Cancer Letters 591 (2024) 216860

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

# Nanomaterials in crossroad of autophagy control in human cancers: Amplification of cell death mechanisms

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ARTICLE INFO

*Keywords:*
Autophagy
Apoptosis
Cell death
Nanoparticles
Cancer therapy

ABSTRACT

Cancer is the result of genetic abnormalities that cause normal cells to grow into neoplastic cells. Cancer is characterized by several distinct features, such as uncontrolled cell growth, extensive spreading to other parts of the body, and the ability to resist treatment. The scientists have stressed the development of nanostructures as novel therapeutic options in suppressing cancer, in response to the emergence of resistance to standard medicines. One of the specific mechanisms with dysregulation during cancer is autophagy. Nanomaterials have the ability to specifically carry medications and genes, and they can also enhance the responsiveness of tumor cells to standard therapy while promoting drug sensitivity. The primary mechanism in this process relies on autophagosomes and their fusion with lysosomes to break down the components of the cytoplasm. While autophagy was initially described as a form of cellular demise, it has been demonstrated to play a crucial role in controlling metastasis, proliferation, and treatment resistance in human malignancies. The pharmacokinetic profile of autophagy modulators is poor, despite their development for use in cancer therapy. Consequently, nanoparticles have been developed for the purpose of delivering medications and autophagy modulators selectively and specifically to the cancer process. Furthermore, several categories of nanoparticles have demonstrated the ability to regulate autophagy, which plays a crucial role in defining the biological characteristics and response to therapy of tumor cells.

## Introduction

Eukaryotes possess the ability to recycle and eliminate most of their internal components through a process called autophagy. This pathway has evolved a considerable time ago and is highly preserved [1]. As a catabolic process, autophagy mediates the synthesis of substrates that aid cells in maintaining homeostasis during times of food scarcity [2,3]. Autophagy plays a comparable role in breaking down faulty or harmed

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https://doi.org/10.1016/j.canlet.2024.216860
Received 30 January 2024; Received in revised form 24 March 2024; Accepted 2 April 2024
Available online 6 April 2024
0304-3835/Published by Elsevier B.V.

organelles and cellular components through a process known as self-digestion. Autophagy processes have a crucial role in various areas of biology, such as immunology, inter-cellular signaling, regulation of stem cells in tissues, and maintenance of barrier tissue integrity [4–8]. Autophagy can be triggered in response to various physical, chemical, or biological stimuli. The process can be triggered in reaction to cellular stress, immune response, organelle quality control, prolonged dietary restriction, or tissue remodeling [9]. Due to the abnormality of having an excessive amount of the macromolecular self-degradation pathway, autophagy in physiological conditions can either aid in cell survival or induce cell death [10]. Autophagy's role in human longevity and health is widely recognized due to its function as the primary pathway for enhancing survival in response to stress and maintaining cellular quality control [5,11]. Many human diseases and illnesses can be caused by defects in autophagy. These involve disorders of the nervous system, muscles, malignancies, aging, the lungs, liver, and heart, as well as metabolic disorders like diabetes [12]. At least three types of autophagy have been identified for the transfer of lysosomes to proteins (Fig. 1). One type of autophagy is microautophagy, where the lysosomal membranes fold inward, allowing the cell to take in cargo more easily [13].

Furthermore, chaperone-mediated autophagy differs from other types of autophagy in that it does not rely on the detection of certain membrane characteristics to identify cargos. Instead, cargos are detected by chaperones that include a distinct pentapeptide pattern [14]. Individual substrates will be translocated across the lysosomal membrane after they have unfolded. Finally, during macroautophagy, a cytosolic vesicle termed the autophagosome is produced. This vesicle is a double-membrane transporter of cargo [15]. After the omegasome forms, macroautophagy's initial stage driven by BECN1 (Beclin-1) and a few autophagy-related genes (ATGs) moves on to the next stage. Next, the macrophages elongate, the autophagosomes mature, and the lysosomes fuse with the autophagosomes, resulting in the proteolytic destruction of the cargo [3]. The autophagy that has been chosen is specifically macroautophagy of a particular organelle, distinct from what would occur in the event of general macroautophagy. PINK1 has a crucial role as the primary regulator in a specific type of autophagy called selective autophagy, in contrast to macrophagy where other regulators are involved [3]. Selective autophagy achieves its selectivity by either marking or ubiquitinating the cargo. P62 recognizes androgen glucuronide, also known as pentapeptide motif, as a substrate for autophagy during the process of autophagy selection. Following this, the autophagy receptor selectively attaches to the examined cargo, resulting in the formation of the autophagosome [16–18]. Although the mechanisms of various types of autophagy vary significantly, the ultimate outcome remains consistent: inadequate removal of unnecessary organelles by lysosomes.

Nanoparticles refer to small formations that have dimensions ranging from 1 to 100 nm. The industrial and medical sectors are just two of many potential uses for these structures. Since nanoparticles can carry drugs and genes to exact locations, their use in cancer treatment has skyrocketed in recent years. In addition, nanoparticles exhibit fantastic promise as bioimaging candidates and may improve immunotherapy [19]. Chemotherapy medications can be enhanced, and drug resistance can be suppressed by the use of nanostructures in their delivery. As a result, nanoparticles are becoming more and more used in cancer therapy due to their adaptability. Fig. 2 provides the role of nanoparticles in crossing over biological barriers that is beneficial in improving intracellular accumulation and reaching the tumor microenvironment for the suppression of cancer. In recent years, the regulation of autophagy by nanoparticles has shown promising points in cancer therapy [20]. Regarding the importance of nanoparticles in the field of cancer therapy, the current review will focus on the role of nanoparticles in the regulation of autophagy for the treatment of cancer. Table 1 is a summary of the application of nanoparticles in the process of cancer therapy (see Table 2).

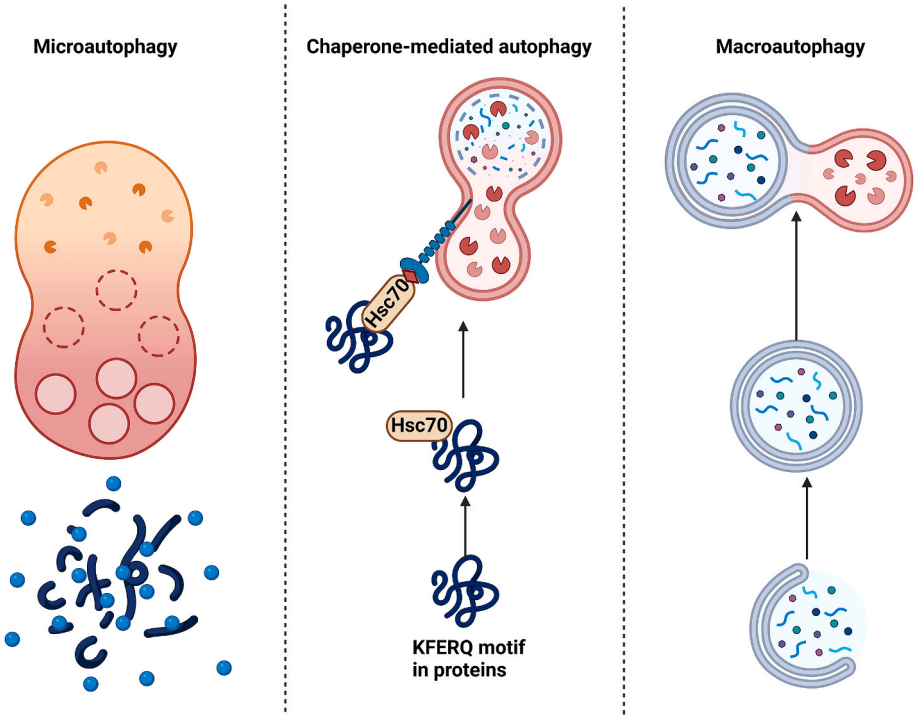


**Fig. 1. The three major types of autophagy.** a) Macroautophagy is the bulky and non-selective type of autophagy in which double-membrane compartments known as autophagosomes can mediate the degradation of cargo through fusion with lysosomes; b) Chaperone-mediated autophagy is the selective type of autophagy in which proteins with the KFERQ motif are identified to be directed for lysosomal degradation; c) Microautophagy is the inward budding of the cell membrane for the degradation of cargo.

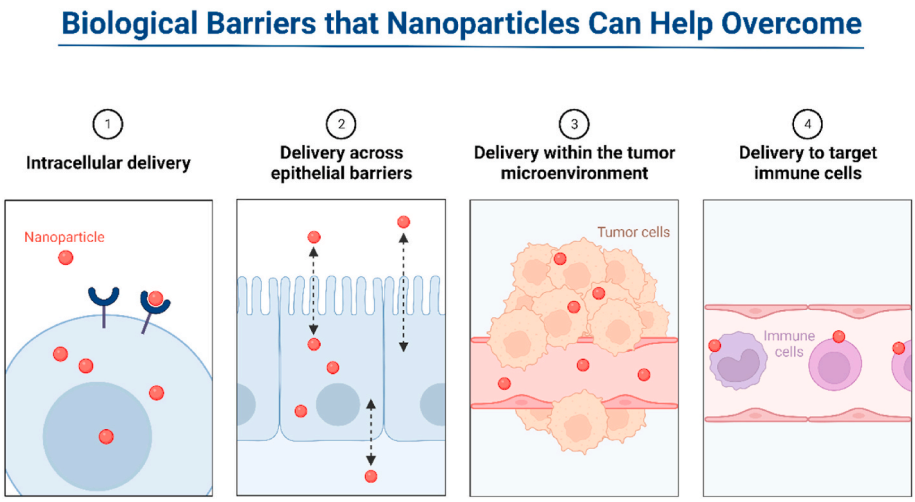


**Fig. 2. The nanoparticles and biological barriers in cancer therapy.** Nanoparticles can help overcome a variety of biological barriers. Nanoparticles have the ability to bind to the receptors upregulated on the surface of tumor cells (this is true for surface-functionalized nanostructures) to enhance the intracellular accumulation of drugs and cargo in cancer cells. Moreover, nanocarriers demonstrate a high ability to cross epithelial barriers. The nanostructures can specifically accumulate in the tumor microenvironment and can target immune cells for the induction of the immune system against cancer cells.

## Autophagy flux

### *Basics and molecular aspects*

The autophagy mechanism has evolved to be considerably conserved, resulting in the rapid discovery of human analogues of the yeast-discovered autophagy-related (ATG) genes and proteins (Fig. 3) [49–51]. Many ATG protein complexes, including ATG5, ATG12, and ATG16L1, must be attached to the membrane of autophagosomes for them to attain their mature state. The microtubule-associated protein 1 light chain 3 (LC3) is a prominent tool for monitoring autophagy both in laboratory environments and in living organisms. LC3 is the mammalian equivalent of yeast ATG8 and is present on the membrane of the autophagosome [52]. The ATG12-ATG5-ATG16L complex facilitates the transport of cytoplasmic LC3 to the maturing autophagosome membrane. This complex aids in LC3 lipidation and separation membrane expansion when it accumulates on the autophagosome surface [53–55]. The autophagosome contains both inner and outer membranes, which consist of LC3II. LC3II is constituted when LC3 binds to phosphatidylethanolamine [56]. LC3II remains attached to autophagosomes until it undergoes destruction in the autolysosomal stage. Hence, the rate of autophagy activation can be assessed by quantifying the amount of LC3II bound to the membrane. ATG4 has the ability to separate the outer membrane LC3II, releasing the inner membrane LC3I for future use. On the other hand, the fusion of autophagosomes with lysosomes breaks down the inner membrane LC3II. LC3II turnover can be used to quantify the level of autophagy or autophagic flux. If the autophagy machinery develops correctly, the presence of lysosomal protease inhibitors stops the breakdown of LC3II that is connected to the inner membrane. This results in an elevation of LC3II levels in the cells that have been treated [57]. Knocking down or down these ATGs has become a prevalent method for understanding the molecular processes of autophagy. The process becomes more intricate due to the multiple rates of interaction between autophagy control and diverse intracellular signaling networks. Autophagy is a metabolic process that produces energy. The hormone glucagon promotes this process, whereas insulin and amino acids inhibit it [58–60]. The mammalian target of rapamycin (mTOR) is located downstream of the insulin receptor. Since mTOR negatively modulates autophagy, its activation prevents autophagy. The pharmacological inhibitor of mTOR, rapamycin, on the other hand, promotes autophagy [61]. Autophagy is induced by the energy-sensitive AMP-activated protein kinase, which inhibits mTOR when there is a lack of energy [62]. The autophagy promoter class III phosphatidylinositol-3-kinase (PI3K) is blocked by 3-methyladenine, which suppresses autophagy [63]. Furthermore, the signaling cascades of inositol-monophosphatase, c-Jun-N-terminal-kinase, and death-associated protein kinase are pathways that control autophagy. Some of these pathways rely on mTOR, while others operate independently [64,65].

### *Pre-clinical models of autophagy*

Autophagy is an auspicious novel focus for cancer therapy, and scientists have developed animal models to get deeper insights into its mechanisms at the pre-clinical stage. Animal models are utilized to improve our understanding of the physiological and pathological aspects of autophagy. In order to examine autophagy in vivo, two mouse models have been developed: “autophagy-monitoring mice” and “autophagy-deficient mice.” For the goal of researching autophagy, mice have also been generated with CIEA NOG, Nlrp3, SumF1, Dram2, TNF-α Tg, ATG4b-c, and PiK3c3 genes knocked out [68–73]. Mitophagy is a recently discovered form of autophagy that selectively targets mitochondria [74]. More precisely, researchers employ mt-Keima transgenic mice and mito-QC transgenic mice as models for investigating mitophagy [75,76]. Through genetic engineering to create mice models for studying autophagy and by manipulating specific receptors like SQSTM1/p62, OPTN, and BCL2L13, the role of selective autophagy in live organisms has been better understood [75,77–79]. However, evaluating autophagy through in vivo mice models has certain challenges. For instance, observing alterations in the organelles of living organisms to research autophagy is not feasible, and doing experiments on mammals to manipulate them is a challenging endeavor. Consequently, zebrafish have recently become widely used as an in vivo model for investigating autophagy, mitophagy, and other types of autophagy [80]. Primate models are fantastic for learning more about autophagy and how it works in normal and aberrant cellular processes. The MARC-145 cells found in monkey kidneys have been used to study the toxic effects of fumonisin B1 and the involvement of autophagy. Reducing cell death in monkey kidney cells exposed to fumonisin B1 is achieved by suppressing autophagy [81]. Monkey models are very valuable when investigating the role of autophagy in neurological diseases. Studies conducted on cynomolgus monkeys have demonstrated that the inhibition of autophagy plays a vital role in the progression of neurological disorders in these primates, as it occurs immediately before to the production of amyloid plaques [82]. A recent study used adult *Macaca*

**Table 1**
The application of nanomaterials in cancer therapy.

| Nanoparticles | Outcomes | References |
|---|---|---|
| Supramolecular Cyclic Dinucleotide nanostructones | Increasing the intracellular delivery of CDG and enhancing STING activation to promote cancer immunotherapy | [21] |
| Polymeric RNA nanocarriers | 200 nm size and providing systemic delivery<br>High anti-tumor activity in breast cancer and specific targeting of CD44+-overexpressed cells | [22] |
| Au@$AgBiS_2$ nanostructures | Stimulation of pyroptosis and accelerating cancer radioimmunotherapy | [23] |
| Co-assembled nanoparticles | The fluorescent nanostructures developed from poly(ethylene glycol)-modified tetraphenylethylene can enhance levels of singlet oxygen upon NIR irradiation and release the Pt drugs in pH of tumor microenvironment for chemo-photodynamic therapy | [24] |
| Photoprotein-conjugated upconversion nanostructures | Generation of superoxide anion radicals as ROS and specific targeting of tumor cells through receptor-mediated cell adhesion<br>Photosensitizing activity and induction of cell death in breast cancer and glioblastoma | [25] |
| Hydroxyethyl starch-polycaprolactone carriers | Co-delivery of doxorubicin and erastin in synergistic cancer therapy<br>Increasing ROS generation through reducing Hedgehog expression | [26] |
| Zinc oxide nanostructures | Exerting high toxicity against ovarian cancer | [27] |
| Biomimetic nanostructures | Stimulation of ferroptosis through enhancing mitochondrial damage to impair progression of glioblastoma | [28] |
| Sodium bicarbonate nanostructures | Inhibition of growth and metastasis<br>Impairing immunosuppressive microenvironment<br>Stimulation of pyroptosis<br>Modulation of lactic acid metabolism | [29] |
| Calcium carbonate nanostructures | Co-delivery of gemcitabine and triapine to overcome drug resistance in pancreatic cancer | [30] |
| PCL/gelatin nanofibers | Co-delivery of doxorubicin-loaded MSN/silver nanostructures to exert cytotoxic impact against melanoma | [31] |
| Self-assembled nanostructures | Co-deliveyr of EGCG and melittin to induce apoptosis, downregulate PD-L1 and impair growth in vivo | [32] |
| Mesoporous nanostructures | GSH-responsive feature<br>Deliveyr of cinnamaldehyde for the immunotherapy and mediation of chemodynamic therapy | [33] |

**Table 2**
An overview of autophagy function in cancers.

| Tumor | Outcome | Reference |
|---|---|---|
| Pancreatic cancer | Biomimetic microenvironmental stiffness can stimulate autophagy for facilitating stemness | [34] |
| Thyroid cancer | Downregulation of AKR1C3 can suppress autophagy-mediated glycolysis through impairing ERK | [35] |
| Ovarian cancer | Hsa_circ_0000585 stimulation cisplatin resistance through upregulation of Beclin-1 to induce autophagy | [36] |
| Prostate cancer | Calotropis procera extract suppresses tumorigenesis through autophagy inhibition | [37] |
| Gallbladder cancer | SNHG15 stimulates autophagy to facilitate tumorigenesis | [38] |
| Hypopharyngeal cancer | LncRNA HOXC-AS2 binds to p62 protein to induce autophagy for promoting tumorigenesis | [39] |
| Pancreatic cancer | Nanomaterials deliver miR-198 to suppress autophagy and overcome gemcitabine resistance | [40] |
| Prostate cancer | ALKBH5 suppresses m6A-modification of TSPAN1 mRNA to impair autophagy | [41] |
| Colorectal cancer | The exosomal lncRNA FAL1 derived from cancer-associated fibroblast can induce oxaliplatin resistance through autophagy suppression | [42] |
| Prostate cancer | REST-impaired lncRNA LINC01801 can transcriptionally induce autophagy in mediating neuroendocrine differentiation of tumor cells | [43] |
| Cervical cancer | Maachiain stimulates AMPK/mTOR/autophagy to disrupt cervical cancer progression | [44] |
| Endometrial cancer | LRG5 stimulates protective autophagy | [45] |
| Pancreatic cancer | IGHG1 downregulation can overcome drug resistance through autophagy and apoptosis induction | [46] |
| Pancreatic cancer | Matrix stiffness mediates protective autophagy to enhance drug resistance | [47] |
| Breast cancer | Diphenyl disulfide upregulates Bax and induces autophagy to accelerate apoptosis | [48] |

*mulatta* to examine the role of autophagy activation status in periodontal lesions [83]. Therefore, among other models, primate models (both in vitro and in vivo) can be utilized to further our understanding of the role of autophagy in diseases [84,85].

### *Autophagy as tumor-suppressor and tumor-promoter*

An early study on the involvement of autophagy in breast cancer revealed that there was a reduction in BECN1 expression and a decrease in autophagy activity [86,87]. Mice that were conditionally heterozygous for BECN1 had drastically impaired autophagy and a high cancer rate [88,89]. Shortly thereafter, it was demonstrated that mice with a widespread mosaic deletion of ATG5 developed tumors, as did animals with a targeted deletion of ATG7 in the liver [90,91]. These findings provide additional evidence that autophagy can effectively prevent the improvement of tumors. The absence of autophagy in cells of Oncomice that produce the oncogene KRAS mutant and MMTVPyMT hampers tumor growth, even in the presence of somatic loss of autophagy. This suggests that autophagy plays a crucial role in carcinogenesis, as the absence of these genes prevents the cell from developing cancer [92–98]. Furthermore, the cancer is unable to progress uncontrolled once ATG is extracted from it [99]. This provides evidence that autophagy, occurring after the cell has already become malignant, contributes to the cancer's ability to survive. Autophagy, as anticipated by its inherent nature, appears to possess a multifaceted role in the progression of tumor metastasis. The function of autophagy in breast cancer metastasis was demonstrated by utilizing a transplantable MMTV-PyMT tumor model with tamoxifen-induced loss of ATGs [100]. Metastasis is facilitated by autophagy because it increases cell resistance to anoikis, also known as detachment-induced cell death [101]. Autophagy streamlines the transformation of a cell into an anoikis-resistant cell. Although there is a concept suggesting that autophagy promotes tumor start and inhibits carcinogenesis in general, there are contradictory pieces of evidence. Liver tumors can develop even in the absence of ATG5, regardless of the absence of cancer cells. Liver cancer has a scarcity of mutations in the ATG gene. Further research is necessary to definitively establish the involvement of ATG protein mutations in the development of human cancer. On top of that, autophagy may not always play a role in tumor initiation. No growth deficit was observed when ATGs were inflated into cancer cell lines that had been promoted by KRAS. In PTEN-lacking cells, autophagy inhibits tumor start, while in PDAC, it promotes development. Further research on the specific form of cancer is necessary because autophagy may have a distinct role in each type of cancer [91,97,102–104]. Autophagy plays a two-fold role in controlling the advancement of cancer, making it a potential target for inhibiting cancer growth, and overcoming resistance to cancer treatment [105,106]. Fig. 2 highlights the function of autophagy in cancer.

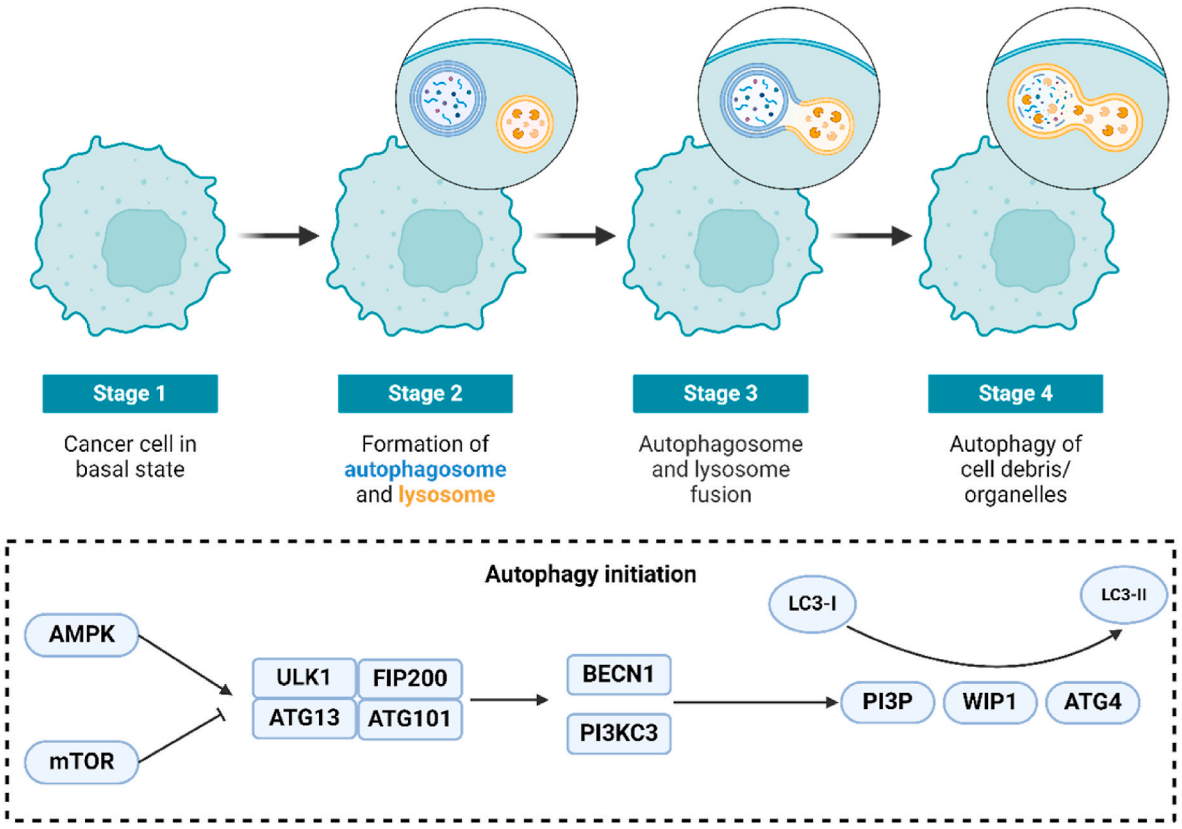


**Fig. 3. The mechanism of autophagy in cells** [66]. The mammalian target of rapamycin (mTOR) complex detects signals of nutrient starvation or pathogen detection and then phosphorylates Unc51-like kinase 1 (ULK-1) and autophagy-related protein 13 (Atg13); then mTOR separates itself from the ULK-1-Atg13-FAK family-interacting protein of 200kD (FIP200) complex. The vacuolar protein sorting 34 (Vps34)-Atg14L-Beclin-1 complex and the ULK-1-Atg13-FAK family--interacting protein of 200kD (FIP) complex help form the membrane, which will later become the autophagosome. The autophagosome elongates and closes, needing the help of proteins Atg2, Atg9, Vps34, and the ubiquitin-like complexes Atg12-Atg5-ATG16L and Atg4B-Atg3-Atg7. Atg4B cleaves the LC3 precursor, getting the LC3 protein from the cytosolic form (LC3 I) to the membrane-bound form of LC3 II (LC3-phosphatidylethanolamine conjugated), and Atg7 and Atg3 work together to make that happen. Where LC3 gets lipidated depends on the location of the Atg12-Atg5-ATG16L complex. This autophagosome then fuses with the lysosome to form the autolysosome. This process happens because of the recruitment of soluble N-ethylmaleimide-sensitive factor attachment (NSF) protein receptor (SNARE) proteins that interact with homotypic fusion, vacuole protein sorting (HOPS), and vesicle trafficking by GTPases. Then, the substances undergo degradation in the lysosome [67].

## Nanomaterials and autophagy flux in cancer

### *Polymeric nanomaterials*

Polymeric nanoparticles are frequently applied to modulate autophagy in cancer therapy. Amino-functionalized nanostructures have been proposed as crucial for the therapy of ovarian cancer. The tumor cells are sustained by autophagy mediated by the nanostructures functionalized with amino acids. Nanoparticles functionalized with amino acids are already harmful, but hindering autophagy makes them much worse. In addition, protecting tumor cells from nanoparticle-mediated toxicity and rescuing ATG4-induced autophagy can be achieved by declining the creation of mitochondrial anion superoxide [107]. On top of that nanoparticles can extend medication sensitivity in tumor cells by preventing autophagy [108].

The oral cavity, pharynx, larynx, and paranasal sinuses make up the upper aerodigestive tract, which is home to the most prevalent epithelial cancer—head and neck squamous cell carcinoma (HNSCC) [109]. Loco-regional recurrence levels are remarkably elevated, with a substantial number of recurrences occurring during the initial years following therapy. Recent investigations illustrate that the five-year survival level of HNSCC is less than 50% [110–112]. It is believed that clinical and pathological considerations play a substantial role in guiding the treatment decision [109,113]. When cancer is resectable, surgery and radiation are the primary treatment choices. Many patients are primarily concerned with managing and surviving the side effects of treatment, which mostly consist of long-lasting difficulties in the central area [114]. Nano-formulations are emerging as a promising medical therapeutic approach for enhanced medication delivery. Through processes such as drug dissolution, passive or active targeting, gradual release, and several other mechanisms, these formulations aim to increase the therapeutic index of the drug [115,116]. The therapeutic index refers to the ratio between the effective dose and the lethal dose of the medicine, and by doing so, these formulations seek to decrease the likelihood of adverse effects caused by the medication. Microparticle-driven drug delivery has been shown to improve the therapeutic index of certain chemotherapeutic drugs by lowering their concentration in healthy tissues through direct cellular uptake and intracellular trafficking. The therapeutic index represents the proportion between the effective dose and the deadly dose of a medicine [117]. Evaporation of emulsification-suspension solvents was used to create chitosan (CS) MPs and CS + PCL MPs. While both types of MPs were made from the same amount of polymer, the CS MPs (300–600 nm) had smaller particles. The micelles produced were uniformly spherical in shape, and numerous CS + PCL micelles were larger than 2000 nm. Whereas 5-fluorouracil (5-FU) encapsulation efficiency in CS MPs is 85.98%, it is below 60% in CS + PCL MPs. An additional cell line, CAL27 cells, HSC3 cells, a pre-clinical animal model (AT84) for HNSCC, and several cancer indices were assessed to determine the efficacy of 5-FU loaded particles in reducing these processes. The data indicate a

38.57% rise in 5-FU EE and a 36% decline in 5-FU drug release (lasting nearly 96 h) following exposure to 5-FU. The metabolic and colony formation investigations further demonstrate the anti-cancer effectiveness of the 5-FU medication, which is significantly enhanced by CS-decorated MPs of PCL. However, the presence of chitosan (CS) on the polycaprolactone (PCL) microspheres (MPs) does not affect the ability of 5-FU encapsulated in the MPs to suppress cell motility in laboratory tests. Furthermore, the study observed an elevation in the protein levels of LC3-II, which serves as an additional confirmation of autophagy. The presence of cleaved PARP1 further supports the occurrence of cell death, as depicted in Fig. 4 [118].

Nanoparticles can be created by combining CS with alginate. For the sake of improving medication sensitivity and inhibiting autophagy in breast tumors, CS/alginate nanostructures can co-deliver doxorubicin and hydroxychloroquine [119]. A different study has created versatile carriers using a polymer complex of polyethyleneimine and oleic acid (PEI-OA) to simultaneously deliver paclitaxel and chloroquine. The nanoparticles exhibit sensitivity towards PD-L1 and CD44, and PD-L1 promotes the internalization of nanostructures by cells. These nanoparticles have the ability to specifically target tumors and inhibit autophagy. Additionally, they increase the presence of $CD4^+$ and $CD8^+$ T lymphocytes at the tumor location [120]. In recent years, genetic tools have emerged as an intriguing technique for controlling autophagy in cancer treatment. Research has shown that siRNA can be utilized to downregulate ATG5 and ATG7, two autophagy-related proteins, in cancer therapy, therefore suppressing supporting autophagy [121–123]. It is recommended to use nanocarriers to transport siRNA in order to enhance its effectiveness in regulating autophagy. The hybrid cell membrane nanostructures have the capability to simultaneously transport doxorubicin and anti-autophagy siRNA, which effectively inhibits drug resistance in breast cancer and decreases ATP production [124].

In addition, there is considerable promise in the combination of hypoxia with photodynamic treatment (PDT) for hypoxic cancers. This endeavor employs the “Chase and Block” strategy to boost cancer treatment efficacy by combining autophagic suppression with synergistic PDT. The utilization of the multi-band emitted upconversion luminescence of NaYbF4:Er@NaGdF4 UCNPs by the photosensitive molecule of organic component (FL) has been demonstrated. This is achieved by enclosing the hydrophobic layer with the amphiphilic polymer DSPE-PEG-COOH. The “ship-in-bottle” approach is employed to develop a “chase” method for cancer treatment. This involves selectively activating the FL (fluorescent dye) using nitroreductase in the tumor microenvironment (TME) to carry out hypoxia-promoted photodynamic therapy (PDT). The nanosystem used in this study consisted of AuNP-HA (Cluster-ATKPS-RGD/HA/Oxa-Gd, HA = hyaluronic acid), which contained AuNP particles ranging in size from 400 to 800 nm. The system also included a positively charged adjuvant known as TKPR, which is composed of peptides that bind to Toll-like receptors, antigens, and tumor cells. Moreover, the nanosystem contained PEG-grafted poly adenine (PEGA)-RGD oligonucleotides encapsulated in AuNP particles with a size of 100 nm. The surface of the AuNP particles was conjugated with a peptide known as PEGylated-TGKRP, and a peptide called Autophagy-inhibiting melittin propeptide (MEL) was attached to the AuNP surface to target tumor cells that overexpress legumain. This propeptide impedes autophagy by disrupting the integrity of the lysosomal membrane. This process eradicates the cancer cells in order to protect themselves and enhances the effectiveness of PDT in eliminating a greater number of cells. Another capability of TME is its capacity to selectively stimulate FL and MEL. The therapeutic tracer also enables upconversion luminescence imaging (Fig. 5) [125].

Preparation of peptide-conjugated poly(β-amino ester) nanoparticles with self-assembling micelle-like structures (P-Bec1) was achieved by a straightforward and modular supramolecular approach. The autophagy inducer can enhance the cytotoxicity of polymer-beclin-1 (P-Bec1) nanoparticles against breast cancer cells. Due to its haploinsufficiency, Bec1 has two primary drawbacks when compared to small-molecule drugs: (i) Bec1 is susceptible to enzymatic degradation and has limited ability to reach tumors effectively. (ii) Bec1 exhibits non-specific and unstable distribution throughout tumor tissues, making it difficult to target specifically. These polymer nanoparticles, which form on their own, can activate autophagy and impede the advancement of breast cancer in living organisms [126]. Importantly, chemoimmunotherapy is

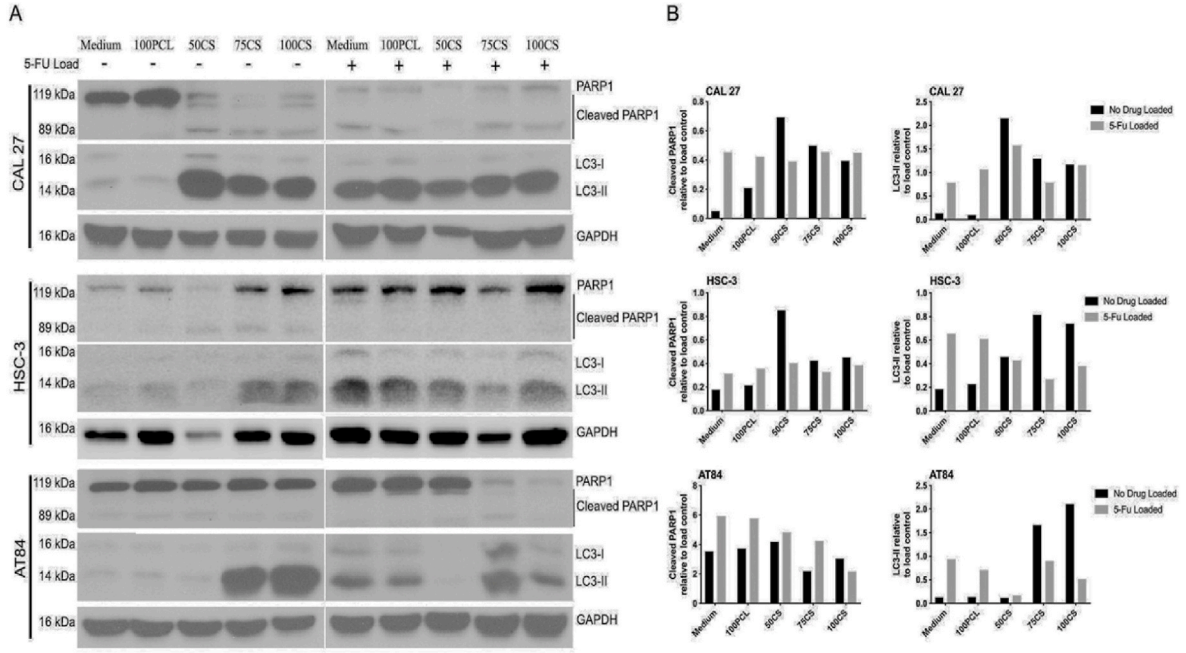


**Fig. 4.** Both apoptosis and autophagy were shown to be activated in HNSCC cells by the MPs and composite sponges used. In order to determine the levels of PARP1, LC3B, and GAPDH protein expression, cells were subjected to treatment with MPs and SPs for a period of 48 h. The results of the panel demonstrate that the CAL27, HSC3, and AT84 cell lines that were treated with samples coating or not coating 5-FU exhibited an enhanced expression of PARP1 and LC3-II cleavage. This points to an increase in the processes of apoptosis and autophagy, respectively, that cause cell death. Reprinted with permission from Ref. [118].

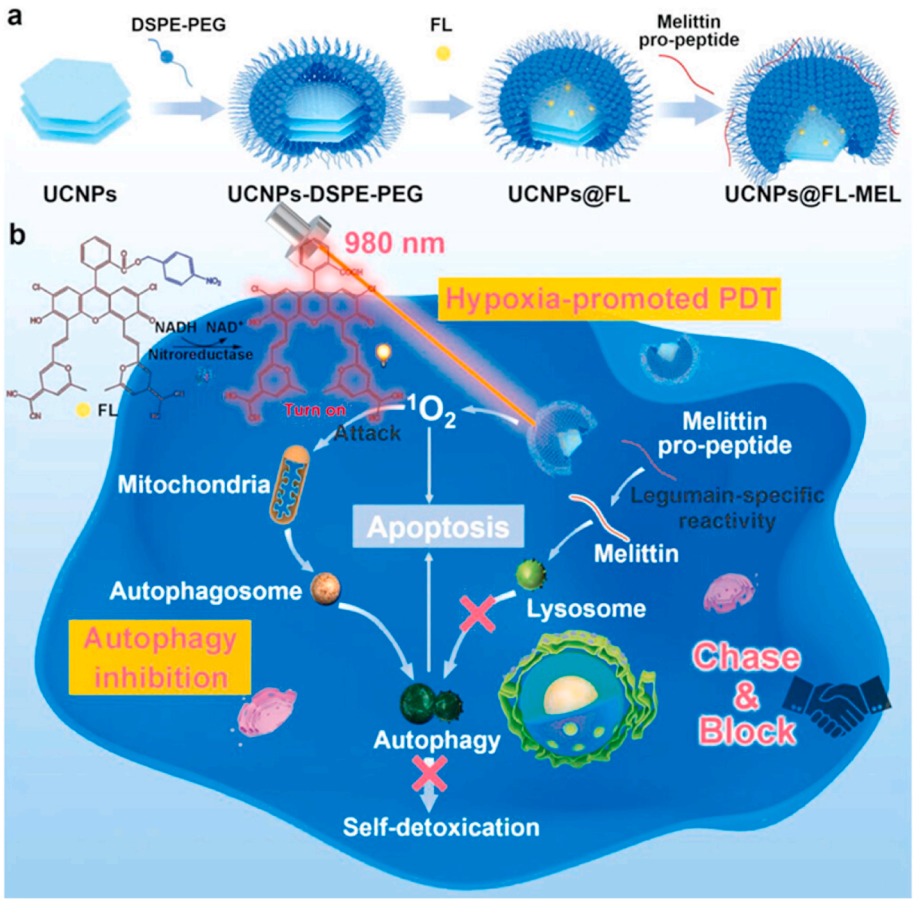


**Fig. 5.** This is an illustration of the process of material synthesis and treatment. Both a) a schematic representation of the creation of UCNPs@FL-MEL and b) the method for combined treatment of hypoxic malignancies generated by hypoxia-promoted photodynamic therapy and autophagy suppression are shown here. Reprinted with permission from Wiley [125].

elevated when tumor-associated macrophages experience re-education to acquire a pro-inflammatory phenotype after chloroquine administration suppresses autophagy (Fig. 6) [127].

Polymeric nanostructures have been extensively utilized to modulate autophagy in human malignancies. The biodegradable polymeric nanoparticles are biocompatible materials that can be used to regulate autophagy in cancer therapy. The use of chiral polymer modified nanostructures has demonstrated their ability to facilitate tumor ablation. Furthermore, these materials induce autophagy as a therapeutic approach for breast cancer treatment [128]. A polymer complex consisting of polyethyleneimine, and oleic acid (PEI-OA) has been employed to create versatile nanostructures for the transportation of paclitaxel and chloroquine, which are chemotherapeutic medicines. These nanostructures can react to PD-L1 and CD44. These structures exhibited a significant increase in the absorption of cells and inhibited the process of autophagy. Moreover, they enhanced the effectiveness of chemotherapy and immune checkpoint inhibitors [120]. While the primary subject of this paper is nanoparticles, it is important to note that polymer-KLAK peptide conjugates have been demonstrated to induce cell death by increasing mitochondrial damage and inhibiting autophagy [129]. Hence, the incorporation of polymers in conjugation can also yield advantageous consequences in regulating autophagy for cancer treatment [130]. In cancer therapy, nanodrugs can be utilized to deliver genes that regulate autophagy. The cationic polymer APEG-PAsp(PEI) (PAPEI) has demonstrated an interaction with LDHA-siRNA. This interaction can augment the effectiveness of oxaliplatin in the treatment of colorectal cancer by promoting autophagy and re-educating tumor-associated macrophages [131]. The nanorobots have been created by combining two amphiphilic triblock polymer peptides through co-self-assembly. These nanorobots are designed to distribute CpG, which in turn induces autophagy for the purpose of cancer immunotherapy [132]. The H1/pHGFK1 nanostructures, when modified with PEG, have the added advantage of increasing the anti-cancer effects of sorafenib against hepatocellular carcinoma. This is achieved by hindering protective autophagy and stemness [133]. Hence, the control of autophagy by nanocarriers holds noticeable relevance in the field of cancer treatment [134].

*Lipid nanomaterials*

Lipid-based nanoparticles have garnered substantial interest in cancer treatment due to their excellent biocompatibility and capacity to incorporate both hydrophobic and hydrophilic medicines [135]. Liposomes, a type of nanomaterial composed of lipids, possess the capability to modulate autophagy in cancer treatment by transporting therapeutic agents. The 188Re-liposomal nanostructures have been created to inhibit both autophagy and mitophagy in the management of ovarian cancer, hence enhancing their responsiveness to drugs [136]. Immunotherapy has significantly transformed the battle against cancer and has demonstrated exceptional effectiveness. Nevertheless, contemporary immunotherapies continue to face the challenge of a limited rate of response, particularly in solid tumors that lack sufficient infiltration of immune cells, sometimes referred to as "cold tumors." As a result, many researchers have proposed the hypothesis that it is feasible to re-educate the "cold tumor" by inhibiting autophagy with SAR405, an extremely specific VPS34 inhibitor. A liposome system was established by combining doxorubicin (DOX), SAR405, and an anti-PD-L1 peptide known as SAR-JY4LIPO. DOX-SAR-JY4LIPO can expand the infiltration

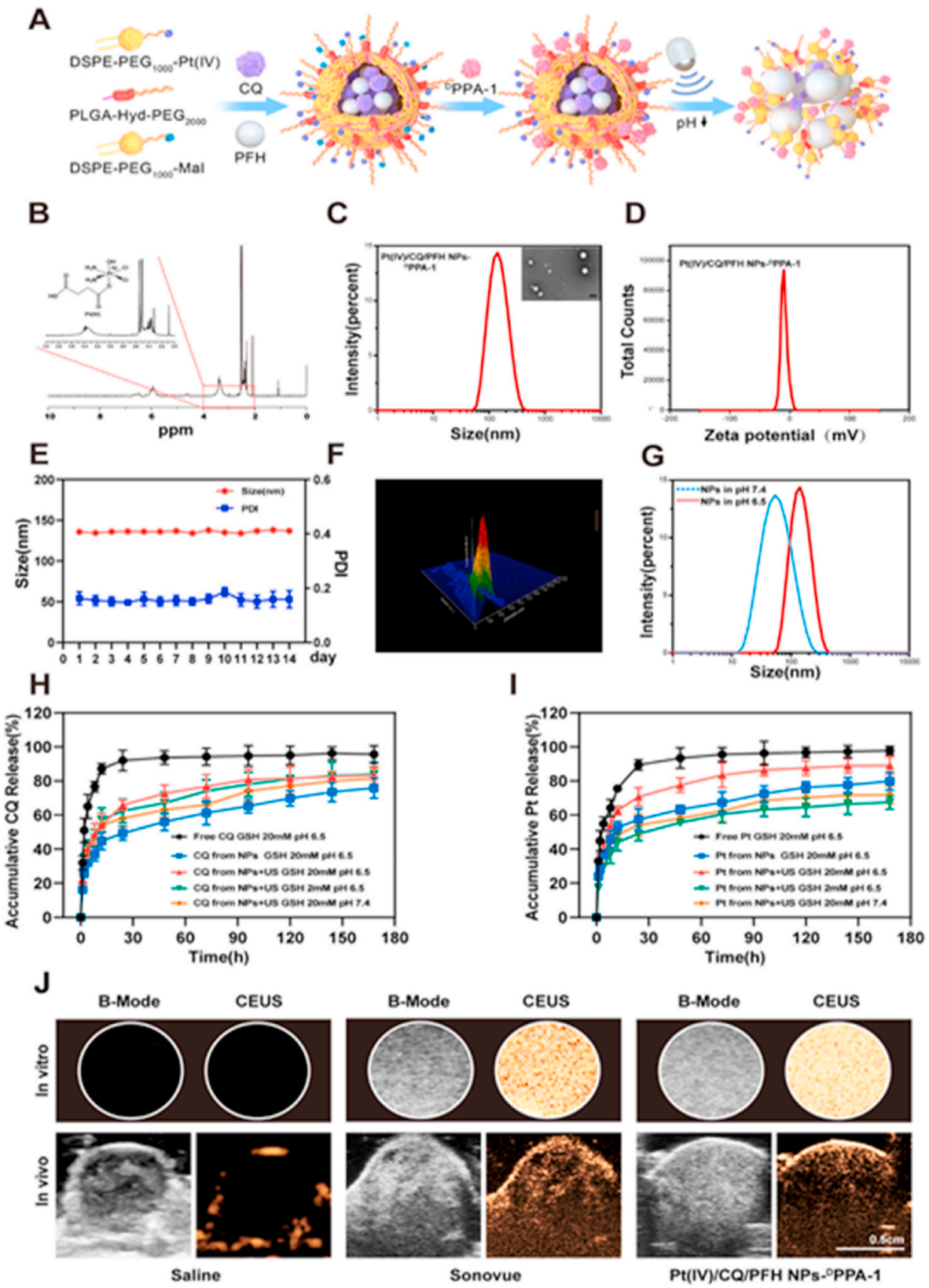


**Fig. 6.** Physicochemical characterization of nanoparticles (NPs) in vitro and in vivo, as well as the effectiveness of ultrasound (US) imaging. In order to create NPs, the synthesis process is utilized. Spectra of Pt(IV) in DMSO-$d_6$ as measured by 1H NMR (B). When seen from the left, the unique peaks are highlighted and amplified. NPs' particle size distribution is seen in (C). The scale bar is equal to 50 nm. Distribution of zeta potentials of nanoparticles (D). The stability of NPs during storage (E). The spread of NPs' concentrations is shown in (F). In both pH 6.5 and pH 7.4, the particle size distribution of NPs is shown in (G). Under a variety of circumstances, the accumulation of chloroquine (CQ) drug release might be seen. Under a variety of circumstances, cumulative cisplatin (Pt) drug release was observed. There was a comparison made between the effectiveness of NPs in US imaging in vitro and in vivo with saline or Sonovue. Reprinted with permission from ACS [127].

of cytotoxic lymphocytes into tumors by streamlining the accumulation of both DOX and SAR405 in lung cancer xenograft animal models. The synergistic tumor chemoattraction takes place due to the immunogenic cell death (ICD) generated by DOX and the increases in chemokines, specifically CCL5 and CXCL10, mediated by SAR405. Based on the aforementioned findings, it is clearly manifest that DOX-SAR-JY4 LIPO is capable of noticeably decreasing tumor burden, metastasis, and recurrence by re-educating the immunosuppressive tumor microenvironment [137].

The effectiveness of immunotherapy for treating cancer is hindered by the remodeling of the tumor microenvironment (TME) and the presence of an immunosuppressive milieu within the tumor. In order to enhance tumor photo-immunotherapy, liposome nanodrugs are created by including chlorin e6 (Ce6) and doxycycline hydrochloride (Doxy). These nanodrugs are designed to overcome both the tumor microenvironment and the immunosuppressive TME. Ce6 exerts dual effects by both suppressing autophagy in cells and successfully inhibiting mitochondrial malfunction. Ce6 will increase the intensity of photodynamic therapy (PDT) to induce immune-compromise disease (ICD) and reactive oxygen species (ROS) to promote immune-suppressive remodeling of the tumor microenvironment (TME) following cell exposure to near-infrared lasers. In addition to increasing ICD and killing impacts, doxy promotes mitochondrial dysfunctions, which boost intracellular ROS production and, in turn, PDT efficacy. Doxory enhances tumor immunogenicity by increasing MHC-I expression on tumor cell surfaces, which in turn improves antigen presentation and CTL recognition. This is achieved by effectively blocking autophagy. In vivo research has revealed that Ce6-based PDT may be an effective anticancer method for enhancing the effectiveness of cancer treatments by means of in situ tumor ablation. In recent times, research into the synergy between PDT and PTT has concentrated on its possible utilizations in cancer treatment [138]. In addition, research has exhibited that Doxy can efficiently instigate the cleavage of caspase-3 precursors, leading to the production of caspase-3 in treatment with paclitaxel [139]. The suggestion is to functionalize liposomes with RGD peptide to enhance their potential for regulating autophagy in cancer therapy [140]. Also, liposomes can transport LY294002, an autophagy inhibitor, which, when combined with chemotherapeutic medicines, can have a synergistic effect on tumor eradication [141]. Furthermore, liposome-mediated autophagy regulation can reduce cancer chemoresistance [142].

Regarding the features of the nanocarrier, there are several significant physicochemical qualities that play a crucial role in drug delivery applications. Among these aspects, the particle size of the nanoparticles is the most important characteristic [143–145]. The capacity of smaller nanoparticles (<50 nm) to penetrate tumors is well-known, but their ease of reintroduction into circulation is also well-known [146,147]. Contrary to expectations, nanoparticles larger than 100–200 nm are believed to exhibit improved retention and reduced clearance at the tumor site. However, this assumption is frequently proven incorrect [148,149]. However, less tumor penetration and dispersion is often observed with larger NPs [150]. Thus, in order to achieve a uniform distribution of NPs within the tumor site, it is necessary to use a size-adjustable method. Consequently, we examined the ability of a fast and gentle chemical bonding process to facilitate the clustering of nanoparticles at the location of the tumor. The Cu (I)-catalyzed azide (N3)-alkyne (ALK) cycloaddition (CuAAC), also known as copper-catalyzed azide-alkyne cycloaddition (CuAAC), is a frequently employed ‘click’ reaction in the field of click chemistry, which is designed for usage in biological contexts [151–154]. It offers a straightforward, robust, and dependable approach for producing pharmaceuticals and novel molecules, making it an excellent choice for synthesis due to its simplicity and cost efficiency. In order to get the highest concentration of nanoparticles (NPs) at the tumor site, the CuAAC click reaction was employed to control the size of the particles. This size regulation is responsible for the penetration and retention effects. As previously shown, the ability to modify the size of micelles can improve the delivery of drugs and their retention at tumor sites [143,146]. A recent investigation utilized CuAAC to create micellar nanoparticles for the simultaneous administration of doxorubicin and wortmannin, which are autophagy inhibitors. The micelles exhibited significant accumulation in the sites affected by melanoma and breast tumors. The micelles increased the expression of p62, while decreasing the expression of LC3-II, hence inhibiting autophagy, and reducing the amount of autophagosomes [155]. The researchers have created micellar nanosystems using an amphiphilic peptide called poly(L-arginine)-poly(L-histidine)-DOX-EMCH. These nanosystems are designed to simultaneously deliver si-Beclin1 (an autophagy inhibitor) and doxorubicin for the treatment of prostate cancer. These micellar nanoparticles can suppress autophagy, which greatly enhances their capability to induce apoptosis and boost cytotoxicity [156]. As a result, nanoparticles made of lipids, such micelles, and liposomes, show great promise as vehicles for cancer treatment utilizing autophagy modulators [157,158].

Liposomes, which are spherical vesicles with a bilayer structure and amphiphilic properties, have the potential to be used as a drug delivery mechanism due to their high biocompatibility, extended circulation in the body, and well-established technology. They may effectively transfer several types of payloads, such as chemotherapeutic medications, proteins, and nucleic acids [159,160]. Liposomes are spherical vesicles composed of two layers. Liposomes can influence autophagy either through their intrinsic characteristics or by supplying autophagy modulators. Our study group discovered that the use of cationic liposomes to prevent autophagy can lead to the occurrence of many cellular and molecular processes [161,162]. These events encompassed necrosis and augmented crossing presenylation, among other occurrences. Our earlier study showed that cationic liposomes can cause cell death by making the lysosome membrane more permeable and blocking the final stage of autophagy. As a result, cathepsin B was released into the cytoplasm, causing mitochondrial malfunction and the generation of reactive oxygen species. These reactive oxygen species are the main factors responsible for cell necrosis. The importance of our research lies in its ability to uncover the cellular toxicity of cationic liposomes and its contribution to the advancement of safer gene delivery systems [161]. In addition, we found that cationic liposomes can stop antigen breakdown in dendritic cells by increasing the lysosomal pH. This provides more insight into the mechanism of cationic liposome-mediated cross-presentation, which in turn enhances cross-presentation and cross-priming of $CD8^+$ T-cell responses [162]. Moreover, the administration of autophagy inhibitors by liposomes holds the potential to effectively inhibit autophagy in cancer cells and overcome therapy resistance caused by autophagy [163,164]. The cytotoxic effect of salinomycin was significantly enhanced in HepG2 cells when it was administered in liposomes incorporating chloroquine [163]. Yang and colleagues developed liposomes as a delivery system for the autophagy inhibitor CQ, along with a cisplatin prodrug. The purpose was to block autophagy and reverse the malignant environment [165]. In triple-negative breast cancer, the presence of CQ reduces the protective effect of cisplatin-induced autophagy on cancer cells, leading to a powerful synergistic therapeutic effect.

In the context of the disease, the presence of CQ intensifies the transformation of M2 macrophages into M1 macrophages, hence increasing their polarization. Liposomal administration of autophagy activators has the potential to both induce excessive autophagy and enhance the efficacy of cancer treatments [166,167]. Hu and collaborators generated liposomes to facilitate the delivery of dihydroartemisinin and adriamycin [166]. Liposomes has the capacity to generate dihydroartemisinin, which can decrease the activity of Bcl-2 and accelerate its separation from Beclin-1. Consequently, there is an upregulation of Bax expression, resulting in the activation of apoptosis in the cells. Upon its release, Beclin 1 has the capacity to induce an excessive level of autophagy, leading to type II programmed cell death. Furthermore, liposomal administration of nonclassical

autophagy-regulating drugs exerts an indirect influence on autophagy, hence serving as a therapeutic approach for cancer treatment. They created nanoliposomes that included the photosensitive dye IR780, which responds to light in the near-infrared range, and bioactive flower head plants (CfAc) that are rich in chlorophyll [167]. In response to near-infrared light, CfAc is generated, which in turn triggers autophagy-mediated cell death. This is achieved by setting off a tumor-specific autophagic response. An innovative nanosystem was created by the researchers. It could distribute copper peroxide nanodots (CPNs) and artemisinin (ART) liposomes all at once [168]. The production of Cu2+ ions from CPN has a dual-catalytic effect, causing intracellular damage through oxidative stress and promoting the accumulation of lipid peroxide, ultimately leading to ferroptosis. Furthermore, the administration of antiretroviral therapy (ART) triggered the process of autophagy, leading to an increase in the level of iron in the body by breaking down ferritin. This, in turn, induced ferroptosis in cancer cells, exhibiting a combinatorial effect. Ultimately, liposomes that transport autophagy modulators possess the capacity to enhance the efficacy of cancer treatments. This can be achieved by reducing the level of protection provided by autophagy, resulting in an excessive amount of autophagy. This excessive autophagy then breaks down autophagy-sensitive proteins such as ferritin, leading to an increase in cell death that is dependent on autophagy-sensitive proteins. Thus, liposomes have the ability to regulate autophagy in human malignancies [169–171].

Micelles are another type of nanoparticle that can be used to control cancer autophagy. Docetaxel and ATG7-siRNA co-delivered in peptide-based micelles inhibit autophagy and improve breast cancer cells' sensitivity to docetaxel [122]. The co-delivery of peptide micelles is an approach that has also been used to treat prostate cancer. doxorubicin and beclin-1-siRNA to prevent protective autophagy [156]. Another approach involved the use of amphiphilic block copolymer to create micelles for the simultaneous delivery of CTG7-siRNA and docetaxel, with the goal of inhibiting carcinogenesis both in laboratory tests and in living organisms. Furthermore, the addition of iRGD peptide to micelles greatly improves the uptake of nanoparticles into tumor cells, thereby inhibiting the protective autophagy induced by docetaxel [123]. Thus, novel insights in cancer treatment can be derived from nanoparticle modulation of autophagy [155,172].

*Carbon nanomaterials*

Graphene oxide, a widely used nanomaterial, is noticeably appealing for a range of biological and medical purposes, such as gene/drug transport, imaging, cellular probing, cellular differentiation, and photothermal therapy [173–179]. Colon cancer cells CT26 and macrophages have the ability to ingest graphene oxide, which promptly starts autophagy and elicits responses mediated by toll-including receptors TLR-4 and TLR-9,12–15. Chemoresistance was illustrated to be remarkable in CT26 cells, indicating that both graphene oxide and the chemotherapeutic drug cisplatin are ineffective in eliminating CT26 cells, whether used alone or in combination. Remarkably, the necrotic pathway was particulalrly observed to be activated under identical circumstances involving the combination of graphene oxide and cisplatin. Synergistic effects were reported in mice with CT26 colon tumors that were injected intratumorally with graphene oxide or cisplatin. These effects were facilitated by the infiltration of immune cells, cell death, and autophagy, resulting in enhanced anticancer outcomes. Overall, these findings indicate that graphene oxide can effectively overcome chemoresistance [180]. As a result, graphene oxide structures show great promise as cancer treatments.

Nanomaterials derived from carbon also show promise as potential cancer therapies for regulating autophagy. Graphene oxide can improve drug sensitivity by inducing early autophagy, necrosis, and nuclear trafficking [181]. The molecular mechanisms influenced by graphene oxide in the therapy of cancer and the control of autophagy have been comprehended. Graphene oxide nanoparticles can enhance the activity of AMPK, which in turn inhibits the mTOR pathway. This leads to an increase in ULK1 expression, which plays a role in the regulation of autophagy and apoptosis. These effects make graphene oxide nanoparticles a potential treatment for colorectal cancer [182]. In addition, graphene oxide composites halt cancer growth by mediating autophagy through the MyD88/TRAF5/TLR-4/-9 axis [183]. Graphene oxide composites have the ability to slow the advancement of osteosarcoma by increasing autophagosome formation, inducing autophagy flux, and upregulating ATG5, ATG7, and LC3-II [184]. Furthermore, the induction of autophagy by graphene oxide nanoparticles can enhance the susceptibility of non-small-cell lung cancer to radiation [185]. The conjugation of chloroquine to graphene oxide has the potential to inhibit pro-survival autophagy and improve necroptotic death in lung tumors [186]. An effective approach involves the integration of graphene oxide-silver nanostructures with cisplatin to enhance the induction of apoptosis and autophagy for the treatment of cervical cancer [187]. One potential mechanism by which carbon nanomaterials affect the immune system in cancer treatment is via stimulating autophagy. In addition to increasing tolerogenic dendritic cells and inhibiting pro-inflammatory T cell responses, graphene quantum dots can promote autophagy [188]. Nanoparticles of graphene oxide may inhibit pro-survival autophagy flux in cancer treatments even when they do not directly influence autophagosomes; this is because they damage lysosome function [189].

Multiple investigations have shown the potential of carbon-based nanomaterials in controlling autophagy in cancer cells. Cannabidiol has been encapsulated in biomimetic carbon monoxide nanocomplexes to induce robust autophagy for the purpose of cancer therapy [190]. Although autophagy may have some protective role at basic rates, it can mediate cell death at high rates; thus, nanomaterials that can extend autophagy at high levels should be utilized. Furthermore, research has indicated that fluorescent nitrogen-phosphorous-doped carbon dots can provoke autophagy in melanoma patients by expanding LC3-II and ATG5 levels while downregulating p62 [191].

*Metal nanomaterials*

Silver nanoparticles are commonly used in cancer treatment. Silver nanoparticles modulate the AMPK/mTOR axis and induce damage to the lysosomal membrane, hence inhibiting autophagy flux for cancer therapy [192]. If we want to know how silver nanoparticles control autophagy in cancer, we need to conduct further studies. One of the most important tools in the fight against cancer is radiotherapy (RT). Tumor recurrence and disease spread, however, restrict radiotherapy's utility in caring for cancer. Even when radiotherapy has a positive effect at first, this usually happens because cancer cells build a resistance [193–195]. Radiation sensitivity enhancement and radioresistance reduction are thus crucial areas of cancer therapy [196]. At least until something new is learned, autophagy prevents cells from dying when DNA is damaged. One lysosomal mechanism that tumor cells use to resist radiation is autophagy. Cancer cells are protected from autophagy or lysosome-mediated destruction, which can occur in response to a variety of stimuli. The use of autophagy inhibitors, such as hydroxychloroquine (HCQ) and chloroquine (CQ), has demonstrated encouraging outcomes in halting autophagy [197,198]. These compounds are also undergoing examination in clinical trials involving radiation therapy or chemotherapy, namely in cases of colon carcinoma (NCT00463169, NCT00602597) and bladder cancer (NCT02559892). The administration of CQ should enhance the susceptibility of cancer cells to chemotherapy or radiation therapy. In an in vivo model, Kasper and colleagues demonstrated that radiation therapy increases the efficacy of chemotherapy by making HCT116 cancer cells more sensitive to radiation [199]. Research has demonstrated that autophagy inhibitors can reduce the survival rate of cancer cells during the healing phase after radiation therapy. The reason for this is that cancer cells become more susceptible to radiation therapy when autophagy inhibitors increase the lysosomal

pH, therefore limiting the degradation of autophagic cargo. Hollow mesoporous silica nanostructures have been utilized for cancer therapy by delivering hydroxychloroquine. These nanoparticles exhibit significant absorption by tumor cells and, by inhibiting autophagy, they increase the susceptibility of colon cancer to radiation therapy [200].

Nanoparticles based on mimicking cell membranes (CMs) have evolved as a method of "learning from nature" in the last decade. These particles are convincing because they are biocompatible, biodegradable, and do not induce immunogenicity [201]. Through the process of modification with CM, nanoparticles acquire the physicochemical characteristics of carriers and the immunological characteristics of cells from which their membranes are produced [202]. Biomimetic mesoporous polydopamine nanostructures have been created for the purpose of administering CQ in cancer treatment. These biomimetic structures successfully bypass the barrier posed by the vasculature and avoid being engulfed by macrophages. Furthermore, these compounds exhibit precise tumor localization and deep tissue penetration, indicating that they effectively inhibit prostate tumor cells through autophagy suppression and photothermal treatment [203].

Metal-organic frameworks (MOFs) are alternative structures utilized for the transportation of substances in cancer treatment. The experiment involved loading liquid metal nanostructures and curcumin, which are autophagy activators, into ZIF-8 MOF structures. Subsequently, the nanocarriers were functionalized with either hyaluronic acid or alendronate. These nanocarriers exhibited a favorable photothermal effect and the capacity to combine at the location of bone metastases. The nanostructures induced a reduction in the effectiveness of autophagy and suppressed the expression of PD-L1 in the treatment of metastatic breast cancer, thereby reducing bone degradation In a different study, doxorubicin and water-based Nyctanthes arbortristis were delivered together using gold nanoparticles to overcome drug resistance and promote autophagy-mediated ferritinophagy via mTOR modulation [204]. The objective of this study was to create $MnO_2$ nanostructures for the purpose of delivering CQ. The $MnO_2$ nanoparticles loaded with CQ augment the production of $O_2$ and improve the pH. The presence of $MnO_2$ nanoparticles enhances the absorption of CQ by cells and facilitates its ability to inhibit autophagy, hence hindering the advancement of bladder tumor [205]. These studies propose that metal-based structures illustrate promise in regulating autophagy for cancer therapy.

The iron oxide nanoparticles have been shown to impair the protective autophagy in enhancing ferroptosis in ovarian cancer stem cells [206]. In human malignancies, stem cells are to blame for tumor recurrence and the emergence of resistance to therapy. As a result, novel information about cancer treatment can be gained by focusing on stem cells and controlling autophagy. In contrast, hepatoma therapy using iron oxide nanostructures improved cytotoxic autophagy [207]. Another mechanism by which silver nanoparticles inhibit autophagy flow is by inducing lysosomal damage [192]. Annona muricata green produced silver compounds can speed up apoptosis by increasing autophagy [208]. Ovarian cancer cells were found to undergo autophagy and apoptosis when treated with a mixture of salinomycin and silver nanostructures [209].

## Nanomaterials-mediated autophagy crosstalk with apoptosis and ferroptosis

### *Basics of apoptosis and ferroptosis*

Nanomaterials have demonstrated promise in modulating autophagy, apoptosis, and ferroptosis, which are significant mechanisms of cell death. Nanoparticles can cause apoptosis and autophagy independently in certain situations. However, in other cases, nanostructures can enhance autophagy, hence influencing apoptosis and ferroptosis in human malignancies. Examining the significance of nanoparticles in cancer therapy can be further emphasized by studying autophagy's relationship with apoptosis and ferroptosis, as autophagy can have either pro-survival or pro-death roles. An explanation of apoptosis and ferroptosis is given before these connections are highlighted.

During the occurrence of apoptosis, such as when DNA damage occurs, caspases (cysteine aspases) are activated through proteolytic cleavage. This activation leads to several biochemical and morphological alterations that are characteristic of apoptosis [210]. Caspase activation can occur via two main routes. The initiation of the extrinsic route occurs by the binding of transmembrane death receptors (CD95, TNF receptor, and TRAIL receptor), which triggers activation. Executioner caspases, such as caspase-3 and caspase-7, undergo cleavage and activation by caspase-8 and procaspase-10. Several proteins can inhibit caspases, which are proteases that cleave extracellular proteins that are distributed throughout the cytoplasm. These proteases are frequently observed in potentially malignant animals. FLIPs and inhibitors of apoptosis proteins, this process can be controlled by HATs and HDACs. At times, activator and effector caspases can be blocked by IAPs and FLIPs. For the intrinsic pathway to occur, there must be a disruption of the mitochondrial membrane, resulting in the release of several proteins including cytochrome *c*, Smac/DIABLO, HtRA2, and others. Cytochrome C and APAF trigger the activation of caspase-9, resulting in the initiation of the apoptotic caspase cascade. Conversely, Smac/DIABLO and HtrA2 attach to IAPs and assist in suppressing their activity [211–213].

Researchers exposed tumor cells to erastin, a small molecule chemical probe, in order to find ferroptosis, a novel form of iron-dependent cell death [214,215]. Ferroptosis is distinguished from other types of cell death by the complete destruction of its outer mitochondrial membrane, similar to necroptosis. The distinction between these two is that ferroptosis exhibits a reduced mitochondrial fraction and does not possess a mitochondrial crest. Simultaneously, it maintains its typical nuclear dimensions without any nuclear condensation [216]. Glutathione peroxidase 4 (GPX4) and its cofactor glutathione (GSH) are involved in this process, which can quickly decrease polyunsaturated fatty acids (PUFAs) that have been oxidized by lipoxygenase [217]. In contrast to usual lipoxygenases, 5-lipoxygenase oxidizes PUFAs rather than GSH to GSSG to start ferroptosis, although normally, lipoxygenases like 12-/15-lipoxygenase oxidize GSH to GSSG without oxidizing PUFAs. The ferroptosis program relies on the cystine/glutamate antiporter (as discussed below) being "turned off," which stops GSH production and renders GPX4 inactive. Cell death caused by excessive lipid peroxidation is known as ferroptosis [214], and class I agents such sulfasalazine, sorafenib, and inhibitors of system XC keep this process going [218]. RSL3 is an instance of a chemical classified as Class II that has been demonstrated to promote ferroptosis. Its mechanism of action involves the covalent binding and deactivation of GPX4 [219].

### *Nanoparticle-mediated autophagy interaction with apoptosis and ferroptosis*

Ovarian cancer has become less treatable with conventional methods. So far, using nanoparticles to treat ovarian cancer has shown promising results. Zinc oxide nanostructures, with a particle size of 20 nm, can reduce cancer cell survival. They are able to accomplish this by causing mitochondrial membrane potential to drop, which triggers cell death. Zinc oxide nanostructures promote apoptosis and autophagy in ovarian cancer via increasing p53 and LC3 levels [220]. Gold nanostructures in the shape of peanuts have been used to treat ovarian cancer and increase ROS production to aid in apoptosis and autophagy, just like zinc oxide nanoparticles [221]. Another approach involves using the calcifying structures to boost reactive oxygen species (ROS), induce cell death (cell death) and autophagy in bladder cancer patients [222]. It is worth mentioning that the nanomaterials can control cancer autophagy-mediated cell death. Mice injected with a therapeutic copper polypyridine complex encased in the natural nanocarrier apoferritin can undergo autophagy-mediated apoptosis in the context of colon cancer treatment [223]. Nevertheless, the autophagy-supportive suppression

expedites cell death and hinders tumor cell proliferation when hepatocellular carcinoma is treated with photothermal therapy using branching Au–Ag nanoparticles coated with polydopamine (PDA) [224].

Previously, the role of zinc oxide nanoparticles in promoting apoptosis was emphasized. The modulation of autophagy by zinc oxide nanostructures seems to have an impact on apoptosis. Zinc oxide nanoparticles induce autophagy and elevate p53 levels, leading to apoptosis in liver cancer [225]. Conversely, nanoparticles can prevent pro-survival autophagy, which in turn increases tumor cell death. Using ROS-responsive PEG-based nanocarriers, triptolide, an autophagy regulator, has been developed for delivery. By elevating ROS levels and lowering autophagy-supporting factors, these nanoparticles induce cell death in breast cancer cells [226]. As a result of hyperthermia, nanoparticles can increase ROS levels. The connection of Beclin-1, Bcl-2, and caspase-3 regulates the interplay between autophagy and apoptosis in these kinds of situations [227]. Nanoparticles that enhance autophagy can also play a role in cancer treatment by coordinating immune system responses. Mesoporous silica nanostructures loaded with zinc-doped disulfiram can mediate both necrosis and apoptosis. Afterwards, dendritic cells are recruited when autophagy degrades damaged organelles, releasing HMGB1, ATP, and antigens. Afterwards, dendritic cells mature into cancer immunotherapy cells that are $CD4^+$ and $CD8^+$ [228]. Insights into the regulation of the immune system have also been observed during the process of autophagy-mediated ferroptosis. Nanoparticles can induce autophagy, which promotes ferroptosis. This process is advantageous for the release of pro-inflammatory cytokines in macrophages and boosts the effectiveness of the anti-PD-L1 antibody in cancer immunotherapy [229].

The present theory proposes that nanoparticles may be useful in cancer treatment by either stimulating or inhibiting autophagy [230]. Research on nanostructures has mostly concentrated on their potential to control cell death and autophagy. Nanostructures made of copper oxide show promise to control breast tumor autophagy and apoptosis. Autophagy suppression enhances apoptosis in breast tumors, even if copper oxide nanoparticles induce autophagy [231]. The nanoparticles face a significant obstacle in their pursuit of supporting autophagy. One example is the cytoprotective autophagy mediated by chitosan nanoparticles, which enhance ROS production [232]. Here, the anti-cancer efficacy of nanoparticles is enhanced by the incorporation of autophagy inhibitors.

The majority of research has been on how zinc oxide nanostructures regulate autophagy in cancer. Nanoparticles of zinc oxide circumvent gastric carcinoma treatment resistance by suppressing autophagy, increasing apoptosis, and reducing proliferation and metastasis [233]. Zinc oxide nanoparticles induce autophagy, which reverses drug resistance, according to results of another trial. Nanostructures made of zinc oxide increase stress in the endoplasmic reticulum and promote autophagy. To reverse medication resistance, these nanoparticles promote cell death and inhibit the proliferation and spread of ovarian cancer [234].

There has been increased emphasis on the molecular processes that nanoparticles govern in regulating apoptosis and autophagy. Nanocarriers of cuprous oxide enhance apoptosis in bladder cancer cells by activating the ERK pathway, which in turn triggers autophagy through upregulating the expression of LC3B, ATG5, and ATG7 [235]. The potential of nanoparticles to regulate molecular pathways has been touted in some instances, but the interaction between autophagy and apoptosis has been disregarded in others. In neurogliomas, quercetin nanostructures can evoke apoptosis and autophagy by downregulating PI3K/Akt, Bcl-2, mTOR, and GAIP and upregulating p53, caspase-3, LC3, and ERK. Thus, quercetin nanoparticles promote apoptosis by activating the LC3/ERK/Caspase-3 axis and autophagy by downregulating Akt/mTOR [236]. Therefore, there is growing evidence that nanostructures can effectively control both apoptosis and autophagy in cancer treatment. In certain situations, the interaction between both processes is influenced by nanocarriers [208,209,237–246].

Nanostructures known as TreMMM, which include trehalose and mSiO2@MnOx-mPEG, can trigger ferroptosis by consuming GSH and inhibiting GPX4. Further, the release of trehalose by these nanoparticles initiates autophagy, which in turn improves tumor cell ferroptosis by increasing ferritin breakdown through NCOA4 [247]. Iron oxide nanostructures treated with polymers can activate autophagy in tumor cells, leading to ferroptosis [248]. Ovarian cancer stem cells can undergo enhanced ferroptosis when superparamagnetic iron oxide nanostructures impede autophagy, which can have a pro-survival function [206]. Thus, nanoparticles govern cancer autophagy and its interactions with apoptosis and ferroptosis. Table 3 is a summary of the nanomaterials in autophagy regulation. Fig. 7 emphasized the function of nanoparticles in the regulation of apoptosis and ferroptosis through controlling autophagy in human cancers. Fig. 8 shows several nanoparticles regulating autophagy in cancer.

## Exosomes and autophagy crosstalk

Proteins, nucleic acids, lipids, and other substances are housed in small vesicles called exosomes, which are characterized by lipid bilayer membranes [250]. The cells contain conserved components such as tetraspanin proteins (CD9, CD63, and CD81), Alix, flotillin, TSG101, immunomodulatory proteins (MHC), heat shock proteins (HSP70 and HSP90), and CD47 [251]. These exosome biomarkers—CD9, CD81, CD63, flotillin, TSG101, and Alix—influence biogenesis, cargo clustering, and exosome secretion, among other processes. With MHC at the helm, the exchange of antigen-related data between immune cells occurs automatically [252]. Exosomes can adjust to the external environment with the aid of HSP70 and HSP90. In addition, CD47 on exosomes produces a signal that instructs them to refrain from being engulfed. This hinders the digestion of exosomes by monocytes and macrophages, leading to an augmentation in their stability within the body [253]. In addition to expressing conserved proteins, exosomes also express cell-specific proteins that are correlated with the source of the donor cells. If we take exosomes made by platelets as an example, we can see that they have CD41a and von Willebrand factor, but exosomes made by T cells have CD3 [254,255]. The origin of parental cells is marked by the presence of exosomes, which also possess some functional characteristics of parental cells. However, the composition and amount of exosomal cargo are determined by the physiological or pathological state of the cells that release them. Exosomes transport several types of cargo, such as microRNAs, siRNAs, and messenger RNAs (mRNAs), which can be

**Table 3**
Nanoparticle-mediated autophagy regulation in cancers.

| Nanoparticle | Outcome | Reference |
|---|---|---|
| Calcium phosphate nanocarriers | The nanocarriers increase calcium levels in the cells to inhibit autophagy in hepatocellular carcinoma therapy | [249] |
| Gold nanostructures | The peanut-shaped gold nanostructures can mediate apoptosis and autophagy in ovarian cancer through regulating ROS levels | [221] |
| Polystyrene nanostructures | Nanostructures restrict the formation of autophagosomes, inhibit autophagy and increase levels of mitochondrial anion superoxide and downregulate ATG4 | [107] |
| ATB0,+-targeted nanoparticles | The inhibition of autophagy can reverse chemoresistance in colorectal tumor | [108] |
| Fol-LSMO nanostructures | They release doxorubicin and mediate hyperthermia to accelerate apoptosis and autophagy in breast tumor | [227] |
| Self-assembled micelles | Delivery of oxaliplatin into the tumor microenvironment to mediate immunogenic cell death and mildly induce autophagy | [157] |
| Silver nanostructures | The silver nanoparticles induce lysosomal injury and impair the lysosomal protease function to finally suppress autophagy flux | [192] |
| Zinc oxide nanostructures | Upregulation of 53 and autophagy stimulation to accelerate apoptosis in liver tumor | [225] |

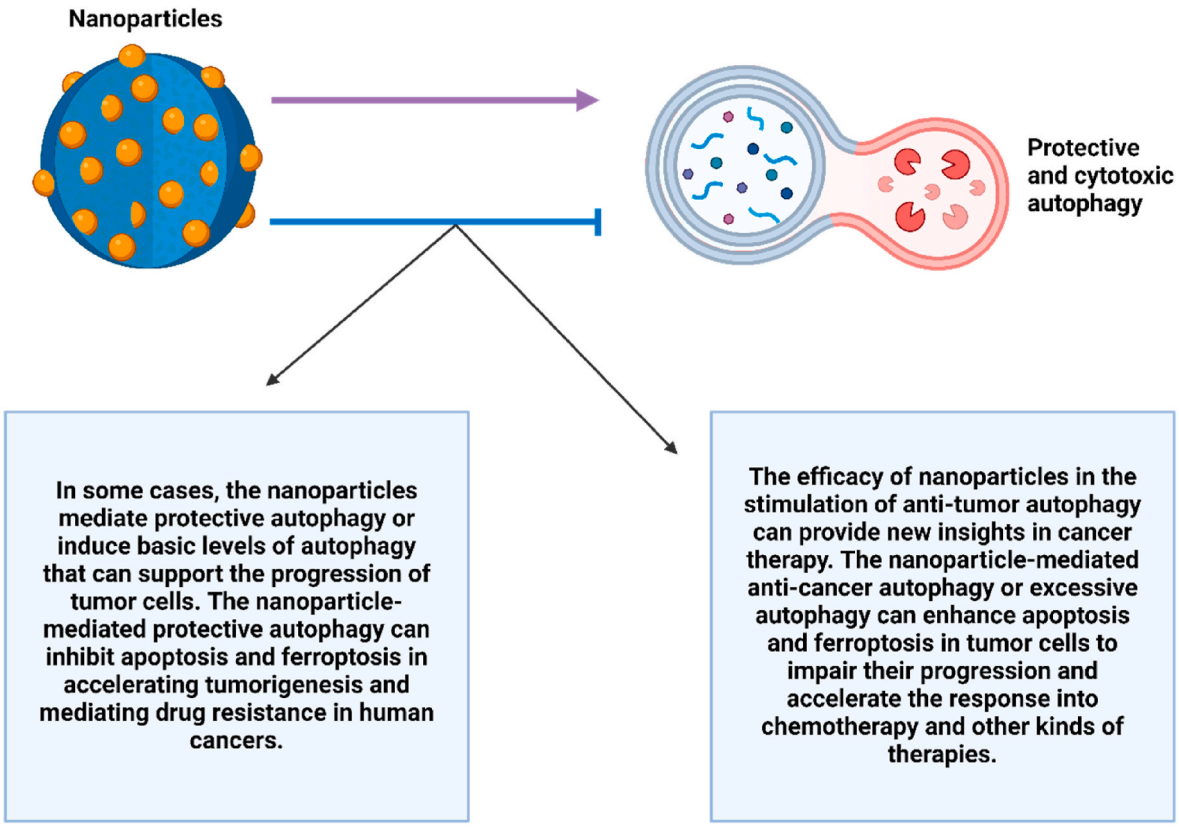


**Fig. 7.** The nanoparticle-mediated autophagy regulation in controlling apoptosis and ferroptosis. The nanoparticles can induce both protective and cytotoxic autophagy in human cancers. The potential of nanoparticles in the stimulation of cytotoxic or excessive autophagy can enhance apoptosis and ferroptosis in tumor cells.

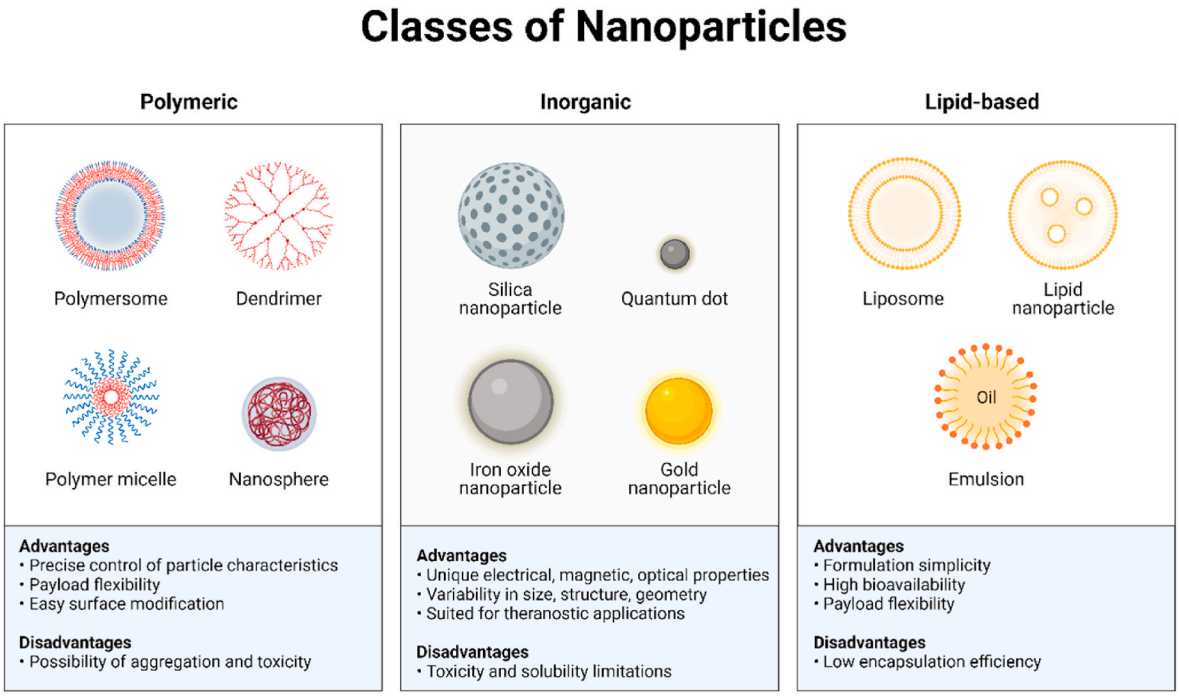


**Fig. 8.** There are several kinds of nanoparticles that their efficacy in the regulation of autophagy has been well-evaluated. Polymeric, lipid and inorganic nanomaterials have been utilized in autophagy regulation. However, there is poor information regarding several nanoparticles including dendrimers, polymerosomes and emulsion nanoparticles. Moreover, exosomes are structures with nano-scale size that can regulate autophagy in cancer.

transmitted to other cells and influence the expression of the genes associated with them. Some of these genes are linked to autophagic proteins [256]. One example is the finding that cardiac cell-derived exosomes exhibit an increase in miR-30a overexpression when exposed to hypoxia [257]. However, it was discovered that bronchial epithelial cells were markedly enhanced by cigarette smoke with respect to exosomal miR-210 [258]. Cells that have been exposed to radiation have shown an elevated level of exosomal miR-7-5p [259].

The mechanisms by which specific ATG proteins regulate exosome production and secretion are currently the topic of several investigations [260,261]. Interestingly, it has been observed that ATG5, which is involved in the process of autophagosome precursor synthesis [262], facilitates the dissociation of vacuolar proton pumps (V1V0-ATPase) from the MVBs. This, in turn, prevents the acidification of the MVB-lumen and contributes to the fusion of the MVB with the plasma membrane [263] in a manner that is canonical autophagy-independent with the process. When Atg5 mutant cells were treated with V-ATP inhibitors, it was observed that the acidity level inside the vesicles (luminal pH) determines whether the multivesicular bodies (MVBs) should fuse with lysosomes for degradation or with the plasma membrane for the release of exosomes [264]. This was proved by the fact that the concentration of the luminal pH was found to be significant. Exosome synthesis in breast cancer cells is reduced as a result of the down-regulation of both ATG16L1, a key autophagy protein that is implicated at various phases of autophagosome biogenesis [262], and ATG5. This, in turn, leads to a reduction in tumor metastasis. Guo and his colleagues have provided evidence for this [263]. Furthermore, G alpha interacting protein (GAIP) and GAIP interacting protein C-terminus (GIPC), those two proteins that were initially identified for G-protein coupled receptor subunit GI alpha [265], have the ability to simultaneously stimulate exosome biogenesis and autophagy flux in pancreatic tumor cells [266]. It has been proven by Murrow and colleagues [267] that the suppression of ATG12–ATG3, which is a complex that is important for a late phase in the development of autophagosomes [262], alters the shape of MVBs, affects late endosome trafficking, and decreases the production of exosomes. The phenomenon in question is attributed to the interaction between ATG12-ATG3 and ALIX, a protein involved in membrane fission and known to interact with ESCRT members involved in exosome release. In addition, inhibiting ALIX leads to a decrease in the normal flow of autophagy, indicating that autophagy and exosome formation are mutually controlled. It is worth mentioning that the lack of ALIX or the decrease in the ATG12-ATG3 complex does not impact the autophagy induced by hunger. This emphasizes the correlation between many complexes that control both the fundamental and stress-induced processes of autophagy [267]. The study conducted by Bader and colleagues reveals that the transmembrane protein ATG9 plays a crucial role in the formation of intracellular vesicles (ILVs) in *Drosophila melanogaster*. Under normal conditions, the loss of ATG9 leads to the inhibition of autophagy and a decrease in the quantity of intracellular vesicles (ILVs) found in amphisomes and autolysosomes [268]. LC3B, sometimes referred to as the Microtubule Associated Protein 1 Light Chain 3 Beta, plays a crucial role in the autophagy process. LC3B is a crucial biomarker for measuring autophagy flux. During the initiation phase, the LC3B conjugation complex enhances the creation of autophagosomes by activating ULK. LC3B plays a crucial role in facilitating the closure, fusion, and transportation of the autophagosome during its maturation phase [269]. LC3B is incorporated into autophagosome membranes and is also drawn to single-membrane phagosomes by a process called LC3-associated phagocytosis (LAP). The formation of autophagosomes is not required for this process [270,271]. Evidence demonstrates that LC3B is found in exosomes, namely in its LC3-I form rather than LC3-II, in a way that is not influenced by ATG7. This discovery indicates that the LAP-like lipidation mechanism may serve a non-degradative purpose in the exosome secretion process. In addition, a study conducted recently has identified a distinct method of secretion in which the components of the LC3 conjugation complex enhance their interaction with RNA binding proteins (RBPs) and short non-coding RNAs to form extracellular vectors (EVs). As a result, these RNAs are ultimately secreted outside of cells [272].

Acquiring resistance to chemotherapies and targeted treatments is a major obstacle in the battle against cancer, and it remains a topic of active investigation [273]. It is crucial to comprehend how cancer cells can develop resistance to chemotherapy if we are to effectively manage cancer. Evidence suggests that pharmaceutical therapies stimulate autophagy upregulation and exosome release [274,275]. This implies that these mechanisms are part of the cancer cell's stress response or survival strategy in response to chemotherapy. Elevations in the levels of autophagy flux and exosome production have been observed in many types of chemotherapy-resistant cancers [276,277]. These results lend support to the idea that this could be the case. One example is the observation that serum from individuals with cisplatin-resistant malignancies and platinum-resistant ovarian cancer cell lines both show an enhanced release of exosomes [278]. Furthermore, it has been found that ovarian cancer cells that are resistant to platinum treatment have an elevated autophagy flux [279]. These discoveries serve as the foundation for studying the therapeutic potential of suppressing autophagy and altering exosome release to overcome chemotherapy resistance. While it remains uncertain if these alterations are a component of the resistance mechanism or merely a result of the changing cellular phenotype, these observations serve as the foundation for further inquiry. Another important aspect to address is the downstream signaling consequences of exosomes derived from chemotherapy-resistant cancer cells. There is a suggestion that exosomes could potentially facilitate the development of drug-resistant characteristics by transmitting microRNA or multidrug-resistant transporter (MDR) proteins [280–282]. This is an explanation that many researchers have offered. Evidence emerged from another context showing that recipient cancer cells become less responsive to cisplatin treatment after receiving exosomes produced by EGFR-mutant PC-9 cells treated with gefitinib [283].

In solid tumor growth and metastasis, angiogenesis—the process of creating new blood networks from preexisting vessels—plays a crucial role [284]. Hypoxia, a frequently observed state in the vicinity of tumors, is a crucial factor in the process of angiogenesis [285]. Autophagy is triggered in hypoxic conditions by the activation of AMPK, a process that operates apart from the HIF-1α pathway. The HIF-1α pathway is important for regulating cellular energy balance [286]. The activation of the HIF-1α pathway, which promotes angiogenesis and consequently initiates the process of exosome biogenesis, in this specific case [287]. Tumor-derived exosomes have the capacity to stimulate endothelial cells to release a diverse range of growth factors and cytokines. In addition, pericytes are able to move through the PI3K/AKT signaling pathway, thereby playing a role in the process of angiogenesis [288]. Malignant mesothelioma cells within the same vein release exosomes. The exosomes may stimulate angiogenesis and vascular rearrangement, which could speed up tumor growth by increasing the mobility of angiogenic cells [289]. Glioma cells have been shown to release exosome-like vesicles, as demonstrated by Svensson and colleagues [290]. These vesicles can transfer tissue factor and stimulate angiogenesis by greatly enhancing the activity of protease-activated receptor 2 in epithelial cells. It is likely that tumor cells, when exposed to low oxygen circumstances, may release exosomes that carry substances promoting the growth of new blood vessels and the spread of cancer cells. This suggests that tumor cells are responding to the hypoxic stress by implementing a compensating mechanism. This can be achieved by promoting the development of blood vessels in the secondary tissue and aiding the spread of cancer cells to other parts of the body [291,292]. Endothelial cells (ECs) experience several stressful conditions within the tumor environment. The variables encompass hypoxia, reduced blood and glucose levels, and nutritional deficiency. When these diseases occur together, they cause disturbances in the structure and function of the vascular system [293]. Tumor vasculature are different from normal tissue vessels in multiple ways, including diameter, permeability, and

stability [294]. These qualities cause a disruption in blood flow, resulting in a decrease in the availability of oxygen and nutrients. Autophagy has been extensively demonstrated to have a key role in extracellular vesicles (ECs) [293]. Autophagy is mainly used by ECs for energy balance maintenance and stress adaptation [295]. Chloroquine (CQ), a substance that inhibits autophagy, has been demonstrated to create strong connections between extracellular vesicles (ECs). This, in turn, decreases the ability of tumor cells to invade and spread to other parts of the body [296]. Maes and colleagues demonstrated this in their research. Autophagy flux is heightened in the extracellular matrix (ECs) under hypoxic settings, and this augmentation happens concurrently with the activation of HIF-1α and VEGF signaling pathways [295]. An increase in autophagy flux in extracellular matrix (EC) cells inside the microenvironment of the tumor is a factor that contributes to the preservation of homeostasis. As a result, the decrease of Atg5 in ECs may exacerbate the abnormalities in the function of tumor arteries, which is an indication of the crucial role that autophagy plays in the homeostasis of ECs [296].

## Conclusion and perspectives

The role of autophagy in tumor growth is context-dependent, which makes it a challenging technique for cancer treatment. Furthermore, autophagy can promote cell survival in specific types of cancer, yet in other cases, it can stimulate the death of cancer cells. If it has been confirmed that autophagy plays a role in the cancer cell's ability to survive or die, then it should be specifically addressed and targeted. Autophagy regulators have been utilized in many cancer therapies, encompassing both artificial and naturally derived compounds. Due to their ability to target cancer cells, nanoparticles have the potential to enhance the impact of autophagy regulators and further inhibit cancer growth. Nanoparticles have a crucial role in cancer treatment. Given the significant role of autophagy in chemoresistance, there is growing interest in enhancing the sensitivity of cancer cells to chemotherapy by either inhibiting or inducing autophagy. Simultaneously introducing chemotherapeutic drugs and autophagy modulators can impact autophagy in a manner that enhances the death of cancer cells. For instance, when autophagy is involved in promoting tumors, the effectiveness of chemotherapy can be significantly enhanced by administering autophagy inhibitors by nanoparticles. Eliminating cytoprotective autophagy increases cancer cell death, hence enhancing the effectiveness of chemotherapeutic treatments against malignancies. In addition, autophagy genes, including ATGs and others, can be selectively influenced using genetically modified tools like shRNA and siRNA to control autophagy. To achieve optimal effectiveness in gene therapy, nanoparticles can be utilized to increase the longevity of genetic entities within targeted cells and enhance their micropinocytosis. Specific nanoparticles also aided in regulating autophagy genes, cellular processes, and the transfer of pharmacological reference genetics. Gold nanoparticles, widely recognized in cancer treatment, can enhance the generation of reactive oxygen species (ROS), so stimulating autophagy and death. This is significant since autophagy typically can promote tumor growth. There is a proposal to improve the cancer cell by employing autophagy inhibitors due to the protective impact of autophagy with nanoparticle-mediated autophagy in the cancer cell. It is important to note that autophagy primarily functions to preserve homeostasis and is activated when it reaches dangerous levels, resulting in cell death in healthy cells. Excessive activation of autophagy results in the death of cells, which is one of the reasons behind chemosensitivity and cancer immunotherapy. The pre-clinical experiments have demonstrated the efficacy of gold nanoparticles in controlling autophagy. Therefore, additional research can be conducted to explore their potential in cancer therapy. According to information available on the clinicaltrials.gov website, researchers have made efforts to assess the significance of autophagy in cancer patients and explore the potential of autophagy regulators for their treatment. This has been done through two clinical studies, namely NCT01292408 and NCT01649947. Nanocarriers, as explained in the main text, offer precise delivery and increased accumulation of cargo within cells, significantly enhancing the effectiveness of autophagy modulators in suppressing cancer. Hence, in order to treat cancer patients, the logical progression would be to utilize the findings from pre-clinical studies. Nevertheless, there remain numerous inquiries that need to be addressed. Which type of nanocarrier is most suitable for delivering autophagy modulators for therapeutic purposes? There are two things that need to be considered when addressing this topic. One advantage is the capacity for mass production. Another factor to consider is biocompatibility. The tolerability and safety characteristics of nanoscopic particles are regarded as indicators for their clinical application. Regarding this matter, nanostructures that rely on lipids and polymers are favored over those that rely on metals and carbon. Scientists have discovered that carbon-based nanoparticles, such as graphene, might cause harm. As a result, scientists have made changes to these nanoparticles by including natural substances, such chitosan, to improve their ability to interact with living organisms.

Endoplasmic reticulum stress is recognized as a controller of both apoptosis and autophagy. Endoplasmic reticulum stress at a modest level triggers autophagy as a means of maintaining homeostasis, whereas high levels of endoplasmic reticulum stress result in autophagic cell death. Despite several studies on the potential of nanostructures in regulating endoplasmic reticulum stress-induced autophagy and apoptosis, the molecular interactions involved have been overlooked. Future research should assess the impact of nanostructures on molecules and proteins associated with endoplasmic reticulum stress, including PERK, IREF1α, CHOP, and ATF4. This evaluation should focus on how these factors regulate apoptosis and autophagy, as well as their interplay in the context of cancer therapy. Further research is needed to explore the involvement of nanoparticle-mediated autophagy in the process of ferroptosis and its impact on the breakdown of GPX4, which plays a crucial role in promoting ferroptosis. Moreover, ferritinophagy is a kind of autophagy-mediated ferroptosis, and the role of nanoparticles in ferritinophagy induction requires investigation.

Exosomes have recently gained recognition as a novel type of nanostructure that can be artificially created in a laboratory setting. Exosomes obtained from immune cells, tumor cells, and normal cells can be modified using aptamers and peptides. These modified exosomes can then be used to deliver therapeutic chemicals for cancer treatment via regulating autophagy. The introduction of bioengineered exosomes in cancer therapy should include the study of exosome-mediated autophagy regulation, regulated molecular pathways, and their interaction with apoptosis and ferroptosis. For instance, scientists have developed bioengineered camouflaged exosomes that induce apoptosis, autophagy, and ferroptosis in melanoma [297]. Nevertheless, it is crucial to focus specifically on exosomes due to their exceptional biocompatibility and origin from within the body's cells. Thus, their clinical utilization may be established in the future for the management of cancer patients.

One area that has gained significant attention, particularly in recent times, is the utilization of biomimetic nanoparticles for cancer therapy. Biomimetic nanoparticles can be created by modifying the surfaces of objects with cell membranes, including those from tumor cells, macrophages, and fibroblasts, among others. There is growing evidence that biomimetic nanocarriers can decrease carcinogenesis [298–301]. While numerous studies have examined the potential of biomimetic nanocarriers in regulating autophagy, there is a lack of biological understanding. Further research is needed to investigate the molecular pathways involved, such as mTOR, AMPK, and ATGs. Furthermore, it is necessary to investigate the interplay between autophagy, apoptosis, and ferroptosis induced by biomimetic nanoparticles. While many types of lipid-based nanostructures have been used to control autophagy in cancer treatment by delivering pharmaceuticals, it is important to note that solid lipid nanoparticles exhibit a high capacity for drug loading and encapsulation efficiency. Hence, it is imperative to closely monitor the utilization of solid lipid nanoparticles loaded with autophagy

modulators for cancer therapy. When it comes to carbon-based nanomaterials, the impact of graphene oxide nanoparticles on autophagy has been comprehended. However, it is important to emphasize the significance of other types of nanostructures, particularly carbon quantum dots. Furthermore, the examination of how nanoparticles that enhance ROS production can regulate autophagy and its interaction with apoptosis and ferroptosis is necessary.

Mounting data has emphasized the role of autophagy in the control of cancer immunotherapy. Autophagy-related genes can serve as indicators of immune responses in tumor cells [302]. Moreover, autophagy shows interaction with a number of cells involved in immune reaction such as myeloid-derived suppressor cells [303]. Therapeutic control of autophagy has the potential to alter the immunosuppressive tumor microenvironment by influencing the release, presentation, recognition, and trafficking of antigens and immune cells [304]. It is worth mentioning that multiple studies have linked autophagy to immunogenic cell death in human malignancies [305–307]. Recent research has demonstrated that nanostructures that control autophagy can induce immunogenic cell death [308]. Additional research into the molecular mechanisms at work and the impact of nanoparticle architecture on the interaction between autophagy and immunogenic cell death is necessary.

## Funding

National Natural Science Foundation of China (Grant No. 82303491); Technology Foundation to support the high-quality development of China Medical University (Grant No. 2023JH2/20200091).

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgment

The authors of this paper used Biorender.com to draw figures.

## References

[1] Q. Wu, D. Sharma, Autophagy and breast cancer: connected in growth, progression, and therapy, Cells 12 (8) (2023).
[2] Z. Yang, D.J. Klionsky, Mammalian autophagy: core molecular machinery and signaling regulation, Curr. Opin. Cell Biol. 22 (2) (2010) 124–131.
[3] M. Bednarczyk, et al., Genes involved in the regulation of different types of autophagy and their participation in cancer pathogenesis, Oncotarget 9 (76) (2018) 34413–34428.
[4] V. Deretic, Autophagy in inflammation, infection, and immunometabolism, Immunity 54 (3) (2021) 437–453.
[5] D.J. Klionsky, et al., Autophagy in major human diseases, EMBO J. 40 (19) (2021) e108863.
[6] J.L. Guan, et al., Autophagy in stem cells, Autophagy 9 (6) (2013) 830–849.
[7] N.C. Chang, Autophagy and stem cells: self-eating for self-renewal, Front. Cell Dev. Biol. 8 (2020) 138.
[8] L. Galluzzi, D.R. Green, Autophagy-independent functions of the autophagy machinery, Cell 177 (7) (2019) 1682–1699.
[9] S.N. Jia, et al., The transcription factor p8 regulates autophagy in response to palmitic acid stress via a mammalian target of rapamycin (mTOR)-independent signaling pathway, J. Biol. Chem. 291 (9) (2016) 4462–4472.
[10] K.R. Parzych, D.J. Klionsky, An overview of autophagy: morphology, mechanism, and regulation, Antioxidants Redox Signal. 20 (3) (2014) 460–473.
[11] O. Conway, et al., Selective autophagy receptors in neuronal health and disease, J. Mol. Biol. 432 (8) (2020) 2483–2509.
[12] E. Wirawan, et al., Autophagy: for better or for worse, Cell Res. 22 (1) (2012) 43–61.
[13] D. Mijaljica, M. Prescott, R.J. Devenish, Microautophagy in mammalian cells: revisiting a 40-year-old conundrum, Autophagy 7 (7) (2011) 673–682.
[14] A. Massey, R. Kiffin, A.M. Cuervo, Pathophysiology of chaperone-mediated autophagy, Int. J. Biochem. Cell Biol. 36 (12) (2004) 2420–2434.
[15] T. Yorimitsu, D.J. Klionsky, Autophagy: molecular machinery for self-eating, Cell Death Differ. 12 (Suppl 2) (2005) 1542–1552. Suppl 2.
[16] W.J. Liu, et al., p62 links the autophagy pathway and the ubiqutin-proteasome system upon ubiquitinated protein degradation, Cell. Mol. Biol. Lett. 21 (2016) 29.
[17] M.O. Faruk, Y. Ichimura, M. Komatsu, Selective autophagy, Cancer Sci. 112 (10) (2021) 3972–3978.
[18] C. Münch, I. Dikic, Hitchhiking on selective autophagy, Nat. Cell Biol. 20 (2) (2018) 122–124.
[19] S. Dabagh, S.A. Haris, Y.N. Ertas, Engineered polyethylene glycol-coated zinc ferrite nanoparticles as a novel magnetic resonance imaging contrast agent, ACS Biomater. Sci. Eng. 9 (7) (2023) 4138–4148.
[20] A. Taheriazam, et al., Graphene oxide nanoarchitectures in cancer biology: nanomodulators of autophagy and apoptosis, J. Contr. Release 354 (2023) 503–522.
[21] L. Xu, et al., Supramolecular cyclic dinucleotide nanoparticles for STING-mediated cancer immunotherapy, ACS Nano 17 (11) (2023) 10090–10103.
[22] T. Kim, et al., Nanoengineered polymeric RNA nanoparticles for controlled biodistribution and efficient targeted cancer therapy, ACS Nano 18 (11) (2024) 7972–7988.
[23] L. Xiao, et al., Multifunctional Au@AgBiS(2) nanoparticles as high-efficiency radiosensitizers to induce pyroptosis for cancer radioimmunotherapy, Adv. Sci. 10 (30) (2023) e2302141.
[24] Y. Zhou, et al., Emissive nanoparticles from Co-assembly of metallatetragon and amphiphilic tetraphenylethylene for cancer theranostics, Inorg. Chem. 62 (37) (2023) 15015–15021.
[25] S.H. Park, et al., Photosensitizing deep-seated cancer cells with photoprotein-conjugated upconversion nanoparticles, J. Nanobiotechnol. 21 (1) (2023) 279.
[26] C. Xu, et al., Doxorubicin and erastin co-loaded hydroxyethyl starch-polycaprolactone nanoparticles for synergistic cancer therapy, J. Contr. Release 356 (2023) 256–271.
[27] A.B. Mousa, et al., Zinc oxide nanoparticles promise anticancer and antibacterial activity in ovarian cancer, Pharm. Res. (N. Y.) 40 (10) (2023) 2281–2290.
[28] Z. Cao, et al., Biomimetic macrophage membrane-camouflaged nanoparticles induce ferroptosis by promoting mitochondrial damage in glioblastoma, ACS Nano 17 (23) (2023) 23746–23760.
[29] B. Ding, et al., Sodium bicarbonate nanoparticles for amplified cancer immunotherapy by inducing pyroptosis and regulating lactic acid metabolism, Angew Chem. Int. Ed. Engl. 62 (40) (2023) e202307706.
[30] Y. Zhao, et al., Co-delivery of gemcitabine and Triapine by calcium carbonate nanoparticles against chemoresistant pancreatic cancer, Int. J. Pharm. 636 (2023) 122844.
[31] M. Tavira, et al., PCL/gelatin nanofibers embedded with doxorubicin-loaded mesoporous silica nanoparticles/silver nanoparticles as an antibacterial and anti-melanoma cancer, Int. J. Pharm. 642 (2023) 123162.
[32] M. Sun, et al., Co-delivery of EGCG and melittin with self-assembled fluoro-nanoparticles for enhanced cancer therapy, Aging (Albany NY) 15 (11) (2023) 4875–4888.
[33] L. Zhu, et al., Glutathione-sensitive mesoporous nanoparticles loaded with cinnamaldehyde for chemodynamic and immunological therapy of cancer, J. Mater. Chem. B 11 (36) (2023) 8717–8731.
[34] T. Gong, et al., Biomimetic microenvironmental stiffness boosts stemness of pancreatic ductal adenocarcinoma via augmented autophagy, ACS Biomater. Sci. Eng. 9 (9) (2023) 5347–5360.
[35] Y. Gao, et al., AKR1C3 silencing inhibits autophagy-dependent glycolysis in thyroid cancer cells by inactivating ERK signaling, Drug Dev. Res. 85 (1) (2024) e22142.
[36] P. Du, X. Xu, Y. Wang, Hsa_circ_0000585 promotes chemoresistance to cis-platin in epithelial cells of ovarian cancer by modulating autophagy, Biochem. Biophys. Res. Commun. 678 (2023) 186–192.
[37] P. Singh, et al., Calotropis procera extract inhibits prostate cancer through regulation of autophagy, J. Cell Mol. Med. 28 (6) (2024) e18050.
[38] H. Min, et al., SNHG15 promotes gallbladder cancer progression by enhancing the autophagy of tumor cell under nutrition stress, Cell Cycle 22 (19) (2023) 2130–2141.
[39] Y. Xiang, et al., lncRNA HOXC-AS2 promotes the progression of hypopharyngeal cancer by binding to the P62 protein mediating the autophagy process, Aging (Albany NY) 15 (21) (2023) 12476–12496.
[40] C. Marin-Muller, et al., Nanoparticle-mediated therapy with miR-198 sensitizes pancreatic cancer to gemcitabine treatment through downregulation of VCP-mediated autophagy, Pharmaceutics 15 (8) (2023).
[41] X. Zhao, et al., ALKBH5 suppresses autophagy in prostate cancer cells via inhibiting m6A-modification of TSPAN1 mRNA, Discov. Med. 36 (180) (2024) 61–70.

[42] S. Zhu, et al., CAF-derived exosomal lncRNA FAL1 promotes chemoresistance to oxaliplatin by regulating autophagy in colorectal cancer, Dig. Liver Dis. 56 (2) (2024) 330–342.
[43] C.H. Chang, et al., REST-repressed lncRNA LINC01801 induces neuroendocrine differentiation in prostate cancer via transcriptional activation of autophagy, Am. J. Cancer Res. 13 (9) (2023) 3983–4002.
[44] J. He, et al., Maackiain suppresses the development of cervical cancer via AMPK priming autophagy, J. Pharm. Pharmacol. 76 (1) (2024) 23–33.
[45] C. Li, et al., LGR5, a prognostic stem cell target, promotes endometrial cancer proliferation through autophagy activation, Transl. Oncol. 40 (2024) 101853.
[46] Y. Tian, et al., Silencing of IGHG1 reverses the resistance of pancreatic cancer to multidrug chemotherapy by modulating autophagy, Environ. Toxicol. 38 (8) (2023) 1835–1845.
[47] H. Pan, et al., Matrix stiffness triggers chemoresistance through elevated autophagy in pancreatic ductal adenocarcinoma, Biomater. Sci. 11 (22) (2023) 7358–7372.
[48] S.Y. Chen, et al., Diphenyl disulfide potentiates the apoptosis of breast cancer cells through Bax proteolytic activation with accompanying autophagy, Environ. Toxicol. 38 (8) (2023) 2022–2030.
[49] C. Sokollik, M. Ang, N. Jones, Autophagy: a primer for the gastroenterologist/hepatologist, Can. J. Gastroenterol. 25 (12) (2011) 667–674.
[50] A. Matsuura, et al., Apg1p, a novel protein kinase required for the autophagic process in Saccharomyces cerevisiae, Gene 192 (2) (1997) 245–250.
[51] N. Mizushima, et al., A new protein conjugation system in human. The counterpart of the yeast Apg12p conjugation system essential for autophagy, J. Biol. Chem. 273 (51) (1998) 33889–33892.
[52] Y. Kabeya, et al., LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing, EMBO J. 19 (21) (2000) 5720–5728.
[53] N. Mizushima, et al., Dissection of autophagosome formation using Apg5-deficient mouse embryonic stem cells, J. Cell Biol. 152 (4) (2001) 657–668.
[54] N. Mizushima, et al., Mouse Apg16L, a novel WD-repeat protein, targets to the autophagic isolation membrane with the Apg12-Apg5 conjugate, J. Cell Sci. 116 (Pt 9) (2003) 1679–1688.
[55] N. Fujita, et al., The Atg16L complex specifies the site of LC3 lipidation for membrane biogenesis in autophagy, Mol. Biol. Cell 19 (5) (2008) 2092–2100.
[56] Y. Ichimura, et al., A ubiquitin-like system mediates protein lipidation, Nature 408 (6811) (2000) 488–492.
[57] D.J. Klionsky, et al., Guidelines for the use and interpretation of assays for monitoring autophagy in higher eukaryotes, Autophagy 4 (2) (2008) 151–175.
[58] R.L. Deter, P. Baudhuin, C. De Duve, Participation of lysosomes in cellular autophagy induced in rat liver by glucagon, J. Cell Biol. 35 (2) (1967) C11–C16.
[59] U. Pfeifer, Inhibition by insulin of the formation of autophagic vacuoles in rat liver. A morphometric approach to the kinetics of intracellular degradation by autophagy, J. Cell Biol. 78 (1) (1978) 152–167.
[60] G.E. Mortimore, C.M. Schworer, Induction of autophagy by amino-acid deprivation in perfused rat liver, Nature 270 (5633) (1977) 174–176.
[61] T. Noda, Y. Ohsumi, Tor, a phosphatidylinositol kinase homologue, controls autophagy in yeast, J. Biol. Chem. 273 (7) (1998) 3963–3966.
[62] K. Inoki, T. Zhu, K.L. Guan, TSC2 mediates cellular energy response to control cell growth and survival, Cell 115 (5) (2003) 577–590.
[63] P.O. Seglen, P.B. Gordon, 3-Methyladenine: specific inhibitor of autophagic/lysosomal protein degradation in isolated rat hepatocytes, Proc. Natl. Acad. Sci. U.S.A. 79 (6) (1982) 1889–1892.
[64] S. Sarkar, et al., Lithium induces autophagy by inhibiting inositol monophosphatase, J. Cell Biol. 170 (7) (2005) 1101–1111.
[65] Y. Wei, et al., JNK1-mediated phosphorylation of Bcl-2 regulates starvation-induced autophagy, Mol. Cell 30 (6) (2008) 678–688.
[66] A. Gęgotek, E. Skrzydlewska, Lipid peroxidation products' role in autophagy regulation, Free Radic. Biol. Med. 212 (2024) 375–383.
[67] E. Rey-Jurado, et al., Contribution of autophagy to antiviral immunity, FEBS Lett. 589 (22) (2015) 3461–3470.
[68] H.-H. Cha, et al., Autophagy induced by tumor necrosis factor α mediates intrinsic apoptosis in trophoblastic cells, Reprod. Sci. 21 (5) (2014) 612–622.
[69] A.A. Goldberg, et al., Regulation of ULK1 expression and autophagy by STAT1, J. Biol. Chem. 292 (5) (2017) 1899–1909.
[70] T. Maruyama, N.N. Noda, Autophagy-regulating protease Atg4: structure, function, regulation and inhibition, J. Antibiot. 71 (1) (2018) 72–78.
[71] M.J. Munson, I.G. Ganley, MTOR, PIK3C3, and autophagy: signaling the beginning from the end, Autophagy 11 (12) (2015) 2375–2376.
[72] M. Pierdominici, et al., Estrogen receptor β ligation inhibits Hodgkin lymphoma growth by inducing autophagy, Oncotarget 8 (5) (2017) 8522.
[73] L. Zheng, et al., Role of autophagy in tumor necrosis factor-α-induced apoptosis of osteoblast cells, J. Invest. Med. 65 (6) (2017) 1014–1020.
[74] A. Kuma, M. Komatsu, N. Mizushima, Autophagy-monitoring and autophagy-deficient mice, Autophagy 13 (10) (2017) 1619–1628.
[75] T.G. McWilliams, et al., mito-QC illuminates mitophagy and mitochondrial architecture in vivo, JCB (J. Cell Biol.) 214 (3) (2016) 333–345.
[76] N. Sun, et al., Measuring in vivo mitophagy, Mol. Cell 60 (4) (2015) 685–696.
[77] H. Harada, et al., Deficiency of p62/Sequestosome 1 causes hyperphagia due to leptin resistance in the brain, J. Neurosci. 33 (37) (2013) 14767–14777.
[78] A. Rodriguez, et al., Mature-onset obesity and insulin resistance in mice deficient in the signaling adapter p62, Cell Metabol. 3 (3) (2006) 211–222.
[79] K. Slowicka, et al., Optineurin deficiency in mice is associated with increased sensitivity to Salmonella but does not affect proinflammatory NF-κB signaling, Eur. J. Immunol. 46 (4) (2016) 971–980.
[80] D.C. Pant, T.Y. Nazarko, Selective autophagy: the rise of the zebrafish model, Autophagy 17 (11) (2021) 3297–3305.
[81] S. Yin, et al., Fumonisin B1 induces autophagic cell death via activation of ERN1-MAPK8/9/10 pathway in monkey kidney MARC-145 cells, Arch. Toxicol. 90 (2016) 985–996.
[82] S. Koinuma, et al., Aging induces abnormal accumulation of Aβ in extracellular vesicle and/or intraluminal membrane vesicle-rich fractions in nonhuman primate brain, Neurobiol. Aging 106 (2021) 268–281.
[83] J.L. Ebersole, et al., Transcriptomic phases of periodontitis lesions using the nonhuman primate model, Sci. Rep. 11 (1) (2021) 9282.
[84] S. Deng, et al., Autophagy in retinal ganglion cells in a rhesus monkey chronic hypertensive glaucoma model, PLoS One 8 (10) (2013) e77100.
[85] F. Xu, et al., Stage-dependent actions of antimüllerian hormone in regulating granulosa cell proliferation and follicular function in the primate ovary, F&S Sci. 1 (2) (2020) 161–171.
[86] Y. Hama, Y. Ogasawara, N.N. Noda, Autophagy and cancer: basic mechanisms and inhibitor development, Cancer Sci. 114 (7) (2023) 2699–2708.
[87] X.H. Liang, et al., Induction of autophagy and inhibition of tumorigenesis by beclin 1, Nature 402 (6762) (1999) 672–676.
[88] X. Qu, et al., Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene, J. Clin. Invest. 112 (12) (2003) 1809–1820.
[89] Z. Yue, et al., Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor, Proc. Natl. Acad. Sci. U.S.A. 100 (25) (2003) 15077–15082.
[90] Y. Inami, et al., Persistent activation of Nrf2 through p62 in hepatocellular carcinoma cells, J. Cell Biol. 193 (2) (2011) 275–284.
[91] A. Takamura, et al., Autophagy-deficient mice develop multiple liver tumors, Genes Dev. 25 (8) (2011) 795–800.
[92] H. Wei, et al., Suppression of autophagy by FIP200 deletion inhibits mammary tumorigenesis, Genes Dev. 25 (14) (2011) 1510–1527.
[93] M.T. Rosenfeldt, et al., p53 status determines the role of autophagy in pancreatic tumour development, Nature 504 (7479) (2013) 296–300.
[94] S. Rao, et al., A dual role for autophagy in a murine model of lung cancer, Nat. Commun. 5 (2014) 3056.
[95] U. Santanam, et al., Atg7 cooperates with Pten loss to drive prostate cancer tumor growth, Genes Dev. 30 (4) (2016) 399–407.
[96] J.Y. Guo, B. Xia, E. White, Autophagy-mediated tumor promotion, Cell 155 (6) (2013) 1216–1219.
[97] S. Yang, et al., Pancreatic cancers require autophagy for tumor growth, Genes Dev. 25 (7) (2011) 717–729.
[98] J.Y. Guo, et al., Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis, Genes Dev. 25 (5) (2011) 460–470.
[99] G. Karsli-Uzunbas, et al., Autophagy is required for glucose homeostasis and lung tumor maintenance, Cancer Discov. 4 (8) (2014) 914–927.
[100] T. Marsh, et al., Autophagic degradation of NBR1 restricts metastatic outgrowth during mammary tumor progression, Dev. Cell 52 (5) (2020) 591–604.e6.
[101] Y.F. Peng, et al., Autophagy inhibition suppresses pulmonary metastasis of HCC in mice via impairing anoikis resistance and colonization of HCC cells, Autophagy 9 (12) (2013) 2056–2068.
[102] Comprehensive and integrative genomic characterization of hepatocellular carcinoma, Cell 169 (7) (2017) 1327–1341.e23.
[103] C.H. Eng, et al., Macroautophagy is dispensable for growth of KRAS mutant tumors and chloroquine efficacy, Proc. Natl. Acad. Sci. U.S.A. 113 (1) (2016) 182–187.
[104] M.T. Rosenfeldt, et al., PTEN deficiency permits the formation of pancreatic cancer in the absence of autophagy, Cell Death Differ. 24 (7) (2017) 1303–1304.
[105] M. Ashrafizadeh, et al., A bioinformatics analysis, pre-clinical and clinical conception of autophagy in pancreatic cancer: complexity and simplicity in crosstalk, Pharmacol. Res. 194 (2023) 106822.
[106] Y. Qin, et al., Autophagy and cancer drug resistance in dialogue: pre-clinical and clinical evidence, Cancer Lett. 570 (2023) 216307.
[107] C. Seca, et al., Autophagy-dependent toxicity of amino-functionalized nanoparticles in ovarian cancer cells, J. Mater. Chem. B 7 (35) (2019) 5376–5391.
[108] Z. Chen, et al., ATB(0,+)-targeted nanoparticles initiate autophagy suppression to overcome chemoresistance for enhanced colorectal cancer therapy, Int. J. Pharm. 641 (2023) 123082.
[109] W. Lydiatt, B. O'Sullivan, S. Patel, Major Changes in Head and Neck Staging for 2018, vol. 38, American Society of Clinical Oncology Educational Book, 2018, pp. 505–514.
[110] J.A. MacDiarmid, et al., Targeted doxorubicin delivery to brain tumors via minicells: proof of principle using dogs with spontaneously occurring tumors as a model, PLoS One 11 (4) (2016) e0151832.
[111] C.C. Reyes-Gibby, et al., Survival patterns in squamous cell carcinoma of the head and neck: pain as an independent prognostic factor for survival, J. Pain 15 (10) (2014) 1015–1022.
[112] G. Cadoni, et al., Prognostic factors in head and neck cancer: a 10-year retrospective analysis in a single-institution in Italy, Acta Otorhinolaryngol. Ital. 37 (6) (2017) 458.
[113] S.B. Edge, A.J.C.o. Cancer, AJCC Cancer Staging Manual, vol. 7, Springer, 2010.
[114] C.R. Leemans, P.J. Snijders, R.H. Brakenhoff, The molecular landscape of head and neck cancer, Nat. Rev. Cancer 18 (5) (2018) 269–282.
[115] Y. Li, et al., Co-delivery of curcumin and chrysin through pH-sensitive hyaluronan-modified hollow mesoporous silica nanoparticles for enhanced synergistic anticancer efficiency against thyroid cancer cells, J. Drug Deliv. Sci. Technol. 87 (2023).

[116] Y.Q. Almajidi, et al., Doxorubicin-loaded micelles in tumor cell-specific chemotherapy, Environ. Res. 227 (2023).
[117] S. Hua, et al., Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: pathways for translational development and commercialization, Front. Pharmacol. 9 (2018) 790.
[118] J.M. de Lima, et al., Chitosan/PCL nanoparticles can improve anti-neoplastic activity of 5-fluorouracil in head and neck cancer through autophagy activation, Int. J. Biochem. Cell Biol. 134 (2021) 105964.
[119] H. Zhang, et al., Co-delivery of doxorubicin and hydroxychloroquine via chitosan/alginate nanoparticles for blocking autophagy and enhancing chemotherapy in breast cancer therapy, Front. Pharmacol. 14 (2023) 1176232.
[120] Y. Cheng, et al., Combination of an autophagy inhibitor with immunoadjuvants and an anti-PD-L1 antibody in multifunctional nanoparticles for enhanced breast cancer immunotherapy, BMC Med. 20 (1) (2022) 411.
[121] X. Xiong, et al., Atg5 siRNA inhibits autophagy and enhances norcantharidin-induced apoptosis in hepatocellular carcinoma, Int. J. Oncol. 47 (4) (2015) 1321–1328.
[122] C. Gong, et al., Co-delivery of autophagy inhibitor ATG7 siRNA and docetaxel for breast cancer treatment, J. Contr. Release 266 (2017) 272–286.
[123] M. Zhang, et al., Targeted codelivery of docetaxel and Atg7 siRNA for autophagy inhibition and pancreatic cancer treatment, ACS Appl. Bio Mater. 2 (3) (2019) 1168–1176.
[124] Z.Q. Zhao, et al., Autophagy modulation and synergistic therapy to combat multidrug resistance breast cancer using hybrid cell membrane nanoparticles, J. Biomed. Nanotechnol. 17 (7) (2021) 1404–1416.
[125] Q. Sun, et al., A "chase and block" strategy for enhanced cancer therapy with hypoxia-promoted photodynamic therapy and autophagy inhibition based on upconversion nanocomposites, Adv. Healthcare Mater. 12 (27) (2023) e2301087.
[126] Y. Wang, et al., Self-assembled autophagy-inducing polymeric nanoparticles for breast cancer interference in-vivo, Adv. Mater. 27 (16) (2015) 2627–2634.
[127] X. Yang, et al., Nano-ultrasonic contrast agent for chemoimmunotherapy of breast cancer by immune metabolism reprogramming and tumor autophagy, ACS Nano 16 (2) (2022) 3417–3431.
[128] L. Yuan, et al., Chiral polymer modified nanoparticles selectively induce autophagy of cancer cells for tumor ablation, J. Nanobiotechnol. 16 (1) (2018) 55.
[129] Z.Y. Qiao, et al., Polymer-KLAK peptide conjugates induce cancer cell death through synergistic effects of mitochondria damage and autophagy blockage, Bioconjugate Chem. 28 (6) (2017) 1709–1721.
[130] C. Wang, et al., Combination of polythyleneimine regulating autophagy prodrug and Mdr1 siRNA for tumor multidrug resistance, J. Nanobiotechnol. 20 (1) (2022) 476.
[131] L. Hu, et al., Nanodrugs incorporating LDHA siRNA inhibit M2-like polarization of TAMs and amplify autophagy to assist oxaliplatin chemotherapy against colorectal cancer, ACS Appl. Mater. Interfaces 14 (28) (2022) 31625–31633.
[132] Y. Wang, et al., Engineered CpG-loaded nanorobots drive autophagy-mediated immunity for TLR9-positive cancer therapy, Adv. Mater. (2023) e2306248.
[133] X. Gao, et al., Peglated-H1/pHGFK1 nanoparticles enhance anti-tumor effects of sorafenib by inhibition of drug-induced autophagy and stemness in renal cell carcinoma, J. Exp. Clin. Cancer Res. 38 (1) (2019) 362.
[134] G. Wang, K. Qian, X. Mei, A theranostic nanoplatform: magneto-gold@ fluorescence polymer nanoparticles for tumor targeting T(1)&T(2)-MRI/CT/NIR fluorescence imaging and induction of genuine autophagy mediated chemotherapy, Nanoscale 10 (22) (2018) 10467–10478.
[135] M. Hashemi, et al., Nanoliposomes for doxorubicin delivery: reversing drug resistance, stimuli-responsive carriers and clinical translation, J. Drug Deliv. Sci. Technol. 80 (2023).
[136] C.M. Chang, et al., (188)Re-Liposome can induce mitochondrial autophagy and reverse drug resistance for ovarian cancer: from bench evidence to preliminary clinical proof-of-concept, Int. J. Mol. Sci. 18 (5) (2017).
[137] F. Zhou, et al., A novel tri-functional liposome Re-educates "cold tumor" and abrogates tumor growth by synergizing autophagy inhibition and PD-L1 blockade, Adv. Healthcare Mater. 12 (11) (2023) e2202757.
[138] B. Colak, M.C. Cihan, Y.N. Ertas, 3D-Printed, implantable alginate/CuS nanoparticle scaffolds for local tumor treatment via synergistic photothermal, photodynamic, and chemodynamic therapy, ACS Appl. Nano Mater. 6 (17) (2023) 16076–16085.
[139] H. Xiao, et al., Nanodrug inducing autophagy inhibition and mitochondria dysfunction for potentiating tumor photo-immunotherapy, Small 19 (30) (2023) e2300280.
[140] Y. Ren, et al., Delivery of RGD-modified liposome as a targeted colorectal carcinoma therapy and its autophagy mechanism, J. Drug Target. 29 (8) (2021) 863–874.
[141] Y. Feng, et al., Autophagy inhibitor (LY294002) and 5-fluorouracil (5-FU) combination-based nanoliposome for enhanced efficacy against esophageal squamous cell carcinoma, Nanoscale Res. Lett. 13 (1) (2018) 325.
[142] B. Wang, et al., Combination of apolipoprotein A1-modi liposome-doxorubicin with autophagy inhibitors overcame drug resistance in vitro, J. Pharmaceut. Sci. 103 (12) (2014) 3994–4004.
[143] L. Mei, et al., Effective treatment of the primary tumor and lymph node metastasis by polymeric micelles with variable particle sizes, J. Contr. Release 292 (2018) 67–77.
[144] X. Duan, Y. Li, Physicochemical characteristics of nanoparticles affect circulation, biodistribution, cellular internalization, and trafficking, Small 9 (9-10) (2013) 1521–1532.
[145] Y.N. Ertas, et al., Nanoparticles for targeted drug delivery to cancer stem cells: a review of recent advances, Nanomaterials 11 (7) (2021).
[146] L. Mei, et al., Enhanced tumor retention effect by click chemistry for improved cancer immunochemotherapy, ACS Appl. Mater. Interfaces 10 (21) (2018) 17582–17593.
[147] S. Ruan, et al., Ligand-mediated and enzyme-directed precise targeting and retention for the enhanced treatment of glioblastoma, ACS Appl. Mater. Interfaces 9 (24) (2017) 20348–20360.
[148] S. Ruan, et al., Increased gold nanoparticle retention in brain tumors by in situ enzyme-induced aggregation, ACS Nano 10 (11) (2016) 10086–10098.
[149] W. Xiao, et al., Normalizing tumor vessels to increase the enzyme-induced retention and targeting of gold nanoparticle for breast cancer imaging and treatment, Mol. Pharm. 14 (10) (2017) 3489–3498.
[150] X. Liu, et al., Enhanced retention and cellular uptake of nanoparticles in tumors by controlling their aggregation behavior, ACS Nano 7 (7) (2013) 6244–6257.
[151] H.C. Kolb, M. Finn, K.B. Sharpless, Click chemistry: diverse chemical function from a few good reactions, Angew. Chem. Int. Ed. 40 (11) (2001) 2004–2021.
[152] Q. Sun, et al., A collaborative assembly strategy for tumor-targeted siRNA delivery, J. Am. Chem. Soc. 137 (18) (2015) 6000–6010.
[153] Y. Xianyu, Z. Wang, X. Jiang, A plasmonic nanosensor for immunoassay via enzyme-triggered click chemistry, ACS Nano 8 (12) (2014) 12741–12747.
[154] E. Lallana, et al., Click chemistry for drug delivery nanosystems, Pharmaceut. Res. 29 (2012) 1–34.
[155] J. Rao, et al., Size-adjustable micelles co-loaded with a chemotherapeutic agent and an autophagy inhibitor for enhancing cancer treatment via increased tumor retention, Acta Biomater. 89 (2019) 300–312.
[156] C. Hu, et al., Co-delivery of the autophagy inhibitor si-Beclin1 and the doxorubicin nano-delivery system for advanced prostate cancer treatment, J. Biomater. Appl. 36 (7) (2022) 1317–1331.
[157] X. Wang, et al., On-demand autophagy cascade amplification nanoparticles precisely enhanced oxaliplatin-induced cancer immunotherapy, Adv. Mater. 32 (32) (2020) e2002160.
[158] F. Zhou, et al., Inhibiting autophagy to boost antitumor immunity with tetramethylpyrazine-loaded and PD-L1-targeting liposomal nanoparticles, Eur. J. Pharmaceut. Sci. 190 (2023) 106581.
[159] X. Zhang, et al., Autophagy-modulating biomembrane nanostructures: a robust anticancer weapon by modulating the inner and outer cancer environment, J. Contr. Release 366 (2024) 85–103.
[160] R. Tenchov, et al., Lipid nanoparticles─ from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement, ACS Nano 15 (11) (2021) 16982–17015.
[161] K. Yang, et al., Cationic liposomes induce cell necrosis through lysosomal dysfunction and late-stage autophagic flux inhibition, Nanomedicine 11 (23) (2016) 3117–3137.
[162] J. Gao, et al., Cationic liposomes promote antigen cross-presentation in dendritic cells by alkalizing the lysosomal pH and limiting the degradation of antigens, Int. J. Nanomed. (2017) 1251–1264.
[163] F. Xie, et al., Codelivery of salinomycin and chloroquine by liposomes enables synergistic antitumor activity in vitro, Nanomedicine 11 (14) (2016) 1831–1846.
[164] C.A. Schonewolf, et al., Autophagy inhibition by chloroquine sensitizes HT-29 colorectal cancer cells to concurrent chemoradiation, World J. Gastrointest. Oncol. 6 (3) (2014) 74.
[165] X. Yang, et al., Nano-ultrasonic contrast agent for chemoimmunotherapy of breast cancer by immune metabolism reprogramming and tumor autophagy, ACS Nano 16 (2) (2022) 3417–3431.
[166] Y.-J. Hu, et al., Nanostructured dihydroartemisinin plus epirubicin liposomes enhance treatment efficacy of breast cancer by inducing autophagy and apoptosis, Nanomaterials 8 (10) (2018) 804.
[167] T. Appidi, et al., Light-triggered selective ROS-dependent autophagy by bioactive nanoliposomes for efficient cancer theranostics, Nanoscale 12 (3) (2020) 2028–2039.
[168] Z. Li, et al., Engineering dual catalytic nanomedicine for autophagy-augmented and ferroptosis-involved cancer nanotherapy, Biomaterials 287 (2022) 121668.
[169] X. Zhang, et al., Targeting cancer-associated fibroblast autophagy renders pancreatic cancer eradicable with immunochemotherapy by inhibiting adaptive immune resistance, Autophagy (2024) 1–21.
[170] Y.J. Hu, et al., Nanostructured dihydroartemisinin plus epirubicin liposomes enhance treatment efficacy of breast cancer by inducing autophagy and apoptosis, Nanomaterials 8 (10) (2018).
[171] K. Ren, et al., A neutrophil-mediated carrier regulates tumor stemness by inhibiting autophagy to prevent postoperative triple-negative breast cancer recurrence and metastasis, Acta Biomater. 145 (2022) 185–199.
[172] J. Ye, et al., Verteporfin-loaded supramolecular micelles for enhanced cisplatin-based chemotherapy via autophagy inhibition, J. Mater. Chem. B 10 (14) (2022) 2670–2679.
[173] L. Zhang, et al., Enhanced chemotherapy efficacy by sequential delivery of siRNA and anticancer drugs using PEI-grafted graphene oxide, Small 7 (4) (2011) 460–464.
[174] L. Zhang, et al., Functional graphene oxide as a nanocarrier for controlled loading and targeted delivery of mixed anticancer drugs, Small 6 (4) (2010) 537–544.
[175] S. Goenka, V. Sant, S. Sant, Graphene-based nanomaterials for drug delivery and tissue engineering, J. Contr. Release 173 (2014) 75–88.
[176] S.H. Hu, et al., Quantum-dot-tagged reduced graphene oxide nanocomposites for bright fluorescence bioimaging and photothermal therapy monitored in situ, Adv. Mater. 24 (13) (2012) 1748–1754.

[177] Y. Wang, et al., Aptamer/graphene oxide nanocomplex for in situ molecular probing in living cells, J. Am. Chem. Soc. 132 (27) (2010) 9274–9276.
[178] G.Y. Chen, et al., A graphene-based platform for induced pluripotent stem cells culture and differentiation, Biomaterials 33 (2) (2012) 418–427.
[179] K. Yang, et al., The influence of surface chemistry and size of nanoscale graphene oxide on photothermal therapy of cancer using ultra-low laser power, Biomaterials 33 (7) (2012) 2206–2214.
[180] G.Y. Chen, et al., Graphene oxide as a chemosensitizer: diverted autophagic flux, enhanced nuclear import, elevated necrosis and improved antitumor effects, Biomaterials 40 (2015) 12–22.
[181] K.C. Lin, et al., Graphene oxide sensitizes cancer cells to chemotherapeutics by inducing early autophagy events, promoting nuclear trafficking and necrosis, Theranostics 8 (9) (2018) 2477–2487.
[182] J. Shen, et al., Graphene oxide induces autophagy and apoptosis via the ROS-dependent AMPK/mTOR/ULK-1 pathway in colorectal cancer cells, Nanomedicine (Lond) 17 (9) (2022) 591–605.
[183] G.Y. Chen, et al., Graphene oxide triggers toll-like receptors/autophagy responses in vitro and inhibits tumor growth in vivo, Adv. Healthcare Mater. 3 (9) (2014) 1486–1495.
[184] Z. Tang, et al., Mechanisms of oxidative stress, apoptosis, and autophagy involved in graphene oxide nanomaterial anti-osteosarcoma effect, Int. J. Nanomed. 13 (2018) 2907–2919.
[185] S. Ma, et al., FePt/GO nanosheets suppress proliferation, enhance radiosensitization and induce autophagy of human non-small cell lung cancer cells, Int. J. Biol. Sci. 15 (5) (2019) 999–1009.
[186] B.D. Arya, et al., Graphene oxide-chloroquine nanoconjugate induce necroptotic death in A549 cancer cells through autophagy modulation, Nanomedicine (Lond) 13 (18) (2018) 2261–2282.
[187] Y.G. Yuan, S. Gurunathan, Combination of graphene oxide-silver nanoparticle nanocomposites and cisplatin enhances apoptosis and autophagy in human cervical cancer cells, Int. J. Nanomed. 12 (2017) 6537–6558.
[188] S. Tomić, et al., Graphene quantum dots suppress proinflammatory T cell responses via autophagy-dependent induction of tolerogenic dendritic cells, Biomaterials 146 (2017) 13–28.
[189] Q. Liang, et al., Photo-activated autophagy-associated tumour cell death by lysosome impairment based on manganese-doped graphene quantum dots, J. Mater. Chem. B 11 (11) (2023) 2466–2477.
[190] C. Xiao, et al., Engineering cannabidiol synergistic carbon monoxide nanocomplexes to enhance cancer therapy via excessive autophagy, Acta Pharm. Sin. B 13 (11) (2023) 4591–4606.
[191] V.K. Bajpai, et al., Multifunctional N-P-doped carbon dots for regulation of apoptosis and autophagy in B16F10 melanoma cancer cells and in vitro imaging applications, Theranostics 10 (17) (2020) 7841–7856.
[192] Y. Chen, et al., Silver nanoparticles regulate autophagy through lysosome injury and cell hypoxia in prostate cancer cells, J. Biochem. Mol. Toxicol. 34 (5) (2020) e22474.
[193] M. Salehiabar, et al., Targeted CuFe2O4 hybrid nanoradiosensitizers for synchronous chemoradiotherapy, J. Contr. Release 353 (2023) 850–863.
[194] H. Rashidzadeh, et al., Preparation of alginate coated Pt nanoparticle for radiosensitization of breast cancer tumor, Int. J. Biol. Macromol. 233 (2023).
[195] H. Nosrati, et al., Enhanced in vivo radiotherapy of breast cancer using gadolinium oxide and gold hybrid nanoparticles, ACS Appl. Bio Mater. 6 (2) (2023) 784–792.
[196] B. Colak, Y.N. Ertas, Implantable, 3D-printed alginate scaffolds with bismuth sulfide nanoparticles for the treatment of local breast cancer via enhanced radiotherapy, ACS Appl. Mater. Interfaces 16 (13) (2024) 15718–15729.
[197] D.T. Vogl, et al., Combined autophagy and proteasome inhibition: a phase 1 trial of hydroxychloroquine and bortezomib in patients with relapsed/refractory myeloma, Autophagy 10 (8) (2014) 1380–1390.
[198] M.R. Rosenfeld, et al., A phase I/II trial of hydroxychloroquine in conjunction with radiation therapy and concurrent and adjuvant temozolomide in patients with newly diagnosed glioblastoma multiforme, Autophagy 10 (8) (2014) 1359–1368.
[199] K.M. Rouschop, et al., The unfolded protein response protects human tumor cells during hypoxia through regulation of the autophagy genes MAP1LC3B and ATG5, J. Clin. Invest. 120 (1) (2010) 127–141.
[200] Y. Li, et al., Hydroxychloroquine-loaded hollow mesoporous silica nanoparticles for enhanced autophagy inhibition and radiation therapy, J. Contr. Release 325 (2020) 100–110.
[201] C.-H. Xu, et al., Cell membrane-camouflaged nanoparticles as drug carriers for cancer therapy, Acta Biomater. 105 (2020) 1–14.
[202] N. Jan, et al., Biomimetic cell membrane-coated poly(lactic-glycolic acid) nanoparticles for biomedical applications, Bioeng. Transl. Med. 8 (2) (2023).
[203] X. Huang, et al., Tumor targeting and penetrating biomimetic mesoporous polydopamine nanoparticles facilitate photothermal killing and autophagy blocking for synergistic tumor ablation, Acta Biomater. 136 (2021) 456–472.
[204] P. Chittineedi, et al., Aqueous Nyctanthes arbortristis and doxorubicin conjugated gold nanoparticles synergistically induced mTOR-dependent autophagy-mediated ferritinophagy in paclitaxel-resistant breast cancer stem cells, Front. Pharmacol. 14 (2023) 1201319.
[205] T. Lin, et al., Synergy of tumor microenvironment remodeling and autophagy inhibition to sensitize radiation for bladder cancer treatment, Theranostics 10 (17) (2020) 7683–7696.
[206] Y. Huang, et al., Superparamagnetic iron oxide nanoparticles induce ferroptosis of human ovarian cancer stem cells by weakening cellular autophagy, J. Biomed. Nanotechnol. 16 (11) (2020) 1612–1622.
[207] Y. Xie, et al., Iron oxide nanoparticles as autophagy intervention agents suppress hepatoma growth by enhancing tumoricidal autophagy, Adv. Sci. 7 (16) (2020) 1903323.
[208] M.S. Jabir, et al., Green synthesis of silver nanoparticles using annona muricata extract as an inducer of apoptosis in cancer cells and inhibitor for NLRP3 inflammasome via enhanced autophagy, Nanomaterials 11 (2) (2021).
[209] X.F. Zhang, S. Gurunathan, Combination of salinomycin and silver nanoparticles enhances apoptosis and autophagy in human ovarian cancer cells: an effective anticancer therapy, Int. J. Nanomed. 11 (2016) 3655–3675.
[210] R.W. Johnstone, A.A. Ruefli, S.W. Lowe, Apoptosis: a link between cancer genetics and chemotherapy, Cell 108 (2) (2002) 153–164.
[211] D.R. Green, Apoptotic pathways: paper wraps stone blunts scissors, Cell 102 (1) (2000) 1–4.
[212] X. Wang, The expanding role of mitochondria in apoptosis, Genes Dev. 15 (22) (2001) 2922–2933.
[213] Y. Suzuki, et al., A serine protease, HtrA2, is released from the mitochondria and interacts with XIAP, inducing cell death, Mol. Cell 8 (3) (2001) 613–621.
[214] S.J. Dixon, et al., Ferroptosis: an iron-dependent form of nonapoptotic cell death, Cell 149 (5) (2012) 1060–1072.
[215] X. Tong, et al., Targeting cell death pathways for cancer therapy: recent developments in necroptosis, pyroptosis, ferroptosis, and cuproptosis research, J. Hematol. Oncol. 15 (1) (2022) 174.
[216] B.R. Stockwell, et al., Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease, Cell 171 (2) (2017) 273–285.
[217] B. Hassannia, P. Vandenabeele, T. Vanden Berghe, Targeting ferroptosis to iron out cancer, Cancer Cell 35 (6) (2019) 830–849.
[218] J.Y. Lee, et al., Lipid metabolism and ferroptosis, Biology 10 (3) (2021).
[219] W.S. Yang, et al., Regulation of ferroptotic cancer cell death by GPX4, Cell 156 (1–2) (2014) 317–331.
[220] D.P. Bai, et al., Zinc oxide nanoparticles induce apoptosis and autophagy in human ovarian cancer cells, Int. J. Nanomed. 12 (2017) 6521–6535.
[221] E. Piktel, et al., ROS-mediated apoptosis and autophagy in ovarian cancer cells treated with peanut-shaped gold nanoparticles, Int. J. Nanomed. 16 (2021) 1993–2011.
[222] J.H. Wu, et al., Induction of apoptosis and autophagy by calcifying nanoparticles in human bladder cancer cells, Tumour Biol. 39 (6) (2017) 1010428317707688.
[223] K. Xiong, et al., Autophagy-dependent apoptosis induced by apoferritin-Cu(II) nanoparticles in multidrug-resistant colon cancer cells, ACS Appl. Mater. Interfaces 13 (33) (2021) 38959–38968.
[224] Y. Wang, et al., Inhibition of autophagy promoted apoptosis and suppressed growth of hepatocellular carcinoma upon photothermal exposure, J. Biomed. Nanotechnol. 15 (4) (2019) 813–821.
[225] R. Yang, et al., Zinc oxide nanoparticles promotes liver cancer cell apoptosis through inducing autophagy and promoting p53, Eur. Rev. Med. Pharmacol. Sci. 25 (3) (2021) 1557–1563.
[226] X. Zhang, et al., ROS responsive nanoparticles encapsulated with natural medicine remodel autophagy homeostasis in breast cancer, ACS Appl. Mater. Interfaces 15 (25) (2023) 29827–29840.
[227] N. Kulkarni-Dwivedi, et al., Hyperthermia and doxorubicin release by Fol-LSMO nanoparticles induce apoptosis and autophagy in breast cancer cells, Nanomedicine (Lond) 17 (25) (2022) 1929–1949.
[228] Y. Yang, et al., Activation of autophagy by in situ Zn(2+) chelation reaction for enhanced tumor chemoimmunotherapy, Bioact. Mater. 29 (2023) 116–131.
[229] R. Hu, et al., Topology regulation of nanomedicine for autophagy-augmented ferroptosis and cancer immunotherapy, Sci. Bull. 68 (1) (2023) 77–94.
[230] S. Negi, et al., Nanotherapeutics in autophagy: a paradigm shift in cancer treatment, Drug Deliv. Transl. Res. 12 (11) (2022) 2589–2612.
[231] D. Laha, et al., Interplay between autophagy and apoptosis mediated by copper oxide nanoparticles in human breast cancer cells MCF7, Biochim. Biophys. Acta 1840 (1) (2014) 1–9.
[232] H. Wang, et al., Chitosan nanoparticles triggered the induction of ROS-mediated cytoprotective autophagy in cancer cells, Artif. Cells, Nanomed. Biotechnol. 46 (sup1) (2018) 293–301.
[233] Y.H. Miao, et al., Zinc oxide nanoparticles reduce the chemoresistance of gastric cancer by inhibiting autophagy, World J. Gastroenterol. 27 (25) (2021) 3851–3862.
[234] W. Gu, C. Yang, Zinc oxide nanoparticles inhibit malignant progression and chemotherapy resistance of ovarian cancer cells by activating endoplasmic reticulum stress and promoting autophagy, Exp. Ther. Med. 26 (5) (2023) 508.
[235] Q. Xiong, et al., Cuprous oxide nanoparticles trigger reactive oxygen species-induced apoptosis through activation of erk-dependent autophagy in bladder cancer, Cell Death Dis. 11 (5) (2020) 366.
[236] M. Lou, et al., Quercetin nanoparticles induced autophagy and apoptosis through AKT/ERK/Caspase-3 signaling pathway in human neuroglioma cells: in vitro and in vivo, Biomed. Pharmacother. 84 (2016) 1–9.
[237] Z. Duan, et al., Selenium nanoparticles coupling with Astragalus Polysaccharides exert their cytotoxicities in MCF-7 cells by inhibiting autophagy and promoting apoptosis, J. Trace Elem. Med. Biol. 73 (2022) 127006.
[238] H. Xu, et al., Zn-doped CuO nanocomposites inhibit tumor growth by NF-κB pathway cross-linked autophagy and apoptosis, Nanomedicine (Lond) 14 (2) (2019) 131–149.
[239] Y.L. Cho, et al., Dual role of oxidative stress-JNK activation in autophagy and apoptosis induced by nickel oxide nanoparticles in human cancer cells, Free Radic. Biol. Med. 153 (2020) 173–186.

[240] M. Akter, et al., Green synthesized silver nanoparticles-mediated cytotoxic effect in colorectal cancer cells: NF-κB signal induced apoptosis through autophagy, Biol. Trace Elem. Res. 199 (9) (2021) 3272–3286.
[241] X.J. Mi, et al., Biosynthesis and cytotoxic effect of silymarin-functionalized selenium nanoparticles induced autophagy mediated cellular apoptosis via downregulation of PI3K/Akt/mTOR pathway in gastric cancer, Phytomedicine 99 (2022) 154014.
[242] D. Cui, et al., Selenium nanoparticles fabricated in laminarin polysaccharides solutions exert their cytotoxicities in HepG2 cells by inhibiting autophagy and promoting apoptosis, Int. J. Biol. Macromol. 137 (2019) 829–835.
[243] F.Z. Wang, et al., Codelivery of doxorubicin and shAkt1 by poly(ethylenimine)-glycyrrhetinic acid nanoparticles to induce autophagy-mediated liver cancer combination therapy, Mol. Pharm. 13 (4) (2016) 1298–1307.
[244] T. Zhang, et al., MPA-capped CdTequantum dots induces endoplasmic reticulum stress-mediated autophagy and apoptosis through generation of reactive oxygen species in human liver normal cell and liver tumor cell, Environ. Pollut. 326 (2023) 121397.
[245] T. Yokoyama, et al., EGFR-targeted hybrid plasmonic magnetic nanoparticles synergistically induce autophagy and apoptosis in non-small cell lung cancer cells, PLoS One 6 (11) (2011) e25507.
[246] X. Zhao, et al., Photothermal exposure of polydopamine-coated branched Au-Ag nanoparticles induces cell cycle arrest, apoptosis, and autophagy in human bladder cancer cells, Int. J. Nanomed. 13 (2018) 6413–6428.
[247] J. Yang, et al., Nanomedicine enables autophagy-enhanced cancer-cell ferroptosis, Sci. Bull. 66 (5) (2021) 464–477.
[248] T. Lomphithak, et al., High-dose exposure to polymer-coated iron oxide nanoparticles elicits autophagy-dependent ferroptosis in susceptible cancer cells, Nanomaterials 13 (11) (2023).
[249] G. Yuan, et al., Autophagy-targeted calcium phosphate nanoparticles enable transarterial chemoembolization for enhanced cancer therapy, ACS Appl. Mater. Interfaces 15 (9) (2023) 11431–11443.
[250] H. Xing, et al., Crosstalk between exosomes and autophagy: a review of molecular mechanisms and therapies, J. Cell Mol. Med. 25 (5) (2021) 2297–2308.
[251] D.K. Jeppesen, et al., Reassessment of exosome composition, Cell 177 (2) (2019) 428–445.e18.
[252] R. Kalluri, V.S. LeBleu, The biology, function, and biomedical applications of exosomes, Science 367 (6478) (2020).
[253] S. Kamerkar, et al., Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer, Nature 546 (7659) (2017) 498–503.
[254] R.C. Lai, T.S. Chen, S.K. Lim, Mesenchymal stem cell exosome: a novel stem cell-based therapy for cardiovascular disease, Regen. Med. 6 (4) (2011) 481–492.
[255] C. Frühbeis, D. Fröhlich, E.M. Krämer-Albers, Emerging roles of exosomes in neuron-glia communication, Front. Physiol. 3 (2012) 119.
[256] M.I. Zonneveld, T.G.H. Keulers, K.M.A. Rouschop, Extracellular vesicles as transmitters of hypoxia tolerance in solid cancers, Cancers 11 (2) (2019).
[257] Y. Yang, et al., Exosomal transfer of miR-30a between cardiomyocytes regulates autophagy after hypoxia, J. Mol. Med. (Berl.) 94 (6) (2016) 711–724.
[258] Y. Fujita, et al., Suppression of autophagy by extracellular vesicles promotes myofibroblast differentiation in COPD pathogenesis, J. Extracell. Vesicles 4 (2015) 28388.
[259] M. Song, et al., Bystander autophagy mediated by radiation-induced exosomal miR-7-5p in non-targeted human bronchial epithelial cells, Sci. Rep. 6 (2016) 30165.
[260] M. Colletti, et al., Autophagy and exosomes relationship in cancer: friends or foes? Front. Cell Dev. Biol. 8 (2021) 614178.
[261] L. Salimi, et al., Synergies in exosomes and autophagy pathways for cellular homeostasis and metastasis of tumor cells, Cell Biosci. 10 (2020) 1–18.
[262] T. Nishimura, S.A. Tooze, Emerging roles of ATG proteins and membrane lipids in autophagosome formation, Cell Discov. 6 (1) (2020) 32.
[263] H. Guo, et al., Atg5 disassociates the V1V0-ATPase to promote exosome production and tumor metastasis independent of canonical macroautophagy, Dev. Cell 43 (6) (2017) 716–730. e7.
[264] M. Mauthe, et al., Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion, Autophagy 14 (8) (2018) 1435–1455.
[265] L. De Vries, et al., GIPC, a PDZ domain containing protein, interacts specifically with the C terminus of RGS-GAIP, Proc. Natl. Acad. Sci. USA 95 (21) (1998) 12340–12345.
[266] S. Bhattacharya, et al., GAIP interacting protein C-terminus regulates autophagy and exosome biogenesis of pancreatic cancer through metabolic pathways, PLoS One 9 (12) (2014) e114409.
[267] L. Murrow, R. Malhotra, J. Debnath, ATG12–ATG3 interacts with Alix to promote basal autophagic flux and late endosome function, Nat. Cell Biol. 17 (3) (2015) 300–310.
[268] C. Bader, et al., Atg9 is required for intraluminal vesicles in amphisomes and autolysosomes, Biol. Open 4 (11) (2015) 1345–1355.
[269] N. Mizushima, T. Yoshimori, Y. Ohsumi, The role of Atg proteins in autophagosome formation, Annu. Rev. Cell Dev. Biol. 27 (2011) 107–132.
[270] O. Florey, et al., Autophagy machinery mediates macroendocytic processing and entotic cell death by targeting single membranes, Nat. Cell Biol. 13 (11) (2011) 1335–1343.
[271] J. Martinez, et al., Microtubule-associated protein 1 light chain 3 alpha (LC3)-associated phagocytosis is required for the efficient clearance of dead cells, Proc. Natl. Acad. Sci. USA 108 (42) (2011) 17396–17401.
[272] A.M. Leidal, et al., The LC3-conjugation machinery specifies the loading of RNA-binding proteins into extracellular vesicles, Nat. Cell Biol. 22 (2) (2020) 187–199.
[273] J. Xu, R. Camfield, S.M. Gorski, The interplay between exosomes and autophagy–partners in crime, J. Cell Sci. 131 (15) (2018) jcs215210.
[274] A. Ertmer, et al., The anticancer drug imatinib induces cellular autophagy, Leukemia 21 (5) (2007) 936–942.
[275] W.-L. Sun, et al., Autophagy protects breast cancer cells from epirubicin-induced apoptosis and facilitates epirubicin-resistance development, Autophagy 7 (9) (2011) 1035–1044.
[276] Z.J. Yang, et al., The role of autophagy in cancer: therapeutic implications, Mol. Cancer Therapeut. 10 (9) (2011) 1533–1541.
[277] D.d. Yu, et al., Exosomes in development, metastasis and drug resistance of breast cancer, Cancer Sci. 106 (8) (2015) 959–964.
[278] J. Yin, et al., Secretion of annexin A3 from ovarian cancer cells and its association with platinum resistance in ovarian cancer patients, J. Cell Mol. Med. 16 (2) (2012) 337–348.
[279] A. Pastò, et al., Resistance to glucose starvation as metabolic trait of platinum-resistant human epithelial ovarian cancer cells, Oncotarget 8 (4) (2017) 6433.
[280] A.S. Azmi, B. Bao, F.H. Sarkar, Exosomes in cancer development, metastasis, and drug resistance: a comprehensive review, Cancer Metastasis Rev. 32 (2013) 623–642.
[281] E. Torreggiani, et al., Multimodal transfer of MDR by exosomes in human osteosarcoma, Int. J. Oncol. 49 (1) (2016) 189–196.
[282] D.H. Bach, et al., The role of exosomes and miRNAs in drug-resistance of cancer cells, Int. J. Cancer 141 (2) (2017) 220–230.
[283] X.-Q. Li, et al., Exosomes derived from gefitinib-treated EGFR-mutant lung cancer cells alter cisplatin sensitivity via up-regulating autophagy, Oncotarget 7 (17) (2016) 24585.
[284] L. Salimi, et al., Synergies in exosomes and autophagy pathways for cellular homeostasis and metastasis of tumor cells, Cell Biosci. 10 (1) (2020) 64.
[285] B. Muz, et al., The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy, Hypoxia 3 (2015) 83–92.
[286] I. Papandreou, et al., Hypoxia signals autophagy in tumor cells via AMPK activity, independent of HIF-1, BNIP3, and BNIP3L, Cell Death Differ. 15 (10) (2008) 1572–1581.
[287] H.W. King, M.Z. Michael, J.M. Gleadle, Hypoxic enhancement of exosome release by breast cancer cells, BMC Cancer 12 (2012) 421.
[288] P. Kucharzewska, et al., Exosomes reflect the hypoxic status of glioma cells and mediate hypoxia-dependent activation of vascular cells during tumor development, Proc. Natl. Acad. Sci. USA 110 (18) (2013) 7312–7317.
[289] D.W. Greening, et al., Secreted primary human malignant mesothelioma exosome signature reflects oncogenic cargo, Sci. Rep. 6 (2016) 32643.
[290] K.J. Svensson, et al., Hypoxia triggers a proangiogenic pathway involving cancer cell microvesicles and PAR-2-mediated heparin-binding EGF signaling in endothelial cells, Proc. Natl. Acad. Sci. U.S.A. 108 (32) (2011) 13147–13152.
[291] J.E. Park, et al., Hypoxic tumor cell modulates its microenvironment to enhance angiogenic and metastatic potential by secretion of proteins and exosomes, Mol. Cell. Proteomics 9 (6) (2010) 1085–1099.
[292] M. Hassanpour, et al., Distinct role of autophagy on angiogenesis: highlights on the effect of autophagy in endothelial lineage and progenitor cells, Stem Cell Res. Ther. 9 (1) (2018) 305.
[293] M.B. Schaaf, et al., Autophagy in endothelial cells and tumor angiogenesis, Cell Death Differ. 26 (4) (2019) 665–679.
[294] D.W. Siemann, The unique characteristics of tumor vasculature and preclinical evidence for its selective disruption by Tumor-Vascular Disrupting Agents, Cancer Treat Rev. 37 (1) (2011) 63–74.
[295] I. Filippi, et al., Different adaptive responses to hypoxia in normal and multiple myeloma endothelial cells, Cell. Physiol. Biochem. 46 (1) (2018) 203–212.
[296] H. Maes, et al., Tumor vessel normalization by chloroquine independent of autophagy, Cancer Cell 26 (2) (2014) 190–206.
[297] T. Feng, et al., Exosome camouflaged coordination-assembled Iridium(III) photosensitizers for apoptosis-autophagy-ferroptosis induced combination therapy against melanoma, Biomaterials 301 (2023) 122212.
[298] Y.T. Bai, et al., Nanomedicines in oral cancer: inspiration comes from extracellular vesicles and biomimetic nanoparticles, Nanomedicine (Lond) 17 (23) (2022) 1761–1778.
[299] H. Wang, et al., Cell membrane biomimetic nanoparticles for inflammation and cancer targeting in drug delivery, Biomater. Sci. 8 (2) (2020) 552–568.
[300] L. Meng, et al., Biomimetic nanoparticles for DC vaccination: a versatile approach to boost cancer immunotherapy, Nanoscale 15 (14) (2023) 6432–6455.
[301] L. Li, et al., Functional biomimetic nanoparticles for drug delivery and theranostic applications in cancer treatment, Sci. Technol. Adv. Mater. 19 (1) (2018) 771–790.
[302] J. Yang, et al., A novel autophagy-related gene signature associated with prognosis and immune microenvironment in ovarian cancer, J. Ovarian Res. 16 (1) (2023) 86.
[303] J. Nie, D. Wang, M. Li, The crosstalk between autophagy and myeloid-derived suppressor cell responses in cancer, Clin. Transl. Oncol. 25 (10) (2023) 2832–2840.
[304] Z. Jin, et al., Regulation of autophagy fires up the cold tumor microenvironment to improve cancer immunotherapy, Front. Immunol. 13 (2022) 1018903.
[305] L. Xu, et al., Norcantharidin induces immunogenic cell death of bladder cancer cells through promoting autophagy in acidic culture, Int. J. Mol. Sci. 23 (7) (2022).

[306] T.H. Tran, et al., Repurposing thioridazine for inducing immunogenic cell death in colorectal cancer via eIF2α/ATF4/CHOP and secretory autophagy pathways, Cell Commun. Signal. 21 (1) (2023) 184.
[307] N. Ishimwe, et al., Autophagy impairment through lysosome dysfunction by brucine induces immunogenic cell death (ICD), Am. J. Chin. Med. 48 (8) (2020) 1915–1940.
[308] S. Zhang, et al., Autophagy-amplifying nanoparticles evoke immunogenic cell death combined with anti-PD-1/PD-L1 for residual tumors immunotherapy after RFA, J. Nanobiotechnol. 21 (1) (2023) 360.