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Review

Regulating Autophagy in Nanomedicine: Advancing Cancer Therapy

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Abstract: Autophagy, a cellular process responsible for degrading and recycling damaged organelles and proteins, plays a crucial role in maintaining cellular homeostasis and responding to stress. In cancer therapy, autophagy exhibits dual roles, acting as both a protective mechanism for cancer cells and a therapeutic target. Nanomedicine, with its ability to precisely deliver drugs and modulate biological processes at the cellular level, offers novel opportunities to regulate autophagy and enhance the efficacy of cancer treatments. This review explores the intricate relationship between autophagy and nanomedicine, highlighting how nanoparticles can be engineered to modulate autophagic pathways to either promote cancer cell death or inhibit tumor survival. We discuss various strategies, such as the use of nanocarriers, including nanoparticles, nanocapsules, and nanogels, to selectively target autophagy-related proteins and pathways in cancer cells. Furthermore, the potential of combining autophagy modulation with other therapeutic approaches, including chemotherapy, photodynamic therapy (PDT), photothermal therapy (PTT), sonodynamic therapy (SDT), immunotherapy and multiple therapeutics, is examined. Understanding the complex interplay between autophagy and nanomedicine is essential for developing advanced therapeutic strategies that can overcome treatment resistance and improve cancer outcomes. This review provides a comprehensive overview of current advancements and future directions in regulating autophagy in nanomedicine for cancer therapy.

Keywords: autophagy; nanomedicine; cancer therapy

1. Introduction

Autophagy, a critical cellular process that maintains cellular homeostasis by degrading and recycling damaged organelles, proteins, and other macromolecules, plays a vital role in cell survival under stress conditions [1,2]. It is primarily a protective mechanism that helps cells adapt to nutrient deprivation, oxidative stress, and other environmental challenges. In cancer cells, autophagy's role is paradoxical; it can act both as a survival strategy and as a barrier to treatment efficacy, depending on the context [3,4]. On one hand, autophagy helps tumor cells adapt to the hostile tumor microenvironment, contributing to resistance against chemotherapy, radiotherapy, and other stress-inducing treatments. On the other hand, autophagy can also function as a tumor-suppressive mechanism by preventing the accumulation of damaged proteins and organelles, thus protecting against tumorigenesis. The dual nature of autophagy in cancer-where it can either promote tumor survival or suppress tumor growth-has made it a compelling target for therapeutic interventions. Given the complexity of autophagy's role in cancer, the modulation of autophagy in cancer therapy has become a crucial area of research. Either

inhibiting or activating autophagy at specific stages could potentially enhance the therapeutic efficacy of cancer treatments.

Nanomedicine, the application of nanotechnology in medicine, has emerged as a transformative approach to cancer therapy. By harnessing the unique properties of nanomaterials, such as their small size, high surface area, and ability to be engineered for specific functions, nanomedicine enables the precise delivery of therapeutic agents to cancer cells [5–7]. This precision enhances the effectiveness of treatments while reducing systemic toxicity. Moreover, nanomedicine offers the opportunity to modulate various biological processes at the cellular and molecular levels, including autophagy, which is a critical aspect of cancer cell survival and treatment resistance [6]. The ability to regulate autophagy through nanoparticles represents a novel strategy for overcoming some of the longstanding challenges in cancer therapy.

Nanoparticles can be designed to either induce or inhibit autophagy in cancer cells, depending on the therapeutic goal. For example, autophagy inhibitors such as chloroquine, hydroxychloroquine, and other small molecules can be encapsulated within nanoparticles to block the survival-promoting effects of autophagy during chemotherapy or radiotherapy [8–10]. By interfering with the autophagic process, these nanoparticles may sensitize tumor cells to conventional therapies, overcoming the resistance that often limits treatment efficacy. Conversely, nanoparticles can also be engineered to deliver autophagy-inducing agents, promoting the degradation of dysfunctional proteins and organelles in cancer cells, thereby enhancing cell death and inhibiting tumor progression [11,12]. This selective modulation of autophagic pathways can provide a targeted approach to therapy that minimizes damage to surrounding healthy tissue, a major limitation of current cancer treatments.

A variety of strategies have been developed to harness the potential of nanomedicine in regulating autophagy. Nanocarriers, such as liposomes, dendrimers, and polymeric nanoparticles, can deliver autophagy-modulating agents directly to cancer cells, thereby improving the pharmacokinetics and biodistribution of the drugs [13–15]. In addition, the surface properties of these nanoparticles can be modified to enhance their ability to target specific cancer cells, further increasing the specificity and efficiency of the treatment. Nanocapsules, which consist of small molecules designed to interact with autophagy-related proteins and pathways, are also being explored as potent tools to regulate autophagy in cancer cells. These nanocapsules can either activate or inhibit autophagy through specific molecular mechanisms, such as targeting key autophagic proteins like Beclin-1, ATG5, and LC3, or modulating signaling pathways such as the PI3K-Akt-mTOR pathway [16,17]. Additionally, the development of nanogels, which combine various nanomaterials with therapeutic agents, opens up new avenues for simultaneously targeting multiple aspects of autophagy, improving treatment outcomes [18,19].

The potential of combining autophagy modulation with other therapeutic modalities, such as chemotherapy, photodynamic therapy (PDT), photothermal therapy (PTT), sonodynamic therapy (SDT), and immunotherapy, has gained significant attention. By integrating autophagy regulation with these approaches, it may be possible to enhance therapeutic efficacy, overcome treatment resistance, and reduce side effects. For instance, nanoparticles that regulate autophagy could be used in combination with PDT or PTT to improve the sensitivity of tumor cells to light-based therapies, or with immunotherapy to enhance the immune response against cancer cells [18,20,21]. The synergistic effects of these combined therapies may provide a powerful strategy for treating cancers that are resistant to conventional treatments.

As the field of nanomedicine continues to evolve, understanding the intricate relationship between autophagy and cancer therapy is crucial for the development of more effective and personalized treatment strategies. While significant progress has been made in designing nanoparticles to regulate autophagy, challenges remain in terms of optimizing nanoparticle design, delivery systems, and the personalization of therapies to account for the heterogeneity of cancer cells. Furthermore, the safety and biocompatibility of nanoparticles need to be carefully evaluated to minimize any potential toxicity. Nonetheless, the regulation of autophagy through nanomedicine holds immense promise for advancing cancer therapy and overcoming the barriers that hinder the success of current treatment modalities. This review aims to provide a comprehensive overview of the current advancements in this field and explore future directions for the application of nanomedicine in regulating autophagy to improve cancer treatment outcomes (Figure 1).

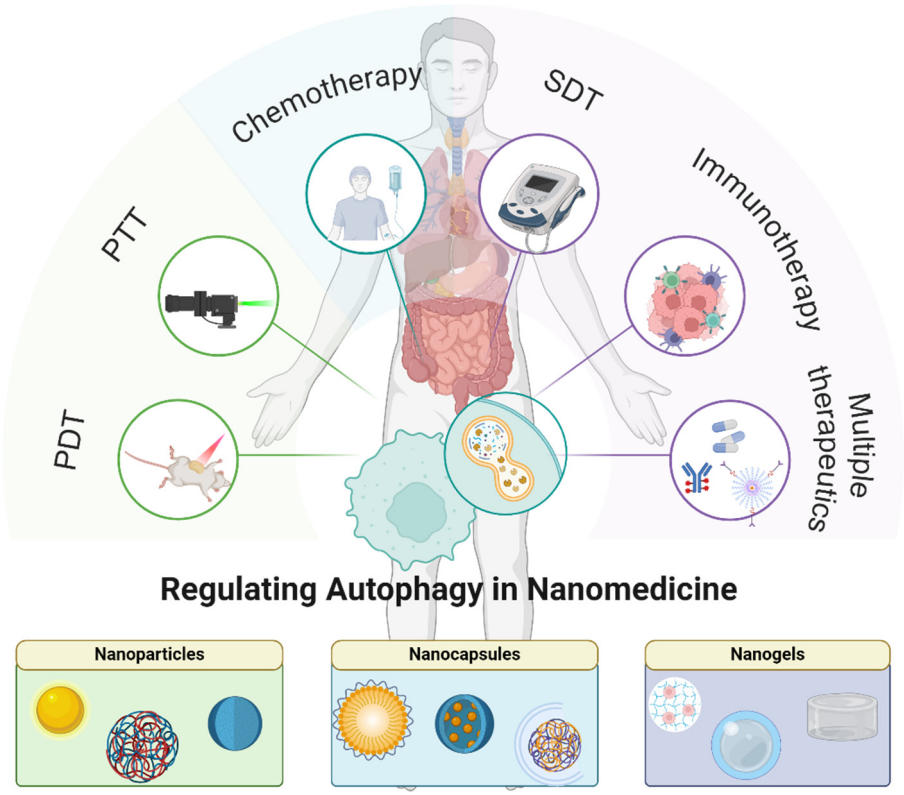

Figure 1. Schematic diagram of regulating autophagy in nanomedicine for cancer therapy. The schematic illustrations in the figures were created with BioRender.com.

2. The Role of Autophagy in Cancer

Autophagy is a highly conserved, intracellular degradation process that involves the lysosomal-mediated breakdown of cytoplasmic components. This process serves as a cellular quality control system, responsible for maintaining cellular homeostasis and responding to various stress conditions [22]. In the context of cancer, autophagy plays a multifaceted role, acting both as a tumor-suppressive and tumor-promoting mechanism. This dual role depends largely on the type of cancer, the stage of the disease, and the microenvironment in which the tumor resides. In this section, we will explore the detailed mechanisms of autophagy, including the processes involved in the formation of autophagosomes, fusion with lysosomes, the various types of autophagy, and the dual nature of autophagy in cancer.

2.1. Autophagic Processes

Autophagy is initiated when cells sense stressors such as nutrient deprivation, hypoxia, or cellular damage, leading to the activation of autophagy-related (ATG) proteins [23,24]. The autophagic process is characterized by the formation of a double-membraned vesicle called the autophagosome, which encapsulates portions of the cytoplasm, including damaged organelles, protein aggregates, or pathogens, for degradation and recycling (Figure 2).

Formation of Autophagosomes: The formation of autophagosomes begins with the nucleation of the phagophore, a membrane structure that originates from the endoplasmic reticulum (ER), Golgi apparatus, or specialized regions of the plasma membrane. The Unc-51-like kinase 1 (ULK1) complex is among the key regulatory proteins that trigger this nucleation step. Upon activation by cellular signals such as mTOR (mechanistic target of rapamycin) inhibition during nutrient scarcity, the ULK1 complex initiates the formation of the phagophore. Once nucleated, the phagophore elongates and engulfs portions of the cytoplasm. The elongation process involves the recruitment of ATG proteins, including ATG5, ATG12, and microtubule-associated protein 1 light chain 3 (LC3). LC3, in particular, is involved in the expansion of the phagophore membrane, and its lipidation is critical for the closure of the autophagosome. LC3-II, the lipidated form of LC3, is considered a marker for autophagosomes and is widely used to study autophagic activity.

Fusion with Lysosomes: Once the autophagosome has completed its membrane closure, it moves toward lysosomes for degradation. The fusion of the autophagosome with the lysosome is mediated by a complex

machinery that includes the HOPS (homotypic fusion and vacuole protein sorting) complex, the ras-related protein GTPases (RAB GTPases), and soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNARE proteins). These fusion forms an autolysosome, where the engulfed cellular material is degraded by lysosomal hydrolases, including cathepsins, lipases, and proteases. The degradation products, such as amino acids, lipids, and sugars, are then recycled back into the cytoplasm, contributing to cellular homeostasis and energy production.

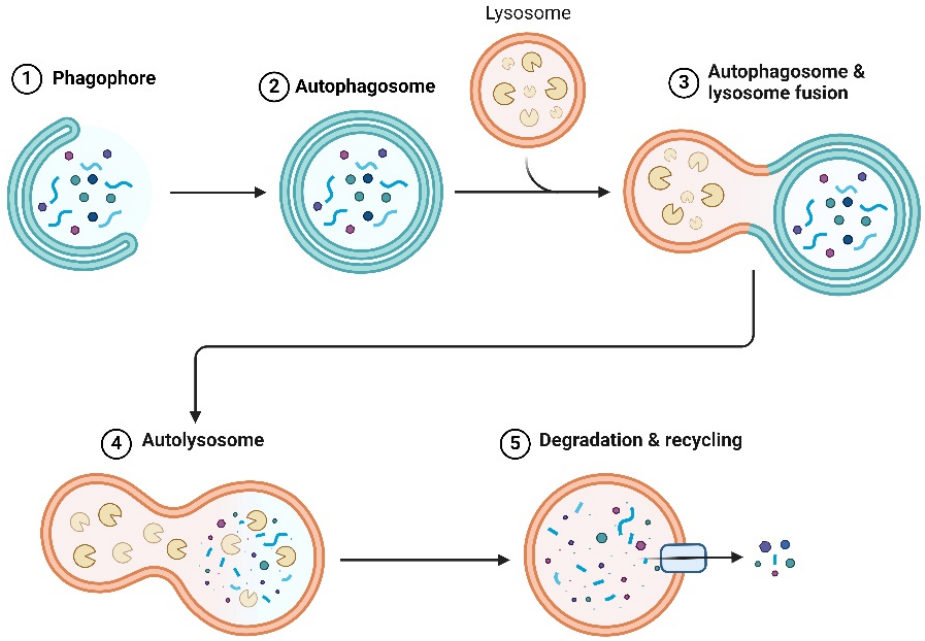

Figure 2. Schematic illustration of autophagic process. Autophagy is a cellular process involved in the degradation and recycling of organelles and proteins. During this process, a double-membrane structure known as the autophagosome engulfs and sequesters specific cellular components. The autophagosomes subsequently fuse with lysosomes, where their contents are degraded by lysosomal enzymes. Autophagy functions as a quality control mechanism that maintains cellular homeostasis and supplies essential nutrients during periods of stress or nutrient deprivation. The schematic illustrations in the figures were created with BioRender.com.

2.2. Types of Autophagy

Autophagy can be classified into different types based on the nature of the substrate and the mechanisms involved in the process [25,26]. The major types of autophagy include macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (Figure 3).

Macroautophagy: Macroautophagy is the most widely studied form of autophagy and involves the sequestration of large portions of cytoplasm, including entire organelles. It is characterized by the formation of autophagosomes, which are large, double-membraned vesicles that contain cytoplasmic material [9,27,28]. This process is tightly regulated by autophagy-related genes and is primarily responsible for the removal of damaged or dysfunctional cellular components.

Microautophagy: In contrast to macroautophagy, microautophagy involves the direct engulfment of cytoplasmic material by the lysosome itself, without the formation of autophagosomes [29,30]. The lysosomal membrane undergoes invagination to capture small portions of the cytoplasm, which are then degraded within the lysosome. Microautophagy plays a significant role in maintaining cellular homeostasis by removing smaller substrates and is particularly important in certain types of stress, such as oxidative damage.

Chaperone-Mediated Autophagy (CMA): Chaperone-mediated autophagy is a selective form of autophagy where specific substrates are targeted for degradation. This process is mediated by the chaperone protein HSC70, which recognizes and binds to a specific pentapeptide motif on the substrate proteins. The substrate is then translocated directly into the lysosome via a lysosomal membrane receptor known as LAMP-2A (lysosomal-associated membrane protein 2A) [31,32]. CMA plays a crucial role in removing damaged or misfolded proteins and regulating the turnover of certain intracellular proteins.

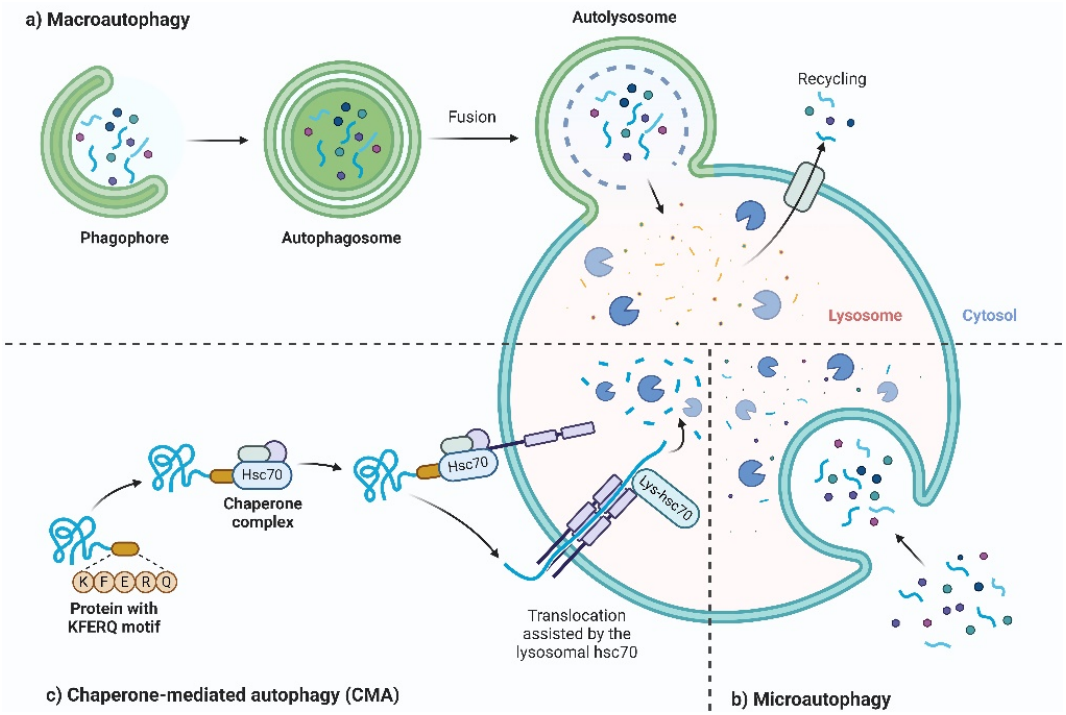

Figure 3. Three distinct types of autophagy. (**a**) Macroautophagy, (**b**) Microautophagy and (**c**) Chaperone-mediated autophagy. The schematic illustrations in the figures were created with BioRender.com.

2.3. Dual Role of Autophagy in Cancer

Autophagy plays a complex and context-dependent role in cancer, acting as both a tumor suppressor and a tumor promoter [33]. This dual role depends on the stage of cancer, the cellular context, and the type of stress encountered by the cancer cells.

Tumor-Suppressive Role: At the early stages of cancer development, autophagy acts as a protective mechanism, preventing the accumulation of damaged organelles and proteins that could otherwise lead to genomic instability, oxidative stress, and cell transformation. Autophagy is also involved in the removal of dysfunctional mitochondria (mitophagy), which helps reduce the production of reactive oxygen species (ROS) and prevents DNA damage [34,35]. In this context, autophagy acts as a barrier to tumorigenesis by maintaining cellular integrity and preventing the accumulation of oncogenic mutations. In addition to its role in cellular quality control, autophagy can also suppress inflammation in the tumor microenvironment, which is known to contribute to tumor progression. By degrading inflammasomes and other inflammatory mediators, autophagy limits chronic inflammation, thus reducing the risk of tumorigenesis [36,37].

Tumor-Promoting Role: As cancer progresses, the role of autophagy becomes more complex, and in many cases, autophagy can promote tumor survival, particularly in conditions of nutrient deprivation, hypoxia, or chemotherapy treatment. Tumor cells often experience metabolic stress due to rapid growth and limited blood supply, leading to autophagy activation as a survival mechanism. In this setting, autophagy helps cancer cells maintain energy homeostasis by recycling cellular components, thus supporting their survival in hostile microenvironments. Moreover, autophagy has been shown to contribute to resistance against various cancer therapies, including chemotherapy and targeted therapies [38,39]. By promoting the degradation of chemotherapeutic agents or damaged organelles, autophagy helps tumor cells survive treatment and continue proliferating. Therefore, autophagy inhibition has been proposed as a potential therapeutic strategy to enhance the efficacy of cancer therapies.

2.4. Autophagy as a Therapeutic Target

Given its dual role in cancer, targeting autophagy as a therapeutic strategy requires a careful approach. In some cases, autophagy inhibition could enhance the effectiveness of cancer treatments by promoting tumor cell death, particularly in chemotherapy-resistant tumors. However, in other cases, autophagy inhibition could lead to tumor progression, especially in cancers where autophagy is tumor-suppressive in nature. Thus, the therapeutic modulation of autophagy in cancer must be personalized, taking into account the specific context and stage of the disease.

Autophagy is an essential cellular process that contributes to the maintenance of homeostasis, particularly in cancer cells under stress. The mechanisms underlying autophagy, including the formation of autophagosomes, fusion with lysosomes, and the various types of autophagic processes, are complex and tightly regulated. The dual role of autophagy in cancer, acting as both a tumor suppressor and a promoter, underscores its importance in tumor biology. Understanding the intricate dynamics of autophagy in cancer will be crucial for developing targeted therapeutic strategies that can manipulate this process to improve cancer treatment outcomes.

3. Types of Nanocarriers for Autophagy Regulation for Cancer Therapy

Nanocarriers have become an essential tool in advancing cancer therapies due to their ability to deliver therapeutic agents in a targeted, controlled, and efficient manner. One of the promising approaches in cancer treatment involves the modulation of autophagy, a process by which cells degrade and recycle components to maintain homeostasis. Autophagy plays a complex role in cancer, acting as a double-edged sword-while it can promote tumor growth by supporting cancer cell survival under stressful conditions, it can also contribute to tumor suppression. As a result, the regulation of autophagy has gained significant attention in cancer therapy. The delivery of autophagy modulators using nanocarriers has shown promising results in overcoming the limitations of traditional treatments such as poor drug bioavailability, side effects, and off-target toxicity. This section highlights the various types of nanocarriers employed in autophagy regulation for cancer therapy, including nanoparticles, nanocapsules, and nanogels, examining their mechanisms, advantages, and challenges.

3.1. Nanoparticles in Autophagy Regulation

Nanoparticles (NPs) are one of the most commonly used nanocarriers in cancer therapy due to their versatility in drug delivery. These particles can range in size from 1 to 150 nm and can be made from various materials, including polymeric nanoparticles and inorganic nanoparticles. The size, surface charge, and composition of nanoparticles are crucial factors that influence their interaction with cells, drug release profiles, and their ability to modulate autophagy.

(a) Polymeric Nanoparticles

Polymeric nanoparticles, composed of biocompatible and biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and polyethylenimine (PEI), have shown great promise in delivering autophagy inhibitors or inducers to cancer cells [40,41]. These materials are often designed to encapsulate hydrophobic drugs, which would otherwise have poor solubility in physiological conditions. For example, certain chemotherapeutic agents, such as paclitaxel, have been encapsulated in PLGA-based nanoparticles to enhance their cytotoxicity by simultaneously inhibiting autophagic processes that might otherwise protect cancer cells from drug-induced damage (Figure 4a) [42,43]. Furthermore, nanoparticles can be engineered with specific ligands on their surfaces to target autophagy-related proteins or receptors on tumor cells, thereby promoting the internalization of the therapeutic payload. Polymeric nanoparticles can also be used to deliver RNA-based therapies, including small interfering RNA (siRNA) or messenger RNA (mRNA), aimed at silencing key genes involved in autophagy pathways, such as Beclin-1 or Atg5 [44–46].

(b) Inorganic Nanoparticles

Inorganic nanoparticles (INPs) have garnered significant attention in the field of cancer therapy due to their unique physicochemical properties, including high surface area, biocompatibility, and ease of functionalization. These nanoparticles can regulate autophagy, a process that plays a crucial role in cancer progression by either supporting tumor cell survival or inducing cell death. By targeting autophagic pathways, INPs can be engineered to enhance therapeutic efficacy, either by promoting cell death in cancer cells or by overcoming drug resistance. Several types of inorganic nanoparticles have been explored for autophagy modulation in cancer therapy, including gold (AuNPs), silver nanoparticles (AgNPs), silica (SiNPs), iron oxide (IONPs), copper-based nanoparticles (CuNPs), and other INPs [47].

Gold nanoparticles are well-known for their biocompatibility and ease of functionalization. They can be engineered to interact with autophagy-related proteins or used for photothermal therapy, promoting autophagic cell death in cancer cells upon near-infrared (NIR) irradiation [48–50]. Studies have demonstrated that polyethylene glycol-conjugated gold nanoparticles (PEG-AuNPs) inhibit TAMs M2 polarization through autophagy intervention, inducing antitumor immunotherapy and inhibiting tumor growth by disrupting lysosomal function and autophagic flux in both in vitro and in vivo models (Figure 4b) [51]. Silver nanoparticles (AgNPs) also exhibit similar autophagy-modulating effects, with their size and surface charge playing significant roles in

their interaction with cancer cells. By promoting oxidative stress, AgNPs can initiate autophagy-mediated cell death, presenting a potential strategy for enhancing the efficacy of cancer therapies [52–55]. In particular, AgNPs trigger the formation of reactive oxygen species (ROS), which activate key signaling pathways that lead to autophagy. This process is often associated with the suppression of mTOR (mechanistic target of rapamycin) activity, a negative regulator of autophagy. Similarly, silica nanoparticles (SiNPs) are highly versatile and can be modified for controlled drug delivery. Their porous nature allows for the encapsulation of autophagy-modulating agents, enhancing the regulation of autophagic flux in cancer cells, and offering targeted delivery [56–59]. IONPs have magnetic properties that allow for targeted therapy via an external magnetic field. Their ability to generate reactive oxygen species (ROS) induces autophagy and enhances tumor destruction, particularly in combination with magnetic hyperthermia [60–64]. At the molecular level, the mechanism by which IONPs induce autophagy involves several key signaling pathways. One of the most notable is the AMPK-mTOR pathway. ROS generated by IONPs activate AMP-activated protein kinase (AMPK), which inhibits the mTOR (mechanistic target of rapamycin) pathway, a negative regulator of autophagy. When mTOR is suppressed, autophagy is upregulated, leading to the degradation of damaged cellular components and promoting cell death in tumor cells. Moreover, copper nanoparticles, including copper oxide (CuO) and copper sulfide (CuS), are highly effective in inducing oxidative stress and ROS production, which triggers autophagic cell death [65–68]. These nanoparticles also possess photothermal properties that can further enhance cancer therapy. In addition to these, nanoparticles made from other inorganic materials, such as palladium (Pd), Graphene Oxide (GO), calcium phosphate (CaP) and Quantum dots (QD), have shown promise in modulating autophagy for cancer therapy. PdNPs, for instance, can be used in hydrogenation reactions that generate ROS, thus activating autophagy in cancer cells [69,70]. At the molecular level, the ROS generated by PdNPs can activate key signaling pathways involved in autophagy. For example, ROS can induce the phosphorylation of the protein complex mTOR (mechanistic target of rapamycin), a major negative regulator of autophagy, which results in the activation of autophagic processes. CaP nanoparticles are bioactive and can regulate autophagy by influencing intracellular calcium levels. Their ability to deliver both therapeutic agents and autophagy modulators makes them ideal for enhancing the efficacy of cancer therapies [71–73]. Graphene oxide has a large surface area and can be functionalized to carry autophagy-modulating drugs. GO also generates ROS under UV light, triggering autophagy and enhancing cancer cell death [74–76]. Quantum dot (QD) are semiconductor nanoparticles with unique optical properties, enabling real-time tracking of autophagic processes. Their high surface area and ability to be functionalized make them excellent candidates for targeted delivery of autophagy modulators in cancer therapy [77–79].

These inorganic nanoparticles offer diverse strategies for autophagy regulation, either by inducing autophagic cell death or by modulating autophagic flux to overcome therapeutic resistance in cancer cells. However, challenges remain in optimizing their biocompatibility, controlling their biodistribution, and ensuring selective targeting of tumor cells. Future advancements in nanoparticle design and understanding of the autophagy mechanism will be crucial for enhancing the clinical effectiveness of these strategies in cancer therapy.

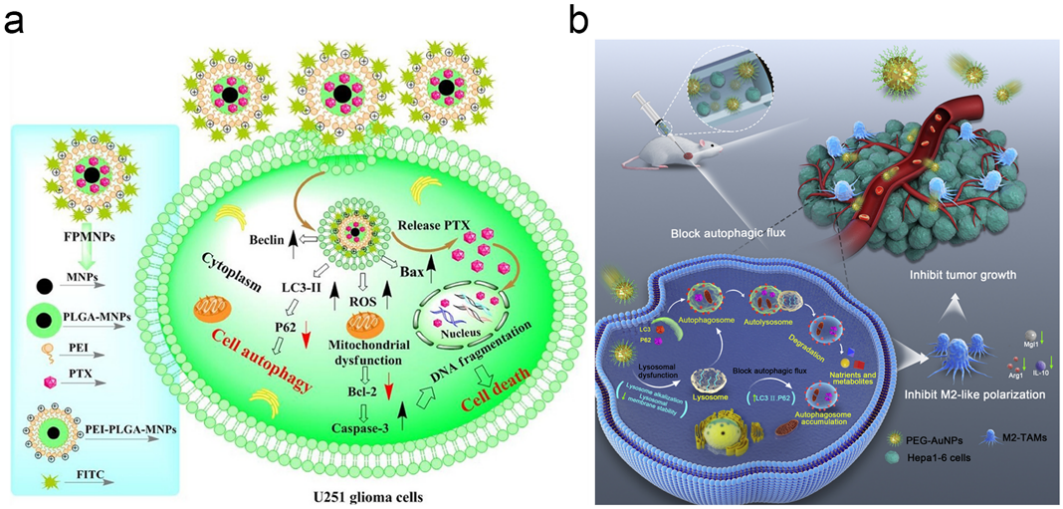

Figure 4. Nanoparticles in autophagy regulation for cancer therapy. (**a**) Schematic illustration of the fabrication of PLX-loaded multifunctional magnetic nanoparticles and their delivery into glioblastoma U251 cells for the assessment of antitumor effects. (**b**) Schematic representation of the mechanism underlying PEG-AuNPs-induced antitumor immunotherapy, which involves the inhibition of TAMs M2 polarization through the induction of lysosomal dysfunction and the suppression of autophagic flux [42,51]. Copyright 2023, Elsevier.

3.2. Nanocapsules in Autophagy Regulation

Nanocapsules are a subclass of nanocarriers designed to enclose therapeutic agents within a core structure, typically made from polymers, lipids, or proteins, with an outer shell. The encapsulation allows for the protection of sensitive drugs from degradation and facilitates controlled drug release. Nanocapsules can vary in size, but typically range from 10 to 1000 nm. These nanocarriers can be engineered to target specific cancer cells or tissues, increasing the therapeutic index and minimizing systemic toxicity.

(a) Polymeric Nanocapsules

Polymeric nanocapsules are particularly attractive for autophagy modulation because they can be loaded with a wide range of therapeutic agents, including hydrophobic drugs, gene therapies, and small molecule inhibitors of autophagy. For example, a nanocapsule made of PLGA could encapsulate a drug like chloroquine, which inhibits autophagy, and deliver it directly to tumor cells [80–83]. Chloroquine works by inhibiting the autophagic flux, leading to the accumulation of autophagic vesicles and subsequent cell death. Polymeric nanocapsules can also be functionalized with targeting ligands, such as antibodies or aptamers, to improve their selectivity for cancer cells [84]. This strategy helps to avoid off-target effects and enhance the accumulation of the drug at the tumor site, where it can influence autophagy pathways and sensitize the tumor to other forms of therapy, such as chemotherapy or radiation.

(b) Liposomal Nanocapsules

Liposomal nanocapsules, as advanced drug delivery systems, have gained significant attention in nanomedicine, particularly for targeting autophagy in cancer therapy. Liposomes are lipid-based nanocapsules composed of one or more phospholipid bilayers surrounding an aqueous core. These structures are highly biocompatible and can encapsulate both hydrophilic and hydrophobic drugs. Liposomes can be modified to release their payload in response to the acidic environment of the tumor microenvironment or by incorporating pH-sensitive lipids. This targeted delivery can be further fine-tuned by incorporating autophagy modulators into the liposomal formulations, such as chloroquine or hydroxychloroquine, which inhibit autophagic flux and sensitize tumor cells to chemotherapy [85,86]. For instance, the study explored the antifibrotic activity of hydroxychloroquine (HCQ) in overcoming extracellular matrix (ECM) barriers, enhancing the bio-distribution and anticancer efficacy of liposomal doxorubicin in both systemic and local (via injectable alginate hydrogel) administration. HCQ treatment reduced collagen and hyaluronan levels, inhibited autophagy, and improved drug delivery in breast cancer cell 4T1 tumor models, resulting in enhanced therapeutic outcomes for both intravenous and intratumoral applications of liposomal doxorubicin (Figure 5a,b) [87]. The study presents a promising strategy to enhance drug delivery and efficacy by targeting ECM components, though the long-term effects and clinical applicability of HCQ as an adjunct therapy in various tumor types need further investigation. In addition to autophagy inhibitors, liposomal nanocapsules can also encapsulate autophagy-inducing agents like rapamycin or spermidine, which promote autophagy in cancer cells [88]. By carefully balancing the modulation of autophagic activity, liposomal nanocapsules can selectively push cancer cells toward either autophagic cell death or sensitization to other therapeutic modalities. This approach has shown promise in overcoming resistance mechanisms, particularly in aggressive cancers where autophagy can protect tumor cells from traditional therapies.

3.3. Nanogels in Autophagy Regulation

Nanogels are highly cross-linked, hydrophilic polymer networks capable of swelling in aqueous environments. These structures are particularly useful for the delivery of water-soluble drugs, proteins, and nucleic acids, and their flexibility allows for the encapsulation of both small molecules and larger biomolecules. The unique properties of nanogels make them a promising candidate for autophagy regulation in cancer therapy.

(a) Polymeric Nanogels

Polymeric nanogels have emerged as a promising platform in nanomedicine, particularly for targeting autophagy in cancer therapy. Polymeric nanogels made from materials such as poly(N-isopropylacrylamide) (PNIPAM), polyethylenimine (PEI), or chitosan have been explored for their potential to deliver autophagy inhibitors or autophagy-related gene therapies [89,90]. One of the key advantages of nanogels is their ability to respond to environmental stimuli such as pH, temperature, and ionic strength. This makes them ideal for controlled drug release in the tumor microenvironment, where conditions are often acidic, and the ability to deliver autophagy modulators at precise times can significantly improve therapeutic effects. In addition to delivering small molecule inhibitors like chloroquine or hydroxychloroquine, nanogels have also been used to deliver gene therapies that

target autophagy-related genes. For example, nanogels can encapsulate siRNA targeting autophagy-related genes like Beclin-1 or Atg5, leading to the silencing of these genes and subsequent inhibition of autophagy in cancer cells (Figure 5c,d) [91]. Polymeric nanogels offer a highly promising approach to cancer therapy by targeting autophagy. Their ability to deliver both autophagy modulators and other therapeutic agents, along with their flexibility in design, positions them as a powerful tool in the fight against cancer.

(b) Thermoresponsive Nanogels

Thermoresponsive nanogels are a subtype of nanogels that undergo a phase transition in response to temperature changes. These nanogels are particularly attractive for cancer therapy, as the temperature-sensitive transition can be exploited to control drug release at tumor sites, where elevated temperatures can be induced through methods like hyperthermia [92,93]. Thermoresponsive nanogels loaded with autophagy inhibitors can, therefore, release their payload upon localized heating, ensuring that the drug is delivered only to the tumor tissue. These nanogels have the potential to enhance the therapeutic efficacy of autophagy modulation by increasing the intracellular concentration of autophagy inhibitors at the tumor site, while minimizing off-target effects in normal tissues.

The use of nanocarriers in the regulation of autophagy for cancer therapy represents a powerful strategy to overcome some of the limitations of conventional treatment approaches. By employing nanoparticles, nanocapsules, and nanogels, researchers can deliver autophagy modulators with increased specificity, improved bioavailability, and controlled release profiles. Each type of nanocarrier offers distinct advantages, and ongoing research will continue to refine these technologies to maximize their potential in clinical settings. However, challenges related to scalability, long-term safety, and off-target effects must still be addressed before these therapies can be widely adopted in cancer treatment.

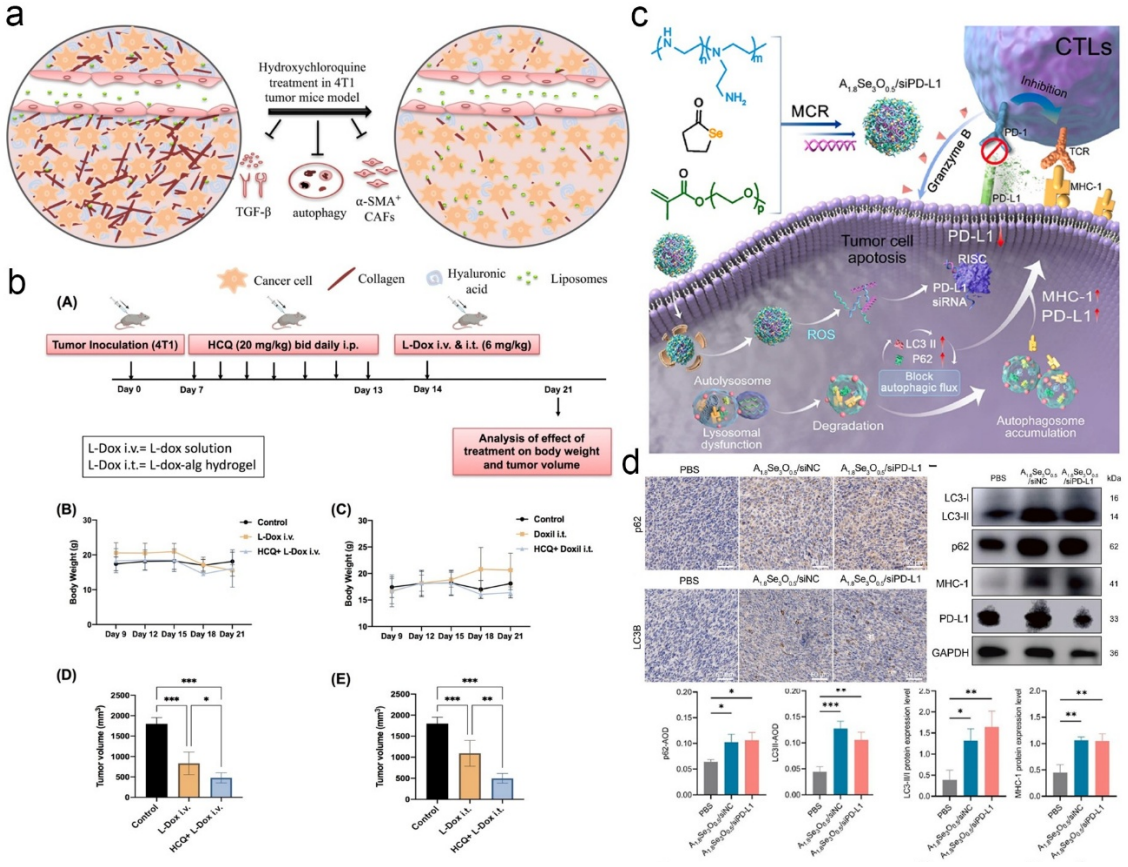

Figure 5. Nanocapsules and nanogels in autophagy regulation for cancer therapy. (**a**) A schematic representation depicting the mechanism of hydroxychloroquine in alleviating stress within solid tumor tissues and its subsequent effect on enhancing the distribution of liposomal doxorubicin. (**b**) In vivo assessment of the anti-cancer efficacy of liposomal doxorubicin following hydroxychloroquine (HCQ) treatment in 4T1 tumor tissues. (**c**) Schematic representation of the synthesis and antitumor mechanisms of $A_{1.8}Se_3O_{0.5}$/siPD-L1 nanogels. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. (**d**) Impact of $A_{1.8}Se_3O_{0.5}$/siPD-L1 nanogels on immune cells and tumor cells within the tumor microenvironment [87,91]. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Copyright 2024, Elsevier.

4. Combination Therapy with Nanomedicine Targeting Autophagy

4.1. Combination of Chemotherapy with Nanomedicine Targeting Autophagy

The combination of chemotherapy with nanomedicine targeting autophagy has emerged as a promising strategy to enhance the efficacy of cancer treatment. Chemotherapy, despite its widespread use, is often limited by issues such as drug resistance, non-specific toxicity, and relapse. Autophagy, a cellular process involved in the degradation of damaged organelles and proteins, plays a complex role in cancer. While autophagy can act as a protective mechanism under stress, promoting cancer cell survival, it can also induce cell death in certain contexts. Therefore, modulating autophagy through nanomedicine provides an opportunity to optimize the therapeutic outcomes of chemotherapy [94].

Autophagy plays an important role in different host cells, providing key metabolites, especially amino acids, to proliferate tumor cells. Autophagy also supports the secretion of pro-inflammatory cytokines such as IL-6, IL-8, and IL-1β, which create a tumor-enabling immune microenvironment by directly promoting tumor cell proliferation and regulating innate and adaptive immune cells [95]. There is a strong link between autophagy and chemotherapy. Due to the negative effects of mild autophagy on chemotherapy, the use of autophagy inhibitors provides a new therapeutic strategy for improving the effect of chemotherapy. Autophagy inhibitors, such as hydroxychloroquine (HCQ), are in Phase I and Phase II clinical trials in combination with multiple standard chemotherapies. Studies have shown that inhibition of autophagy can alter the response of normal and tumor cells to other treatments, with the maximum tolerated dose (MTD) of HCQ associated with concurrent treatment [96]. In summary, nanomedical drug delivery systems have the potential to improve the effectiveness of chemotherapy, but at the same time face challenges such as MDR and immune clearance.

Liang et al. developed a peptide conjugate, Nap-AZD-Yp, that selectively enhances tumor sensitivity to chemotherapy by forming intracellular nanofibers and releasing the autophagy inducer AZD8055. This approach not only improves the therapeutic effect of doxorubicin on tumors but also reduces its toxic side effects on normal tissues, making it a promising strategy for cancer treatment [96]. In addition, Lu et al. found that gold nanoparticles (GNPs) and mesoporous silicon nanoparticles (MSNs) were potential candidates for drug delivery (Figure 6a) [97]. They attached GNPs to amino-functionalized MSNs via relatively weak gold-nitrogen bonds to form NMSNs. Subsequently, these nanocomposites gold nanoparticles capping mesoporous silica nanoparticle (GCMSNs) were taken up by cells, GNPs were shed from NMSNs, and intracellular release of drugs in NMSNs was achieved through competitive binding of intracellular glutathione to GNPs. In addition to acting as a gating mechanism, GNPs also acted as an inducer of oxidative stress. GCMSNs caused higher levels of oxidative stress in lung cancer cells (A549) than normal cells (3T3-L1). The growth-inhibiting effects observed in cancer cells might be due to GCMSNs-induced mitochondrial dysfunction, which was caused by mitochondria-mediated autophagy triggered by oxidative stress (Figure 6b–f). Further, GCMSNs were loaded with camptothecin, demonstrating an enhanced synergistic therapeutic effect in combination with chemotherapy and oxidative stress strategies. GNPs, as an inducer of oxidative stress, could be used in combination with chemotherapy drugs to enhance the therapeutic effect. This strategy may enhance cancer cell death by increasing oxidative stress while reducing the effect on normal cells. The study by Lu et al. provides a novel nanocomposite GCMSNs that combines chemotherapy and oxidative stress strategies and exhibits a selective and effective therapeutic effect on cancer cells.

Ultimately, combining chemotherapy with nanomedicine that targets autophagy presents a novel approach to overcome the limitations of conventional cancer therapies. By fine-tuning the regulation of autophagy, this strategy offers a more precise and effective method to tackle chemoresistance, enhance drug delivery, and promote targeted tumor cell death. However, further studies are required to fully understand the intricate relationship between autophagy and cancer, as well as to optimize nanomedicine formulations for clinical use.

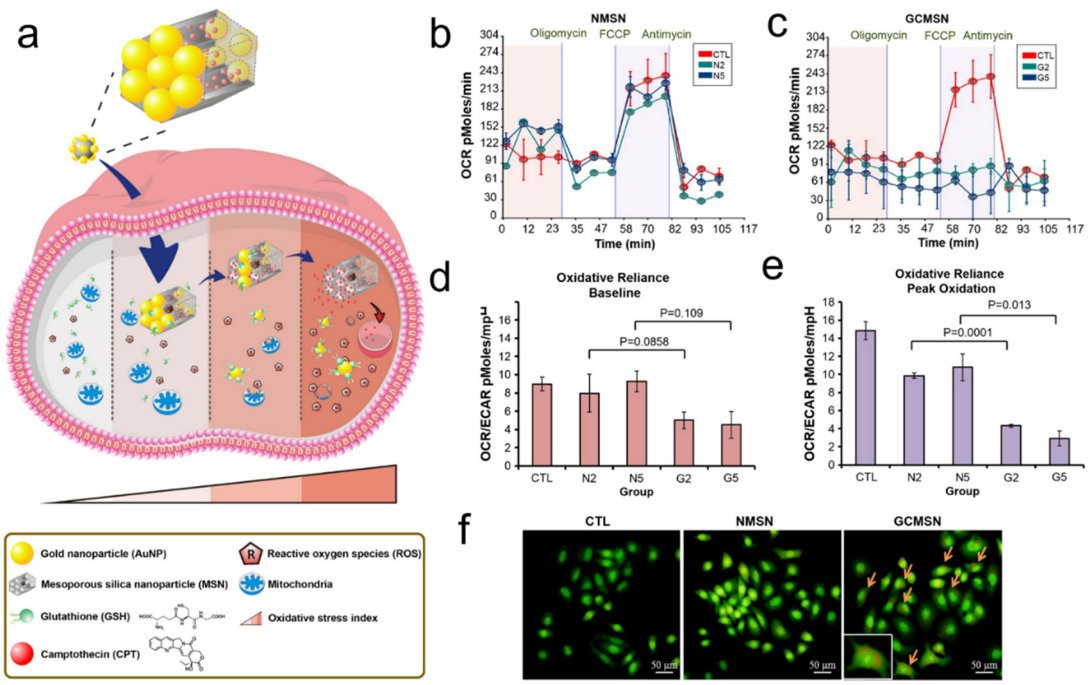

Figure 6. Combination of chemotherapy with nanomedicine targeting autophagy. (**a**) Schematic illustration of the performance of CPT-loaded GCMSNs combining the chemotherapy and oxidative stress strategy; The OCR measurement for A549 cells treated with (**b**) NMSN and (**c**) GCMSN, respectively; (**d**) Oxidative reliance performed by the ratio of OCR:ECAR at the baseline of 0~28 min; (**e**) Oxidative reliance in the period of peak oxidation (52~80 min); (**f**) GCMSNs induced autophagy in A549 cells analyzed by fluorescence microscopy, The existence of AVOs was indicated by the red fluorescence (orange arrows) [97]. Copyright 2015, Elsevier.

4.2. Combination of PDT with Nanomedicine Targeting Autophagy

The combination of PDT with nanomedicine targeting autophagy represents an innovative strategy to enhance cancer treatment outcomes. PDT involves the use of photosensitizers that, upon activation by light, generate reactive oxygen species (ROS) capable of inducing cellular damage and tumor cell death [98]. However, the effectiveness of PDT is often limited by the hypoxic tumor microenvironment, inadequate delivery of photosensitizers, and the ability of cancer cells to develop resistance mechanisms such as autophagy. Autophagy, a process by which cells degrade damaged components, can serve as a protective mechanism, allowing cancer cells to survive under oxidative stress induced by PDT. Therefore, modulating autophagy in conjunction with PDT offers a promising approach to overcome these challenges and improve therapeutic outcomes.

Chang et al. developed an irradiation-free 2D PDT nanosystem based on a rational combination of two-dimensional (2D) $CaAl_2O_4$:Eu,Nd persistent Luminescent nanosheets (CAO PLNSs), and a photosensitiser verteporfin with mitochondria-targeting capabilities [99]. This 2D CAO PLNSs acted as an internal "optical cell" capable of continuous output of cytotoxic singlet oxygen ($^1O_2$). In addition, Sun et al. proposed a "chase and block" strategy that synergizes photodynamic therapy (PDT) and autophagy inhibition to enhance cancer treatment [100]. This strategy uses an organic photosensitive molecule (FL) encapsulated in a hydrophobic layer of upconversion nanoparticles (UCNPs) and amphiphilic polymer DSPE-PEG-COOH, which activates FL under near-infrared (NIR) light to promote PDT (Figure 7a). As shown in Figure 7b, phagophore (pink arrow), autolysosome (blue arrow), and a small amount of vacuoles (orange arrow) could be observed in the UCNPs@FL + light group, indicating that UCNPs@FL+ light induced normal autophagy in tumor cells. The co-localization of UCNPs@FL-MEL with lysosomes (Figure 7c) indicated membrane fusion and reduced stability of the lysosomal membrane and escape of the material from the lysosome. Combined with the autophagy inhibiting melittin pro-peptide, the autophagy process could be inhibited by destroying the lysosomal membrane, thereby preventing cancer cells from saving themselves and enhancing the effects of PDT. The DSPE-PEG polymer extends circulation time and ensures better tumor retention, allowing the strategy to target hypoxic tumors effectively by utilizing enhanced penetration and retention (EPR) effects. This strategy offers a promising approach for improving PDT efficacy in hypoxic tumor environments, combining both molecular activation and autophagy disruption.

In summary, the combination of PDT with nanomedicine targeting autophagy offers a promising approach to improve the efficacy of cancer therapy. By modulating autophagy, either through inhibition or activation, in

conjunction with PDT, this strategy can overcome therapeutic resistance, enhance drug delivery, and increase the overall cytotoxicity against tumors. However, further research is needed to optimize nanoparticle formulations and better understand the complex interactions between autophagy and PDT for clinical translation.

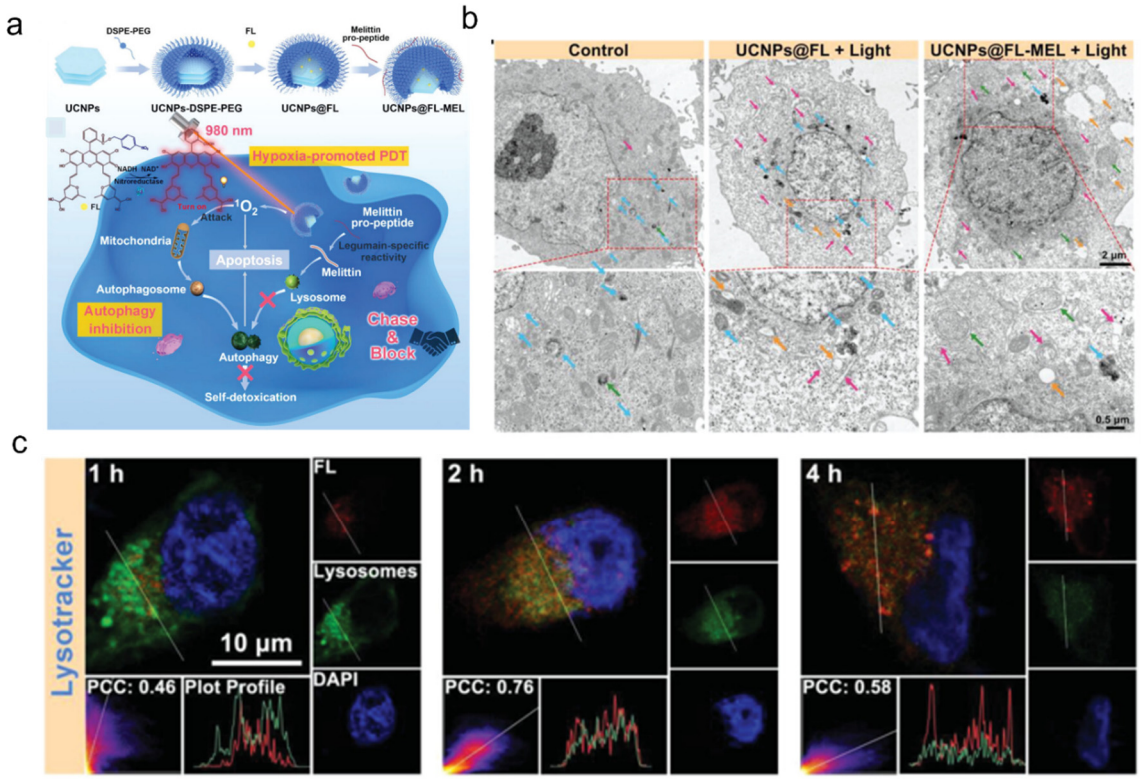

Figure 7. Combination of PDT with nanomedicine targeting autophagy. (**a**) Schematic diagram for the synthesis of UCNPs@FL-MEL and the synergistic therapy of hypoxic tumors induced by hypoxia-promoted photodynamic therapy and autophagy inhibition; (**b**) Bio-TEM images of HeLa cells after different treatments. The pink, blue, green, and orange arrows represent the phagophore, autolysosome, autophagosome and vacuoles, respectively; (**c**) Fluorescence images of UCNPs@FL-MEL (red fluorescence of FL) co-localized with lysosomes (green fluorescence) [100]. Copyright 2023, Wiley.

4.3. Combination of PTT with Nanomedicine Targeting Autophagy

Traditional photothermal conversion agents have the problem of inadequate safety, which limits the use of photothermal therapy (PTT) in clinical applications. To improve the safety and effectiveness of PTT, researchers are developing novel nanomaterials that can improve photothermal conversion efficiency, increase the accumulation of PTT agents in tumor tissues, and reduce side effects by combining with other therapies. The autophagy process is activated when cancer cells receive photothermal therapy, and the inhibition of autophagy can significantly enhance the effect of photothermal killing cancer cells. The application of nanomedicine in PTT offers a promising therapeutic strategy to improve diagnostic accuracy and therapeutic efficacy by guiding PTT-chemotherapy combination therapy with precise multimodal imaging. Regulating autophagy has emerged as a promising strategy for enhancing nanomedicine-mediated PTT. By constructing tumor-activated autophagy regulatory factors, autophagy induced by PTT can be effectively blocked and synergistic sensitization to tumor phototherapy can be realized.

Photothermal therapy exerts an antitumor effect by regulating autophagy, thus representing a novel solution to tumor elimination. However, conventional PTT usually cause severe pain due to the use of high temperature. To overcome this disadvantage, Deng et al. introduced ultrafast low-temperature photothermal therapy (LTPTT), a novel approach to tumor treatment that operates at 38–43 °C to minimize thermal pain [101]. The therapy utilizes GFS particles composed of folic acid, graphene oxide (GO), and the HSP90 inhibitor SNX-2112 to induce autophagic cell death in tumor cells. By activating autophagy and promoting T cell recovery, LTPTT not only eliminates tumors but also enhances natural immunity against them. This innovative LTPTT strategy effectively overcomes the pain associated with conventional PTT while simultaneously enhancing tumor elimination and immune response, representing a significant advancement in cancer treatment.

Mu et al. developed the PPG@PB-HCQ nanofiber membrane as an implantable platform combining PTT and autophagy inhibition to enhance tumor cell killing (Figure 8a) [102]. The membrane's effectiveness was due to the combination of Prussian blue (PB) and HCQ, which blocked autophagosome-lysosome fusion, as confirmed by specific protein expression patterns (Figure 8b). In B16 tumor-bearing mice, the PPG@PB-HCQ membrane demonstrated a potent antitumor effect, validating the synergistic strategy of PTT and autophagy inhibition. The study of Mu et al. provides a novel therapeutic strategy combining photothermal therapy and autophagy inhibition to enhance the killing effect of tumor cells by blocking the fusion of autophagosome and lysosome, which brings new hope to the field of cancer therapy. The heat generated by the photothermal process can trigger pro-survival autophagy, thereby improving the efficacy of PTT. However, few studies have focused on nanoagent induced autophagy, which may impair the efficacy of autophagy mediated PTT. Peng et al. developed a nanoagent called DCPF to enhance the efficacy of PTT by inducing thermosynergistic pro-survival autophagy (Figure 8c) [103]. DCPF treatment under NIR increased fluorescence by 32.87%, indicating enhanced autophagy via DCPF-mediated photothermal therapy (PTT). The combination of CQ and DCPF-mediated PTT resulted in a 28% increase in cell death and nearly complete inhibition (95.4%) (Figure 8d). Using the autophagy inhibitor chloroquine, DCPF-mediated PTT showed a clear synergistic effect in both in vitro and in vivo tumor models (HeLa), suggesting that the efficacy of image-guided PTT could be enhanced by modulating nanomaterial-induced autophagy. This study presents an innovative approach to boosting PTT efficacy through precise modulation of autophagy, offering a promising strategy for more effective cancer treatment.

In conclusion, combining PTT with nanomedicine that targets autophagy holds significant promise for improving cancer therapy outcomes. The dual-action of inducing direct thermal damage while modulating autophagic pathways provides a comprehensive strategy to effectively target and kill tumor cells. Continued research in this domain is crucial for optimizing nanoparticle designs and achieving successful clinical translations that can revolutionize current oncological treatments.

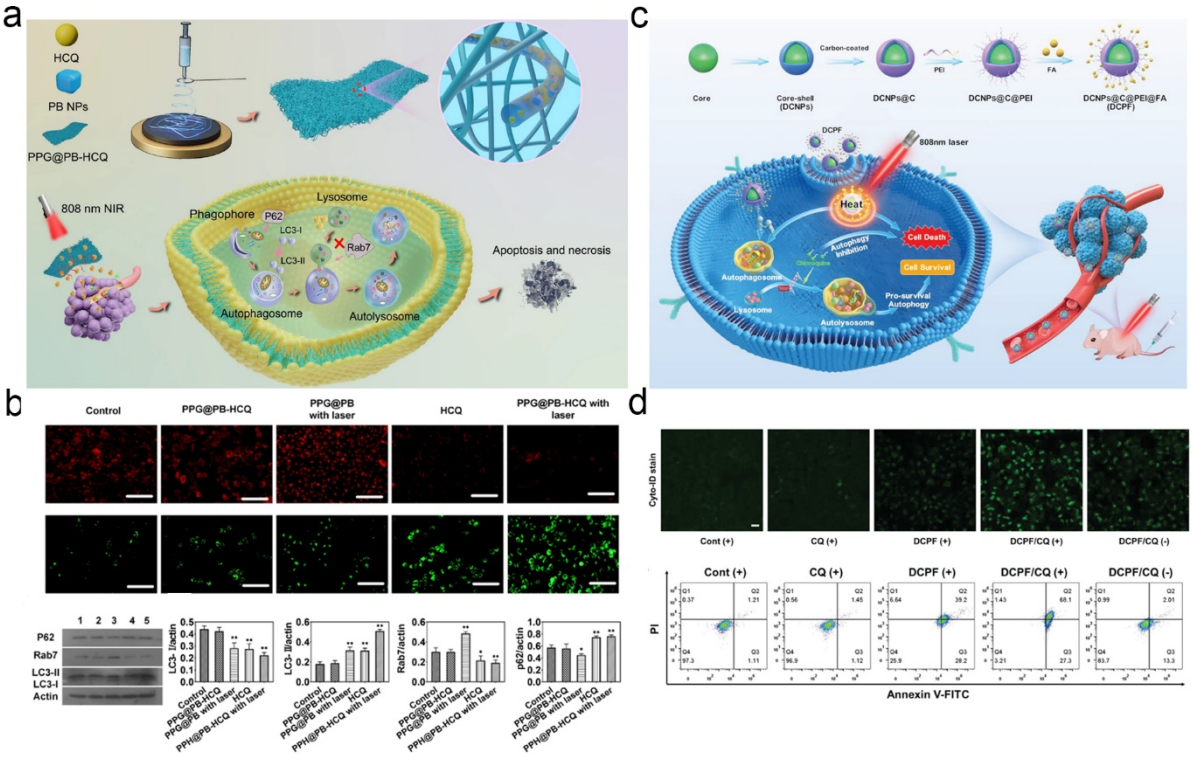

Figure 8. Combination of PTT with nanomedicine targeting autophagy. (**a**) The schematic illustrates the fabrication of the PPG@PB-HCQ nanofiber membrane via electrospinning and the biological mechanism underlying its enhanced antitumor effect, driven by the synergistic interaction between photothermal therapy (PTT) and autophagy inhibition. (**b**) Fluorescence staining and western blot assays. (n = 3, mean ± SD, * $p < 0.05$, ** $p < 0.01$). Scale bars, 50 μm. [102] Copyright 2023, Wiley. (**c**) Schematic illustration of the construction of DCPF and the working mechanism of inhibiting pro-survival autophagy to promote photothermal therapy of visualized tumors. (**d**) Staining of autophagic vacuoles using the fluorescent autophagosome marker Cyto-ID kits (Scale bar: 25 μm) and assessment of cell apoptosis and necrosis following various treatments, analyzed by flow cytometry. All data are presented as a mean ± S.D. (n = 5). [103]. Copyright 2022, Wiley.

4.4. Combination of SDT with Nanomedicine Targeting Autophagy

Ultrasound-triggered sonodynamic therapy (SDT), as an emerging cancer treatment method, has indeed attracted attention due to its advantages of high tissue penetration, high spatiotemporal selectivity and non-invasive. The mechanism of SDT includes the production of ROS through ultrasonic activation of acoustic sensitizers, which can cause oxidative stress of tumor cells, eventually leading to apoptosis and necrosis [104]. However, its clinical application is often limited by insufficient accumulation of SDT agents in tumors, which leads to insufficient production of ROS, and the cytoprotective effects of autophagy that affect therapeutic efficacy. To improve the accumulation of SDT agents in tumors, researchers are exploring the use of nanotechnology to improve their delivery efficiency. For example, by encapsulating traditional SDT agents in nanoparticles, their aggregation and intracellular transport efficiency in tumors can be enhanced [105]. To improve the efficiency of ROS generation, researchers are developing novel sonosensitizer, both organic and inorganic, as well as platforms based on metal-organic frameworks (MOFs) that can improve drug loading rates and effectively promote ROS dispersion, thereby improving the therapeutic efficiency of SDT. Autophagy may play a cytoprotective role in tumor cells, thus resisting the therapeutic effect of SDT.

To address the issue, Wang et al. developed platelets loaded with a sonosensitizer, which was based on functionalized boron nitride nanoparticles carrying chlorin e6 (BNPD-Ce6) [106]. This study investigated the use of BNPD-Ce6-mediated sonodynamic therapy (SDT) targeted towards glioblastoma (GBM) cells, showing that it induced ferroptosis and significant cell death in GBM cells while sparing macrophages (Figure 9a). The therapy activated macrophages through immuno-stimulatory autophagy, enhancing its toxicity to GBM cells, and platelet-mediated delivery of BNPD-Ce6 improved sonotoxicity by overcoming the lack of immunogenicity in the tumor cells. In vivo studies demonstrated that SDT slowed GBM growth and improved survival in animal models, with macrophages playing a crucial role in the therapeutic efficacy. The study highlights a novel approach to GBM treatment by combining ferroptosis induction with immune system modulation, offering a promising alternative to conventional therapies. However, the complexity of the therapy and its reliance on platelet-mediated delivery may limit its scalability and clinical translation, warranting further research into its practical application.

Gao et al. developed a macrophage-mimicking green algae (Chl) system (MChl) as a drug carrier, enhancing tumor targeting and oxygen supply via photosynthesis [9]. By constructing supermolecular conjugates with β-cyclodextrin-modified MChl and amantadan-modified liposomes, they achieved synergistic effects of local oxygenation, sonodynamic therapy (SDT), and autophagy inhibition, significantly improving melanoma treatment and inducing a robust anti-tumor immune response (Figure 9b). The study presents an innovative approach combining macrophage-mimicking algae with SDT for melanoma therapy, showing promising results in tumor targeting and immune activation. However, the complexity of the system and challenges in clinical translation could limit its widespread application.

Similarly, The CCP@HP@M cascade nanoreactor developed by Zhang et al. was used in enhanced SDT for the treatment of colorectal cancer. Zhang et al. designed a cascade nanoreactor CCP@HP@M by integrating the acoustic-sensitized agent Ce6 and the autophagy inhibitor chloroquine into hollow polydopamine (HP) nanocarriers modified by tumor cell membranes pre-doped with platinum nanoparticles [8]. This design aimed to enhance the efficacy of SDT by modulating ROS and autophagy (Figure 9c). HP nanocarriers exhibited superoxide dismutase (SOD) mimicking activity, capable of converting O_2^- to O_2 and H_2O_2, while platinum nanocases further catalyzed excess H_2O_2 to produce toxic ·OH and O_2. This cascade significantly enhanced the efficiency of SDT in tumor cells. During SDT, the ROS produced could induce autophagy, and activated autophagy helped tumor cells survive by inhibiting apoptosis (Figure 9d). This cascade nanoreactor provides a promising strategy for enhancing SDT eradication of tumors.

In conclusion, the combination of Sonodynamic Therapy with nanomedicine targeting autophagy offers a multifaceted strategy to improve cancer treatment. By precisely targeting the tumor microenvironment and simultaneously modulating both ROS production and autophagic activity, this approach has the potential to significantly enhance therapeutic outcomes. However, further research is needed to optimize nanoparticle design, understand the complex interplay between autophagy and cell death, and evaluate the clinical feasibility of this promising combination therapy.

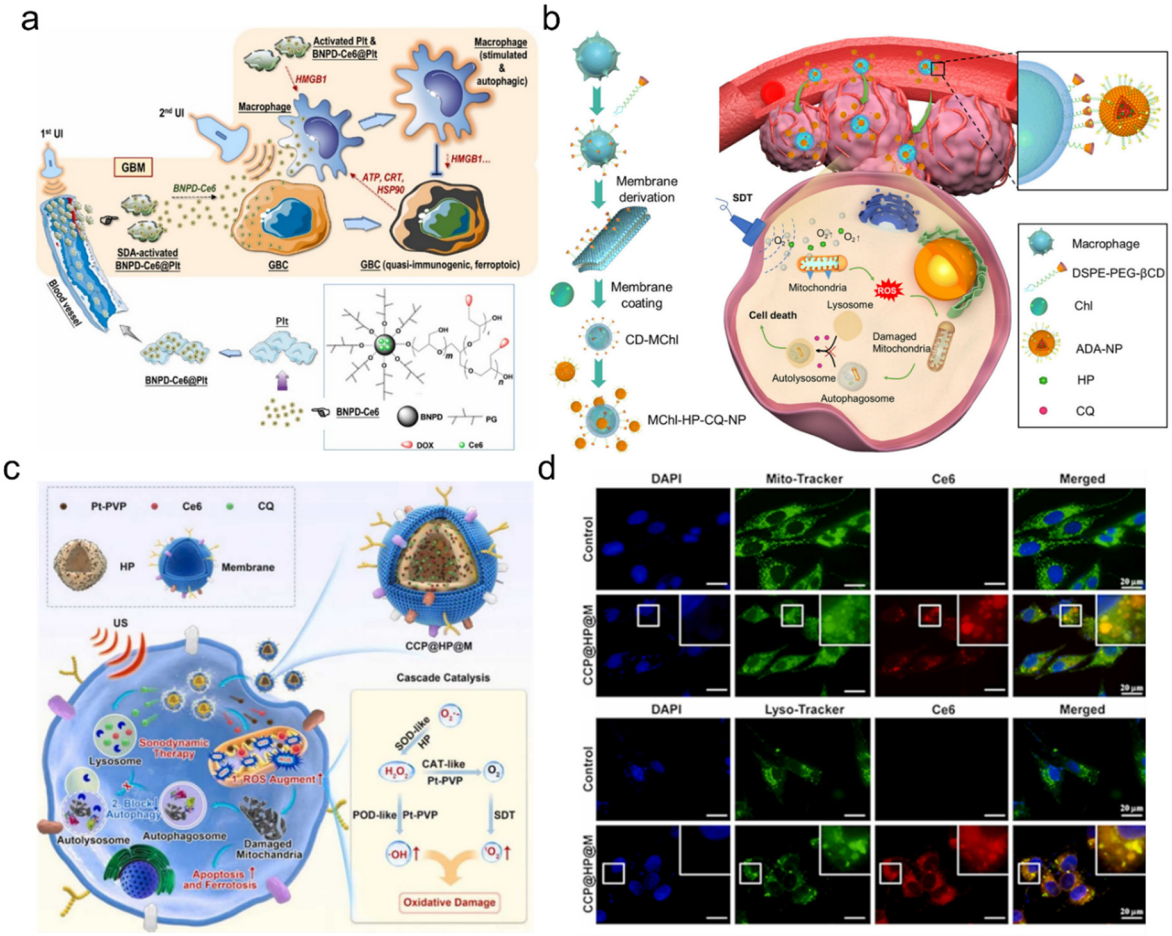

Figure 9. Combination of autophagy and sonodynamic therapy (SDT). (**a**) Schematic diagram for the working mechanism of targeted SDT of GBM reconciled by ultrasound-activated BNPD-Ce6@Plt, involving a synergistic effect of macrophage stimulation, tumor cell ferroptosis and platelet activation activated by the SDA [106]. Copyright 2025, Elsevier. (**b**) Schematic diagram of MChl-CQ-HP-NP conjugate preparation and the delivery of MChl hitchhiking to tumor tissues and enhanced antitumor immunotherapy [9]. Copyright 2023, American Chemical Society. (**c**) Schematic illustration of the cascade nanoreactor for enhancing SDT on colorectal cancer. (**d**) Fluorescence images of subcellular location of CCP@HP@M after 4 h. Ce6 fluorescence (red), Mito-Tracker Green (detect mitochondria) or Lysol-Tracker Green (detect lysosome), and DAPI (blue) [8]. Copyright 2023, Elsevier.

4.5. Combination of Immunotherapy with Nanomedicine Targeting Autophagy

The combination of immunotherapy with nanomedicine targeting autophagy presents a cutting-edge approach in cancer treatment, leveraging the synergistic effects of immune modulation and autophagy regulation. Immunotherapy, particularly immune checkpoint inhibitors (ICIs) like anti-PD-1 and anti-CTLA-4 antibodies, has revolutionized cancer treatment by enhancing the body's immune response against tumors. However, despite the success of immunotherapy in certain cancers, many patients develop resistance, which can be linked to the tumor microenvironment (TME), immune evasion strategies, and autophagy, a cellular process involved in maintaining cellular homeostasis under stress.

Nanomedicine plays a crucial role in the precise delivery of therapeutic agents, including both immune checkpoint inhibitors and autophagy modulators, to the tumor site. For instance, the use of nanoparticles such as liposomes or micelles allows for the co-delivery of autophagy inhibitors like chloroquine alongside immune checkpoint inhibitors [107,108]. Chloroquine, by inhibiting autophagy, enhances the effectiveness of ICIs by reducing the survival of immune-suppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). This simultaneous inhibition of autophagy and immune checkpoint blockade potentiates the immune system's ability to recognize and destroy tumor cells. Additionally, nanoparticles can be engineered to target specific immune cells within the tumor microenvironment (TME), further enhancing the therapeutic effects of immunotherapy. For example, dendritic cell-targeting nanoparticles can deliver both antigens and immunotherapeutic agents, stimulating a robust immune response while concurrently blocking autophagic

survival mechanisms in the tumor [109,110]. This approach not only improves immune cell activation but also inhibits tumor-associated immune suppression. Furthermore, by incorporating autophagy inhibitors into the nanoparticle formulation, the inhibition of autophagic pathways can directly promote tumor cell death while simultaneously improving the immune response. Fu et al. developed a BTO/BP-HA semiconductor heterojunction nanocatalyst that enhances immunotherapy by using ultrasound to regulate tumor autophagy (Figure 10a) [111]. The nanocatalyst, when stimulated by ultrasound, facilitates water splitting to produce hydrogen (H_2), which promotes tumor apoptosis and triggers an immune response through immunogenic cell death. By inhibiting autophagy via a sonocatalytic strategy and improving lysosomal pH, the study enhances the efficacy of immunotherapy and strengthens the anti-tumor immune response (Figure 10b). This study introduces a novel ultrasound-driven sonocatalytic approach to enhance immunotherapy by targeting autophagy, showing promising therapeutic potential. However, the complexity of the system and potential side effects in clinical applications remain challenges to be addressed.

In conclusion, combining immunotherapy with nanomedicine targeting autophagy offers a promising strategy to enhance cancer treatment by overcoming the limitations of each therapy alone. Nanomedicine enables efficient delivery of immunotherapy agents and autophagy inhibitors, potentially overcoming immune resistance. However, further research is needed to optimize nanoparticle delivery systems and understand the relationship between autophagy and immune responses.

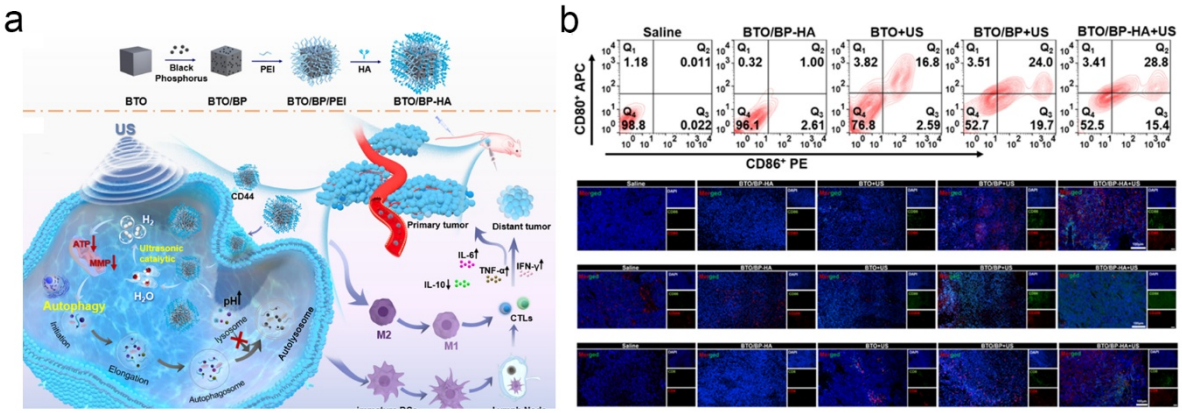

Figure 10. Combination of immunotherapy with nanomedicine targeting autophagy. (**a**) Schematic diagram illustrating how BTO/BP-HA promotes apoptosis, subsequently impairs tumor autophagy, and thereby enhances the efficacy of immunotherapy under ultrasound (US) stimulation. (**b**) Flow cytometry was used to analyze the expression of $CD80^+$ and $CD86^+$ on tumor tissues and $CD80^+/CD86^+$, $CD86^+/CD206^-$, and $CD4^+/CD8^+$ tumor cells isolated from tumors excised from mice subjected to different treatments [111]. Copyright 2024, American Chemical Society.

4.6. Combination of Other Therapies with Nanomedicine Targeting Autophagy

The integration of nanomedicine with various non-traditional therapies targeting autophagy holds great promise for enhancing treatment outcomes in a wide range of diseases. Autophagy, a cellular process responsible for the degradation and recycling of damaged organelles and proteins, plays a key role in cellular homeostasis and disease progression. By modulating autophagy, nanomedicines can amplify the effects of other therapies, improving their efficacy and reducing side effects.

Yang et al. proposed a synergistic approach to enhance tumor starvation therapy by inhibiting autophagy and blocking glucose metabolism, placing cancer cells in a severe energy-deprived state (Figure 11a) [112]. The use of black phosphorus nanosheets (BPNS) as autophagy inhibitors prevents compensatory energy supply, leading to increased apoptosis through the modulation of key kinases like CSNK2A2 and GSK-3β. This combined strategy, which simultaneously blocks both exogenous and endogenous nutrient supply, holds promise for improving cancer treatment efficacy by enhancing tumor starvation therapy. The strategy of combining metabolic inhibition with autophagy blockade presents a promising avenue for developing more effective cancer therapies, potentially overcoming the resistance mechanisms that cancer cells use to evade treatment. In addition, Zhang et al. developed a controllable tumor ablation strategy that integrates fluorescence photosensitizer-activated autophagy with cancer starvation therapy, using AIEgens TPAQ and TPAP to stimulate ROS production and induce lysosomal membrane permeability (Figure 11b) [113]. This combination of photodynamic therapy (PDT) and cancer starvation therapy enhances the efficacy of tumor treatment by overcoming protective autophagy and promoting apoptosis in tumor

cells. This novel approach offers a promising dual-mechanism strategy for improving cancer therapy, with the potential to overcome resistance by targeting both autophagy and energy metabolism in cancer cells. Chen et al. synthesized Co-Fc@HCQ nanoparticles, which combine Fenton reaction-derived ROS production with autophagy inhibition via HCQ, to effectively target and eliminate oral squamous cell carcinoma (OSCC) cells [114]. By incorporating cell membranes (CM) from CAL-27 cells, they further enhanced the tumor-targeting ability and biosafety of the nanoparticles, demonstrating promising therapeutic efficacy in vitro. While the strategy provides an innovative approach for targeting OSCC with enhanced tumor specificity and reduced side effects, its real-world application might be limited by challenges in large-scale synthesis and potential variations in immune responses across different patient populations.

In conclusion, the integration of autophagy-targeting nanomedicines with other therapeutic modalities offers substantial potential for improving the treatment of various diseases. By modulating autophagy in a controlled and targeted manner, nanomedicine can enhance the effectiveness of existing therapies, overcome drug resistance, and optimize therapeutic outcomes across a range of clinical applications. As research continues to uncover the complex role of autophagy in disease, the development of new nanotechnology-based strategies will likely play a pivotal role in advancing personalized medicine.

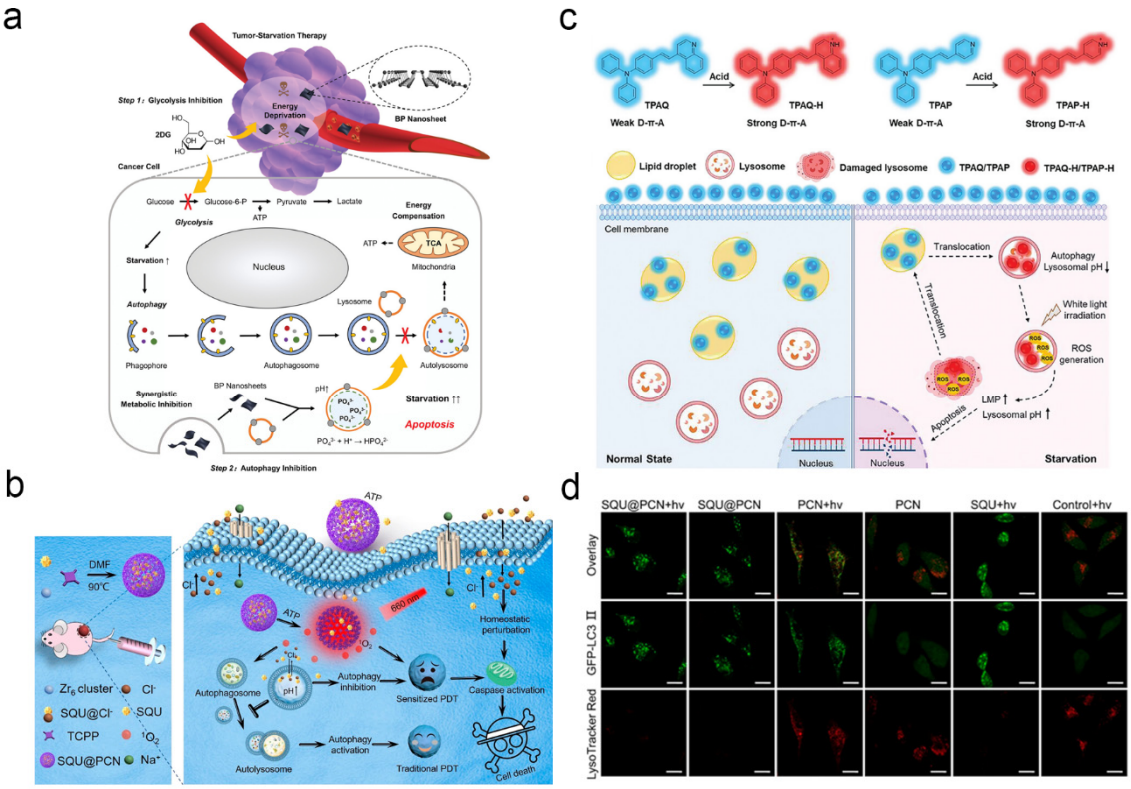

Figure 11. Combination of autophagy and other therapies. (**a**) Schematic diagram for the working mechanism of autophagy inhibition-augmented tumor-starvation therapy [112]. Copyright 2020, Wiley. (**b**) The schematic diagram for the chemical structures of TPAQ and TPAP under different conditions and the working mechanism of TPAQ and TPAP on A549 cells under varied states [113]. Copyright 2023, Wiley. (**c**) Schematic diagram for the preparation of SQU@PCN and the Cancer Cell Death Process by Homeostatic Perturbation Therapy and Sensitized Photodynamic Therapy; (**d**) Fluorescence images of autolysosome formation with GFP-LC3 HeLa cells after different treatment [115]. Copyright 2019, American Chemical Society.

4.7. Combination of Multiple Therapeutics with Nanomedicine Targeting Autophagy

The combination of multiple therapeutics with nanomedicine targeting autophagy offers a sophisticated approach to treat a wide range of diseases by exploiting synergistic effects. By integrating nanomedicine with multiple therapeutic strategies, researchers aim to harness the full potential of autophagy modulation for improved treatment efficacy and reduced side effects.

Wan et al. developed an ATP-regulated ion transport nanosystem, SQU@PCN, combining a porphyrin porous coordination network (PCN) and squaramide (SQU) for tumor treatment via homeostasis perturbation therapy (HPT) and sensitized PDT (Figure 11c) [115]. The system selectively accumulates in tumor sites, where

ATP-triggered coordination with the PCN metal ligand induces the release of SQU, which disrupts intracellular ion balance and induces apoptosis. Additionally, SQU-mediated ion transport alkalinizes lysosomes, inhibiting autophagy and enhancing the efficacy of PDT by preventing autophagy's protective effect (Figure 11d). providing a good example of multi-mode tumor therapy. The SQU@PCN system exemplifies a sophisticated multi-modal approach, effectively combining HPT and sensitized PDT to enhance therapeutic outcomes and overcome the limitations of traditional treatments, offering a promising strategy for tumor eradication and metastasis prevention. As an intracellular protective mechanism, autophagy helps cancer cells survive under harsh conditions, thus impairing the therapeutic effects of traditional PTT and chemodynamic therapy (CDT). Wei et al. developed a nanoplatform for autophagy blockage enhanced PTT and CDT synergetic therapy by loading autophagy inhibitor HCQ into hollow copper sulfide (HCuS). through Fenton-like reaction, HCuS could generate toxic ROS. Meanwhile, PTT-mediated temperature elevation in the tumor region boosted the Fenton-like reaction and ROS production, enhancing the therapeutic effect of CDT [68]. Moreover, the existence of HCQ greatly cloged up the fusion of autophagosomes and lysosomes, hampering the self-protection mechanism of cancer cells, and intensifying the combined treatment of PTT and CDT (Figure 12). Both in vitro and in vivo results evidenced that the combination of photothermal-enhanced chemodynamic therapy with inhibition of autophagy provided a paradigm for developing multifunctional therapeutic nanoagents.

In conclusion, the combination of multiple therapeutics with nanomedicine targeting autophagy represents a powerful and versatile strategy for improving therapeutic outcomes across a range of diseases. The ability of nanomedicine to co-deliver diverse agents, including small molecules, gene therapies, and physical therapy modalities, allows for the precise modulation of autophagy while simultaneously targeting other critical disease pathways. As research advances, these combination approaches will likely become central to the development of next-generation treatments, offering new opportunities for precision medicine and more effective, personalized care.

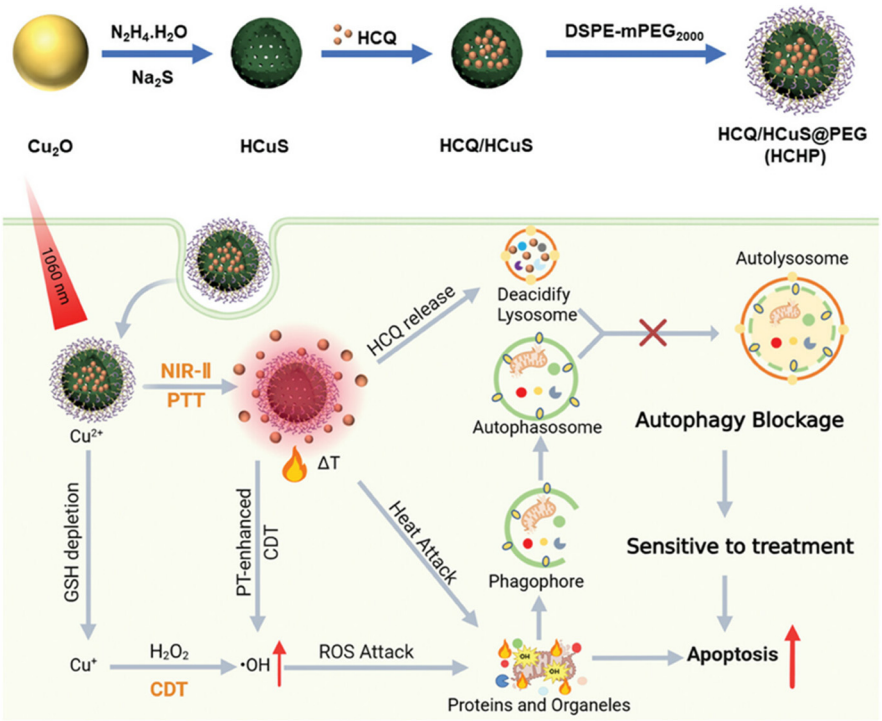

Figure 12. Combination of autophagy and multiple therapeutics. (**a**) The synthesis of HCQ/HCuS@PEG (HCHP) NPs; (**b**) Schematic illustration of HCHP NPs for augmented PTT-CDT therapy by inhibition of autophagy [68]. Copyright 2024, Wiley.

5. Challenges and Future Directions

The regulation of autophagy through nanomedicine offers tremendous potential for enhancing cancer therapy, but several challenges must be addressed to fully harness its benefits. These challenges are not only technical in nature but also relate to the complex biological environment of tumors and the limitations of current nanotechnology platforms. The following sections outline the key challenges and future directions in regulating autophagy through nanomedicine to improve cancer therapy.

5.1. Complexity of Autophagy Pathways

Autophagy is a multifaceted cellular process, intricately regulated by numerous signaling pathways such as mTOR, AMPK, and ULK1. Its dual role in cancer-both as a survival mechanism and a potential therapeutic target-further complicates efforts to manipulate autophagy for cancer treatment. In some cancers, autophagy protects tumor cells from apoptosis under stressful conditions, while in others, it can facilitate tumor suppression. This duality poses a significant challenge in designing effective therapies that either induce or inhibit autophagy at the right time and location. Future research must deepen our understanding of how these pathways interact in different cancer types and stages. Such knowledge could lead to the development of more precise nanomedicines that are tailored to target specific autophagic processes, potentially enhancing the therapeutic benefit while minimizing adverse effects on normal tissues.

5.2. Selective Targeting of Autophagy Mechanisms

While nanomedicine offers promising strategies for targeting cancer cells, one of the biggest challenges lies in the selective modulation of autophagy-related proteins and pathways. Tumors are heterogeneous, and cancer cells can adopt multiple mechanisms to evade therapeutic effects, including the dysregulation of autophagic pathways. Designing nanoparticles that can accurately deliver therapeutic agents to specific autophagy-related proteins or intracellular compartments remains a critical hurdle. The future of nanomedicine will likely involve the development of "smart" nanoparticles that can respond to specific tumor microenvironment signals, such as low pH or hypoxia, to selectively target autophagy regulation in cancer cells. In addition, efforts should focus on enhancing the specificity of nanocarriers to ensure they bind to tumor cells while avoiding normal tissues, thereby reducing systemic toxicity and enhancing the therapeutic index.

5.3. Overcoming Autophagy-Induced Resistance

A significant obstacle in cancer therapy is the development of resistance mechanisms, many of which are driven by autophagic activity. While autophagy can initially suppress tumor growth, its upregulation can enable cancer cells to survive conventional therapies like chemotherapy and radiation. In fact, excessive autophagy may lead to therapeutic resistance, making it more difficult to achieve long-term remission. To address this challenge, combining autophagy modulation with other treatment strategies is essential. This could include combining nanoparticles that target autophagy with chemotherapy, photodynamic therapy (PDT), photothermal therapy (PTT), or immunotherapy. However, this combinatorial approach must be carefully optimized to avoid unintended consequences, such as excessive autophagy that could promote tumor cell survival. Future studies should focus on the development of combinatorial therapies that precisely modulate autophagic flux and synergize with other therapeutic modalities. This could include the use of nanoparticles with controlled-release mechanisms or stimuli-responsive properties that can tailor the release of drugs or autophagy-modulating agents based on the tumor's needs.

5.4. Personalized Cancer Therapies

Cancer is highly heterogeneous, and the effectiveness of autophagy modulation can vary significantly between patients due to differences in tumor type, genetic background, and the tumor's specific autophagic profile. As a result, a "one-size-fits-all" approach to nanomedicine will likely not be sufficient for achieving optimal therapeutic outcomes. To tackle this issue, the future of cancer therapy will likely involve personalized nanomedicines tailored to the specific molecular and autophagic characteristics of individual patients' tumors. This could be achieved through advanced diagnostic tools that profile tumors' autophagic activity, allowing for the identification of patients who are most likely to benefit from autophagy-modulating therapies. Personalized nanomedicine could also include the use of nanoparticles that respond to specific biomarkers or tumor microenvironmental cues, ensuring that autophagy is modulated only in cancer cells. Moreover, the heterogeneity of tumors, both intertumoral and intratumoral, presents a unique challenge when designing personalized therapies. Tumors of the same tissue origin can exhibit considerable variation in their genetic makeup, metabolic states, and response to treatment, making it difficult to develop a one-size-fits-all approach. Therefore, tailoring therapies based on specific tumor profiles, including genetic mutations, expression of surface markers, and metabolic pathways, will be crucial to improving clinical outcomes. Nanomedicines that can respond to these personalized characteristics offer the potential for more effective and less toxic treatments.

An important consideration in this context is the regulation of autophagy, a process that plays a dual role in cancer progression. Autophagy can act as a tumor suppressor in the early stages of tumorigenesis by maintaining

cellular homeostasis, but in established tumors, it can also support cancer cell survival and resistance to therapy. The induction of autophagy and the tumor's response to autophagy modulation can vary significantly depending on the tumor type and its microenvironment. For example, some tumors may rely on autophagy to survive under nutrient-deprived conditions or in response to chemotherapy, while others may exhibit reduced autophagic activity due to genetic mutations or the presence of immunosuppressive cells within the TME.

As a result, it is critical to consider the varied nature of autophagy in different tumor types when designing therapeutic strategies. In some cases, enhancing autophagy may be beneficial to sensitize tumor cells to treatment, while in other cases, inhibiting autophagy may prevent tumor cells from evading cell death. Future research should focus on identifying biomarkers that can predict the autophagic status of individual tumors, allowing for more precise modulation of autophagy and improving the therapeutic outcomes of nanomedicines.

In conclusion, the challenges of addressing tumor heterogeneity and the complexities of the TME necessitate the development of highly customizable and adaptable nanomedicines. By incorporating strategies that target the specific needs of individual tumors and considering the nuanced role of autophagy, we can move closer to realizing personalized and effective cancer therapies.

In considering the future development of autophagy-based therapies, it is crucial to examine their progress in clinical trials and translation. Several clinical trials are currently underway to evaluate the efficacy of autophagy modulation in cancer. For example, clinical studies investigating autophagy inhibitors or activators in cancer treatment, such as the use of chloroquine derivatives, have shown promising preclinical results and are now entering phase I and II trials (ClinicalTrials.gov identifier: NCT02876657, NCT03377735). Furthermore, the translation of autophagy-based therapies faces challenges such as precise drug delivery, off-target effects, and the need for personalized treatment strategies. Although significant progress has been made, further clinical data are necessary to fully understand the long-term safety, efficacy, and optimal dosing regimens for autophagy-based therapies.

5.5. Safety and Toxicity Concerns

Although nanomedicines hold great promise in cancer therapy, their clinical translation remains hampered by concerns about their safety and toxicity. The small size of nanoparticles allows them to enter cells more easily, but it also raises concerns about unintended interactions with healthy tissues and potential accumulation in organs such as the liver or spleen. Furthermore, the modulation of autophagy may have off-target effects that impair normal cellular functions, especially in tissues where autophagy is critical for maintaining homeostasis. To address these concerns, extensive preclinical and clinical testing is necessary to evaluate the safety profile of nanoparticles targeting autophagy. This includes assessing long-term toxicity, bioaccumulation, and potential immune system activation. Future work should focus on designing nanoparticles that are biocompatible, biodegradable, and capable of being safely cleared from the body after completing their therapeutic role.

5.6. Regulatory and Manufacturing Challenges

The regulatory approval process for nanomedicines is intricate and time-consuming, requiring comprehensive data on the safety, efficacy, and quality control of nanoparticles. The production of nanomedicines also faces challenges related to scalability and reproducibility, as small changes in the synthesis process can lead to variations in nanoparticle properties. To facilitate the clinical translation of autophagy-modulating nanomedicines, standardized methods for the synthesis, characterization, and testing of nanoparticles are essential. Additionally, regulatory agencies must develop clear guidelines to streamline the approval process for nanomedicines, ensuring that these promising therapies can reach the clinic in a timely manner.

The future of nanomedicine in regulating autophagy for cancer therapy is incredibly promising, yet numerous challenges must be addressed to maximize its potential. Continued advancements in our understanding of autophagy pathways, the development of selective and safe nanoparticles, and the integration of personalized and combinatorial treatment strategies will be key to overcoming current limitations. As these challenges are met, the role of nanomedicine in cancer therapy will likely expand, offering new avenues for overcoming treatment resistance and improving patient therapeutic effect.

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The authors declare no conflict of interest.

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