with Cet conjugated Ag_2S QDs inhibited autophagy and prevented 5-FU resistance in A549 cells [206]. This experiment demonstrates that scientists should always consider the double-edged sword role of CDs and QDs in cancer via autophagy regulation.

The biological behavior of QDs depends mainly on their surface

modification and the type of agent used for coating these nanosized particles. The subsequent change in behavior has been evaluated in an experiment using two various compounds, including 3-mercaptopropionic (MPA) acid and PEG for surface modification and coating of QDs. Exposing HeLa cells (cervical cancer) to MPA-modified QDs inhibited ROS generation and improved the function of lysosomes. However, PEGylated QDs increased ROS generation in favor of autophagy and apoptosis stimulation and exerted cytotoxicity against cancer cells [207]. The efficiency of QDs is attributed to the increased bioavailability of anti-tumor agents in cancer chemotherapy. Recently, an experiment has prepared black phosphorus quantum dots (BPQDs) camouflaged with a platelet membrane (PLTm) for delivery of Hederagenin (HED) in breast tumor treatment (MCF-7 cells). These HED-loaded QDs stimulated autophagy by upregulating Beclin-1 and LC3-II to enhance the anti-tumor activity of HED against breast cancer (Fig. 6) [208]. Future experiments will shed more light on the potential of carbon-based nanoparticles in delivery of autophagy regulators and its association with cancer treatment [192].

4.4.2. Graphene nanomaterials

Graphene is another allotrope of carbon. It has a honeycomb structure with a high affinity for binding and its electrons involved in aromatic conjugate domains [209]. The most well-known strategy for the synthesis of graphene nanomaterials is Hummer's method [210]. Graphene can be functionalized with various polymers, including PEG [211–213]. These carbon-based nanocarriers have high selectivity towards cancer cells and can be utilized to deliver chemotherapeutic agents in cancer therapy [214]. Furthermore, graphene-based nanoparticles can suppress cancer progression by providing photothermal therapy [215]. Advanced graphene nanoparticles, for instance, graphene modified with CS, have been developed to enhance its cancer treatment capacity [216]. Noteworthy, graphene-based nanoparticles can affect cancer survival via targeting autophagy. The phenomenon of drug resistance is an increasing challenge worldwide [49,217–224]. The application of CP in cancer treatment has a long history, but the resistance of cancer cells should be overcome to enhance the cytotoxicity of CP [220,225]. As an upstream mediator, YBX1 stimulates autophagy and reduces CP cytotoxicity against non-small cell lung cancer cells [226]. Furthermore, autophagy inhibition by hederagenin elevates CP cytotoxicity against lung cancer [227]. Graphene oxide nanostructures have been shown to activate autophagy, enhance CP cytotoxicity against colon cancer cells, and mediate necrosis [228]. This experiment demonstrates the double-edged sword nature of autophagy in CP exposure, and there is no absolute consensus about autophagy inhibition or induction in this case. Therefore, more studies are required to reveal the role of autophagy during CP chemotherapy. Another experiment also highlights the fact that autophagy stimulation elevates CP cytotoxicity. In this way, authors prepared hybrid nanocomposites containing graphene and silver nanoparticles that increase ROS generation in cervical tumors, thereby stimulating apoptosis and autophagy. This nanocomposite and CP exert a synergistic impact on cancer suppression [229].

Various molecular pathways regulating autophagy are affected by graphene nanostructures in cancer therapy. The upregulation of ATG5, ATG7 and LC3-II by graphene nanoparticles leads to autophagy and osteosarcoma suppression [230]. In the case of tumor-promoting autophagy, its inhibition remarkably inhibits cancer progression. An experiment has applied graphene nanoparticles for the delivery of miRNA-101 in breast tumor therapy. These nanoparticles were functionalized by PEG and poly-l-arginine (P-l-Arg) to prepare cationic graphene nanoparticles capable of forming stable complexes with miRNA-101. Autophagy inhibition, apoptosis induction and the triggering of thermal stress mediated by graphene nanoparticles were involved in the anti-breast tumor activity of these nanostructures [231]. It appears that autophagy inhibition by graphene nanoparticles can sensitize lung cancer cells to necroptotic death [232]. Taken together, experiments demonstrate that graphene nanoparticles are potential nanoscale delivery systems for autophagy modulators in cancer, and their anti-tumor activity depends on the role of autophagy [232–234].

4.5. Metal nanomaterials

The Au nanoparticles are chemically inert and have demonstrated low side effects and high biocompatibility, paving their way to treat diseases [235]. For intravenous administration of Au nanostructures, their modification with polyethylene glycol (PEG) is performed to preserve their stability in biological media [236]. Furthermore, Au nanoparticles can be applied as theranostic probes due to their fluorescence capacity beneficial in bioimaging [237]. The multifunctional role of Au nanocarriers has made them appropriate options in cancer therapy. A

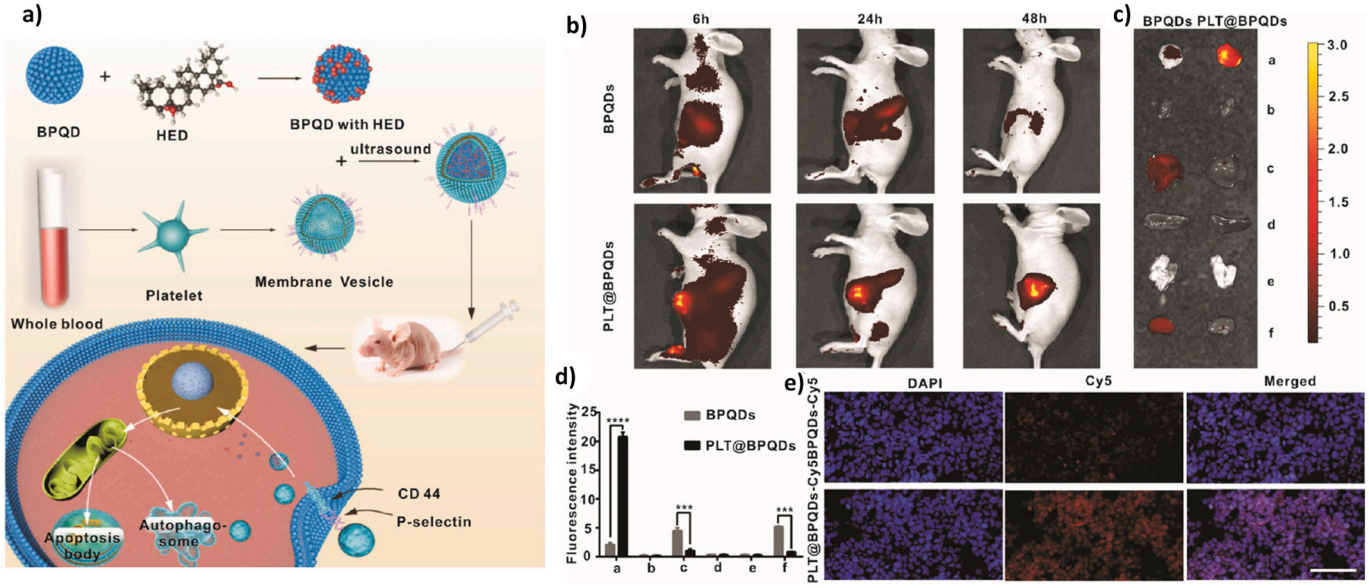

Fig. 6. A) Nanoparticles and their therapeutic application; B) In vivo fluorescence images; C) Ex vivo bioluminescence images; D) Evaluating fluorescence signals quantitatively; E) Fluorescence imaging of tumor tissues.
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recent experiment has shown that Au nanocarriers can reduce breast cancer progression and viability by providing photothermal therapy while simultaneously having bioimaging properties [238]. Au nanoparticles stimulate DNA damage in lung tumors and enhance radiosensitivity [239]. Further, Au nanoarchitectures exert synergistic cancer therapy by gene and drug co-delivery [240]. Efforts have been made to pave the way for the application of Au nanoparticles in clinical trials because of their efficiency in cancer suppression. However, one of the most important features of nanocarriers for clinical application is their biocompatibility. Although Au nanostructures demonstrate high biocompatibility, their adverse impacts can be reduced by using natural sources for their synthesis. In this way, Au nanoparticles were synthesized using a hydroxylated tetraterpenoid deinoxanthin (DX) derived from *Deinococcus radiodurans*. DX functions as a surface-capping agent

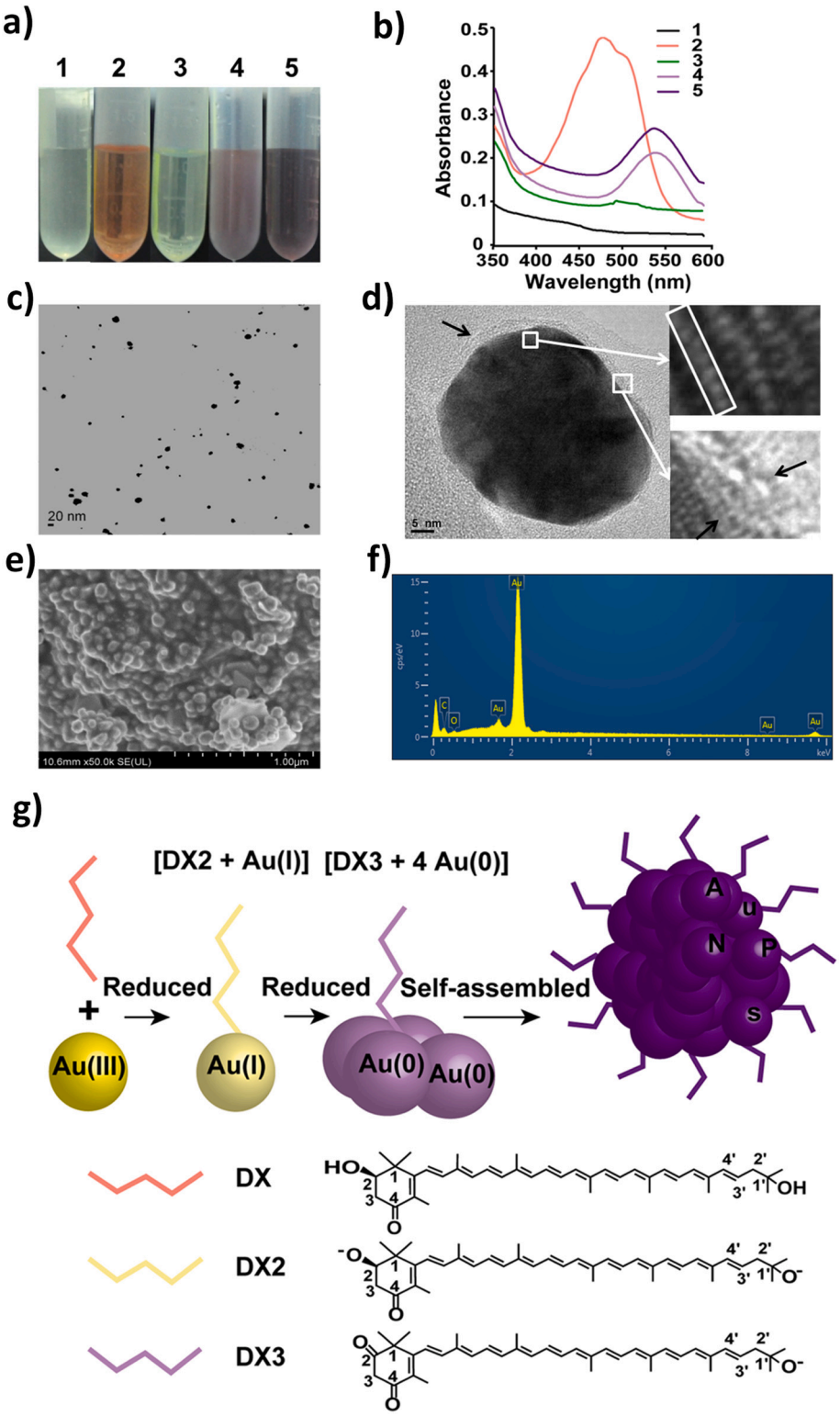

Fig. 7. A–F) Characterization of nanostructures; and G) Synthesis of nanoparticles and conjugation of cargo.
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and increases the stability of Au nanoparticles. Compared to conventional Au nanoparticles, DX-Au nanoparticles demonstrate higher cytotoxicity against breast cancer cells (MCF-7 cells) with no toxicity towards normal cells. These nanoparticles can accumulate in cytoplasm, organelles and nuclei. The ability of DX-Au nanocarriers in reducing the viability and progression of breast cancer cells is attributed to the overgeneration of ROS that subsequently induces apoptosis and autophagy (Fig. 7) [241].

ROS production and its association with autophagy induction are based on alterations in the endoplasmic reticulum (ER). ROS overgeneration negatively affects homeostasis of ER, leading to ER stress that subsequently stimulates apoptosis and autophagy [143,242,243]. A recent experiment showed that Au nanoparticles demonstrate higher anti-tumor activity than CP in lung cancer therapy (A549 cells). Exposure of A549 tumors to Au nanostructures triggers ROS overgeneration, resulting in mitochondrial dysfunction and ER stress followed by apoptosis and autophagy induction that remarkably diminishes survival of lung cancer cells (Fig. 8) [244]. These studies highlight the autophagy induction by Au nanoparticles as a molecular pathway involved in cancer suppression.

On the other hand, Au nanocarriers suppress cancer progression via autophagy impairment. The photothermal ability of Au nanocarriers is beneficial for cancer suppression by reducing cell viability and survival. A combination of titania-coated gold nano-bipyramid (NBP/TiO_2) nanoarchitectures and bortezomib synergistically suppress brain cancer. The anti-tumor activity of NBP/TiO_2 nanoparticles is attributed to their capacity in preventing autophagosome and lysosome fusion and inhibiting lysosomal degradation. This activity of nanostructures sensitizes glioma cells to proteasome inhibited-mediated cell death [245]. Previously, Au nanocarriers showed to stimulate radio-sensitivity [246]. Au nanoparticles trigger autophagy in tumors via LC3-II upregulation and enhancing autophagosome formation. Noteworthy, this autophagy possesses a tumor-promoting role, and its inhibition promotes the capacity of Au nanostructures in inducing apoptosis and increasing radiosensitivity of cancer cells [247]. Generally, Au nanoarchitectures are potential modulators of autophagy in cancer and understanding their association can be advantageous in directing further studies for effective cancer treatment [248].

Silver (Ag) nanocarriers are applied in various fields such as the pharmaceutical industry, cosmetic products, biomedicine for wound healing, infection therapy and suppressing cancer progression [249]. Ag nanoparticles have a high surface area with adjustable particle size [250]. Recently, Ag nanoparticles have made their way into cancer treatment [251]. These nanocarriers function in a concentration- and time-dependent manner in triggering apoptosis in cancer cells and restricting their growth and invasion [252]. Furthermore, Ag nanoparticles can provide photothermal therapy to suppress cancer growth [253]. Recent experiments have highlighted the role of Ag nanoparticles in inhibiting cancer progression via autophagy regulation. The nuclear factor-kappaB (NF-κB) modulates autophagy in colorectal tumor. Exposing these malignant cells to Ag nanostructures results in autophagy induction through down-regulation of NF-κB and upregulation of IκB. Furthermore, Ag nanoparticles trigger autophagy in colorectal cancer cells via protein kinase-B (Akt) and mTOR upregulation. The enhanced level of autophagy leads to apoptosis and, finally, necrosis in colorectal cancer cells [254]. This experiment demonstrated how autophagy regulation by Ag nanocarriers could affect other kinds of cell death mechanisms, such as apoptosis and necrosis. Like Au nanoparticles, Ag nanostructures can promote ROS levels in triggering DNA damage, apoptosis and autophagy in breast tumors. The cytotoxicity of Ag nanoparticles against breast cancer cells is suggested to be concentration-dependent [255]. However, a limitation of the previous experiment is that the role of autophagy as a tumor-promoting or tumor-suppressor factor has not been investigated. Another experiment synthesized Ag nanoparticles from *Penicillium shearii* AJP05 and investigated the cytotoxicity against osteosarcoma cells based on autophagy regulation. Ag nanoparticles were coated with a protein derived from fungi which enhanced its anti-tumor activity. Ag nanoparticles stimulate apoptosis and autophagy in osteosarcoma via ROS overgeneration. However, autophagy exerts a tumor-promoting role and inhibiting this cell mechanism triggers ROS overgeneration and cell death in osteosarcoma cells [256]. Taken together, Ag nanocarriers can modulate autophagy in cancer cells, and its inhibition or induction can reveal its role in cancer progression [257,258]. Furthermore, Ag nanoparticles

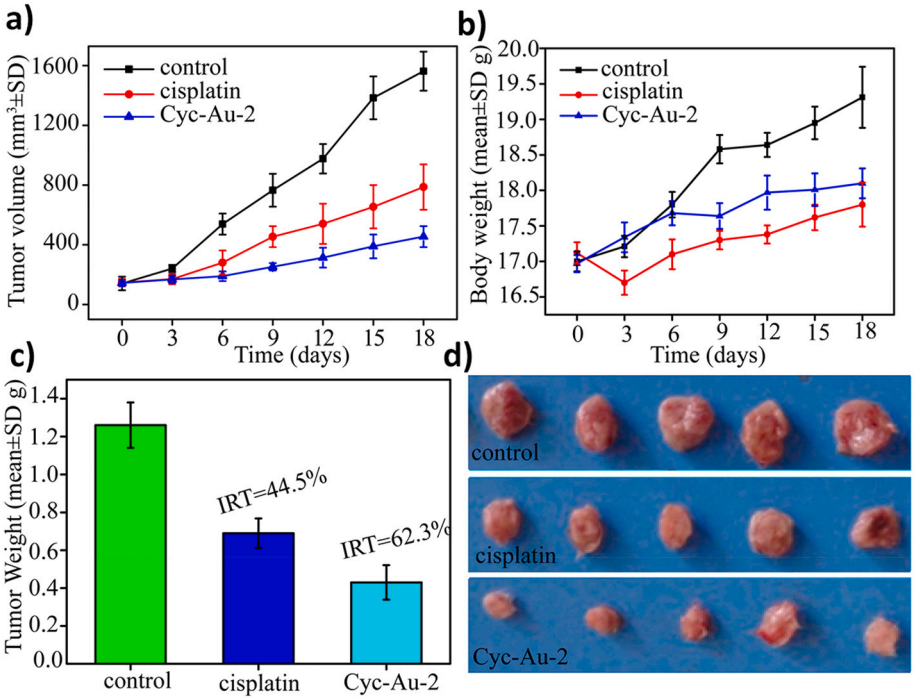

Fig. 8. A) Tumor volume; B) Bodyweight; C) Tumor weight; and D) Tumor images.
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can affect various molecular pathways by affecting autophagy [259]. On the other hand, autophagy induction under hypoxic conditions can hinder Ag nanoparticle-mediated apoptosis in lung cancer [260]. Therefore, autophagy significantly affects the anti-tumor activity of Ag nanoparticles, and the underlying molecular pathways should be highlighted in developing novel therapeutics in the future.

Iron nanoparticles have also been applied in cancer therapy. These nanocarriers can induce apoptosis, provide photothermal therapy and remain at the tumor site [237,261,262]. To date, a few studies have evaluated the role of iron nanoparticles in regulating autophagy in cancer. Due to their small size, iron nanoparticles can accumulate in the mitochondria affecting glucose metabolism of colorectal cancer cells and triggering autophagy [263]. Mitochondrial alterations caused by iron nanoparticles are responsible for the reduction in viability of colorectal cancer cells. The impact of iron nanoparticles on cell death pathways is size-dependent. It has been reported that large iron nanoparticles (15.1 and 30 nm) can induce autophagy in plasma, while small iron nanoparticles (7.3 nm) affect the mitochondria in triggering cell death and increase ROS levels [264]. Concerning the potential of both iron and Ag nanoparticles in affecting autophagy, a recent experiment has prepared iron nanocarriers coated with Ag in oral cancer therapy. The synthesized nanoparticles demonstrated high biocompatibility and cellular uptake. Upon penetration into oral tumor cells, iron ions were released and subsequently triggered apoptosis and autophagy via ROS overgeneration [265]. Metal nanoarchitectures can regulate autophagy in cancer treatment and can be divided into two categories. The first category is nanostructures that can induce or inhibit autophagy in cancer cells by, for instance, enhancing ROS levels. Alternatively, nanostructures can be utilized to deliver autophagy regulators in suppressing cancer progression and increasing the chemosensitivity of tumors. These aims have been investigated in pre-clinical studies (in vivo and in vitro). More efforts should be made to introduce these findings to the clinic and treatment of cancer patients [244,253,266–275]. Fig. 9 provides a schematic representation of targeting autophagy using cargo-loaded nanoparticles (Table 1).

5. Conclusion and remarks

Modulation of autophagy is an important but challenging strategy in cancer therapy since autophagy possesses both tumor-promoting and tumor-suppressing roles and its function is context-dependent. Furthermore, autophagy may demonstrate both pro-survival and pro-death roles in certain types of cancer. Therefore, targeting autophagy should be considered after determining its role. Different kinds of autophagy regulators, including natural and synthetic compounds, have been applied in cancer therapy. The present review shows that nanoparticles can provide targeted delivery of autophagy regulators at the tumor site, enhancing their potential in affecting autophagy and modulating cancer progression. The role of nanoparticles is highlighted in chemotherapy. Drug resistance poses an increasing challenge in today's world. The inhibition or induction of autophagy has drawn significant attention in augmenting the chemosensitivity of cancer cells because of its notable role in chemoresistance. Co-delivery of autophagy regulators and chemotherapeutic agents can affect autophagy in favor of cancer elimination. For instance, when autophagy possesses a tumor-promoting function, delivery of autophagy inhibitors using nanoparticles promotes chemosensitivity. Removing cytoprotective autophagy increases apoptosis in cancers, potentiating the anti-tumor activity of chemotherapeutic agents. Moreover, shRNA and siRNA can be utilized as genetic tools to target autophagy genes, including *ATGs* and modulate autophagy. Nanoparticles enable gene therapy with high efficiency by protecting genetic tools from degradation and increasing their uptake in tumor cells.

In addition to drug and gene delivery in autophagy regulation, some nanoparticles can regulate autophagy genes and affect molecular mechanisms. For instance, Au nanoparticles can enhance ROS generation in favor of autophagy and apoptosis stimulation in cancer therapy. However, the tumor-promoting role of autophagy should also be considered. When nanoparticle-mediated autophagy exerts a cytoprotective role, autophagy inhibitors are suggested to potentate the fight against cancer cells. Another thing to consider is that autophagy preserves homeostasis at the primary level, and inducing autophagy by severe and high levels can be deleterious and result in cell death. However, hyperactivation of autophagy leads to cell death and is an

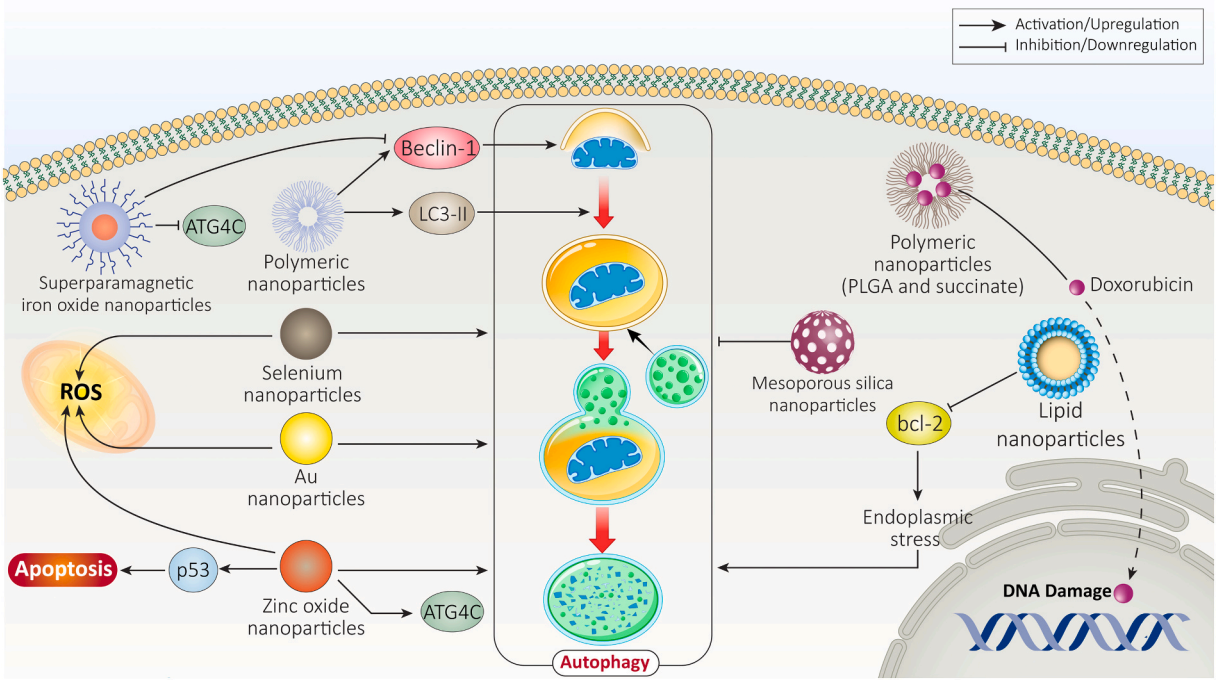

Fig. 9. Nanoparticles regulating autophagy in cancer treatment.

Table 1
Nanoparticles in the regulation of autophagy for cancer therapy.

Nanostructure	Applied agents in nanoparticle synthesis	Drug/gene delivery	Zeta potential (mV) Particle size (nm)	Cancer type	In vitro/ in vivo	Cell line/ animal model	Remarks	Refs
Polymeric nanoparticles	Selenium Hydroxyapatite	–	50–100 nm	Osteosarcoma	In vitro In vivo	MNNG/HOS cells Orthotopic xenograft mouse model	Selenium possesses a chemotherapy role Hydroxyapatite provides bone repair Increasing ROS levels Activating JNK signaling and suppressing Akt/mTOR signaling Triggering apoptosis and autophagy in cancer cells	[276]
Polymeric nanoparticles	Selenium	Laminarin Chloroquine	60 nm	Hepatocellular carcinoma	In vitro	HepG2 cells	Triggering both apoptosis and autophagy in cancer cells Upregulating LC3-II and p62 in autophagy induction Autophagy inhibition using chloroquine promotes cell death	[277]
Polymeric nanoparticles	Selenium	–	30 nm	Colon cancer	In vitro	HCT116 cells	Upregulation of Beclin-1 Triggering autophagy to potentiate cell death in cancer cells	[278]
Polymeric nanoparticles (PLGA and succinate)	–	Doxorubicin Chloroquine	–	Lung cancer	In vitro	A549 cells	Inhibiting autophagy to protect doxorubicin and enhancing nuclear translocation of this chemotherapeutic agent	[279]
Polystyrene nanoparticles	Amino groups	–	+37 to −56.7 mV	Ovarian cancer	In vitro	OVCAR3 cells	Exerting anti-tumor activity in a time- and concentration-dependent manner Autophagy inhibition promotes anti-tumor activity	[280]
Polymeric nanoparticles	PEI PLGA	Paclitaxel	+21.7 mV 80 nm	Brain cancer	In vitro	U251 cells	Inhibiting proliferation and invasion of cancer cells Enhancing accumulation of autophagosomes and LC3-II in triggering autophagy	[281]
Polymeric nanoparticles	–	HGFK1 Sorafenib	+6.68 mV 106.67 nm	Renal cell carcinoma	In vitro In vivo	786-O, and ACHN cells Xenograft mouse model	Suppressing tumor growth Promoting mice survival Exerting synergistic impact with sorafenib Decreasing sorafenib-mediated autophagy by delivery of HGFK1	[282]
Polymeric nanoparticles	PLGA	Curcumin GANT61	−213.3 mV 190–400 nm	Breast cancer	In vitro	MCF-7 cells	Impairing self-renewal capacity of cancer stem cells Inducing both apoptosis and autophagy in reducing the viability of cancer cells	[283]
Selenium nanoparticles	–	–	27.5 nm	Breast cancer	In vitro	MCF-7 cells	A combination of selenium nanoparticles and irradiation exerts synergistic impact via autophagy induction and enhancing ROS levels	[284]
Lipid nanoparticles	–	–	+29.8 mV Up to 136 nm	Cervical cancer	In vitro	HeLa cells	Down-regulation of Bcl-2 expression in endoplasmic stress to trigger autophagy	[285]
Au-Ag nanoparticles	Polydopamine	–	200 nm	Bladder cancer	In vitro In vivo	T24 cells Xenograft model	Providing photothermal therapy and enhancing ROS levels Triggering Akt and ERK signaling pathway Stimulating both autophagy and apoptosis	[286]
Au nanoparticles	Valine	–	−29 mV 20 nm	Breast cancer	In vitro In vivo	MDA-mB-231 cells Mouse model	Enhancing ROS levels Triggering autophagy Exerting cytotoxicity against cancer cells	[287]
Au nanoparticles	–	Quercetin	−19.1 mV 106.7 nm	Neuroglioma	In vitro In vivo	U87 cells Nude mice	Reducing cell viability in a time- and concentration-dependent manner Down-regulating mTOR and	[288]

(*continued on next page*)

Table 1 (*continued*)

Nanostructure	Applied agents in nanoparticle synthesis	Drug/gene delivery	Zeta potential (mV) Particle size (nm)	Cancer type	In vitro/ in vivo	Cell line/ animal model	Remarks	Refs
							PI3K/Akt expressions Upregulation of LC3-II and ERK Inducing autophagy	
Superparamagnetic iron oxide nanoparticles	–	AGO2 MiRNA-3765B	−20 mV 70 nm	Breast cancer	In vitro In vivo	MCF7 and MDA-MB-453 cells Xenograft nude mice	Exerting anti-tumor activity and enhancing cytotoxicity of cisplatin against cancer cells Autophagy inhibition Reducing Beclin-1 and ATG4C expressions	[289]
Zinc oxide nanoparticles	–	–	20 nm	Ovarian cancer	In vitro	SKOV3 cells	Decreasing viability of cancer cells Upregulation of p53 and LC3 Stimulating autophagy	[290]
Zinc oxide nanoparticles	–	–	−5.01 mV 172 nm	Breast cancer	In vitro In vivo	MCF-7 cells Animal models of 4 T1 tumor cells	Enhancing ROS levels Upregulating ATG5 Triggering autophagy	[291]
Hollow mesoporous silica nanoparticles	–	Hydroxychloroquine	+41.15 to −26.50 mV 48.8 nm	Colon cancer	In vitro In vivo	HCT116 cells Xenograft model	Increasing intracellular accumulation of hydroxychloroquine Preventing autophagy as a pro-survival mechanism Enhancing cytotoxicity of irradiation in cancer therapy	[238]
Silica nanoparticles	–	–	86 nm	Colon cancer	In vitro	HCT116 cells	Inducing autophagy by affecting endoplasmic reticulum in colon cancer therapy Enhancing LC3-II levels	[292]
Mesoporous silica nanoparticles	Polydopamine	Chloroquine Glucose consumer glucose oxidase	Up to 235 nm	Hepatocellular carcinoma	In vitro In vivo	HepG2 cells Tumor-bearing mice	The induction of starvation by GOx in cancer cells Providing photothermal therapy Enhancing the potential of starvation and photothermal therapy in cancer suppression via autophagy inhibition	[293]
Cuprous oxide nanoparticles	–	–	–	Bladder cancer	In vitro In vivo	J82, T24, 5637, UM-UC-3 cells Xenografts	Reducing viability of cancer cells in a time- and concentration-dependent manner Inducing apoptosis and cell cycle arrest Upregulation of ERK signaling and autophagy induction in potentiating apoptotic cell death	[294]
TiO_2 nanoparticles	–	5-Fluorouracil	20–30 nm	Gastric cancer	In vitro	AGS cells	Increasing ROS levels Inducing disturbances in lysosome function Suppressing autophagy Promoting cytotoxicity of chemotherapy Triggering apoptosis	[295]
Magnetic iron nanoparticles	PEI	–	25.1 mV 26.3 nm	Cervical cancer	In vitro	HeLa cells	Enhancing ROS levels Upregulation of ATG7 and triggering Akt/mTOR axis Inducing autophagy	[296]

important strategy in chemosensitivity and cancer immunotherapy [270]. As pre-clinical studies highlighted the role of nanoparticles in autophagy regulation, more investigation can be performed for using these agents in the treatment of cancer patients.

Based on information presented in clinicaltrials.gov website, there have been efforts in evaluating role of autophagy in cancer patients and using autophagy regulators for their treatment (NCT01292408 and NCT01649947). As it was discussed in main text, nanocarriers can significantly improve potential of autophagy modulators in cancer suppression via mediating targeted delivery and enhancing intracellular accumulation of cargo. Therefore, the next step can be clinical translation of pre-clinical findings and their use for treatment of cancer patients. Now, this question comes into mind that which nanocarrier type is better for clinical application and delivery of autophagy modulators? The answer is dependent on two determining factors including possibility of large-scale production and biocompatibility of nanoparticle. The safety profile of nanoparticles and their tolerance can be considered important factors in clinical application. From this aspect, the lipid- and polymeric-based nanocarriers are preferred to metal- and carbon-based nanostructures. Based on studies, carbon-based nanoparticles such as

graphene possess toxicity and for improving their biocompatibility, modification with natural productions such as chitosan is performed [297]. Furthermore, metal-based nanoparticles have also adverse impacts on normal cells and have limited clinical application. The large-scale production of nanoparticles is also important and some of the polymers such as hyaluronic acid is expensive and their clinical application is not affordable. Therefore, more investigation should be conducted about clinical application of nanoarchitectures for delivery of autophagy modulators.

Abbreviations

siRNA	small interfering RNA
shRNA	short hairpin RNA
CMA	cheparone-mediated autophagy
AMPK	5′-AMP-activated protein kinase
ULK1	unc-51-like autophagy-activation kinase
ATG	autophagy-related gene
PI3K	phosphoinositide 3-kinase
mTOR	mammalian target of rapamycin
LC3-II	light chain 3-II
LAMP2	lysosomal associated membrane protein 2
SNAREs	soluble NSF attachment protein receptors
PLGA	poly lactic-*co*-glycolic acid
CDK1	cyclin-dependent kinase 1
CS	chitosan
HA	hyaluronic acid
DOX	doxorubicin
HPAH	hyperbranched polacylhydrazone
Au	gold
TrxR	thioredoxin reductase
CP	cisplatin
5-FU	5-flourouracil
RIP3	receptor-interacting protein kinase 3
BBB	blood-brain barrier
FDA	Food and Drug Administration
mTORC1	mTOR complex 1
mTORC2	mTOR complex 2
STAT3	signal transducer and activator of transcription 3
PCD	programmed cell death
FR	folate receptor
CAFs	cancer-associated fibroblasts
PTX	paclitaxel
HCQ	hydroxychloroquine
Wtmm	wortmannin
CDs	carbon dots
NPCDs	nitrogen-phosphorus-doped carbon dots
lncRNAs	long non-coding RNAs
SIRT1	sirtuin-1
QDs	quantum dots
NIR	near-infrared
Cet	Cetuximab
MPA	3-marcaptopropionic
HED	hederagenin
BPQD	black phosphorus quantum dots
ROS	reactive oxygen species
P-l-Arg	poly-l-arginine
PEG	polyethylene glycol
DX	deinoxanthin
ER	endoplasmic reticulum
Ag	silver
NF-κB	nuclear factor-kappaB
Akt	protein kinase-B
SQSTM1	Sequestosome 1
OPTN	optic neuropathy inducing protein
BCL2L13	B-cell lymphoma 2 like protein-13

Declaration of competing interest

The authors declare no conflict of interest.

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