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Review

Nanomedicine in cancer diagnosis and therapeutics

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Abstract: Cancer has emerged as a significant global health challenge, with both its occurrence and death toll rising annually. Studies have shown that early, precise diagnosis and targeted cancer therapy can effectively reduce the mortality rate of malignant tumors. As an emerging field, nanomedicine seeks to unify cancer diagnosis and therapy within a single platform, enabling early detection, precise drug targeting, and minimized harm to healthy tissues. In recent years, nanotechnology has emerged as a powerful tool in oncological applications, revolutionizing both cancer detection and therapeutic interventions, and clinical treatment strategies have also shown a significant trend of shifting from single therapy to combination therapy. Research demonstrates that multimodal combination therapy not only combines the benefits of individual treatment modalities but also generates synergistic effects, yielding significantly superior clinical outcomes compared to monotherapies or simple treatment combinations. Consequently, the integration of nanotechnology with multimodal synergistic approaches has emerged as an innovative paradigm in oncological therapeutics. This article provides a systematic review of the unique characteristics and functional mechanisms of various nanomaterials, while examining their translational applications in oncological diagnostics and therapeutics through nanomedicine approaches.

Keywords: cancer; nanomedicine; early diagnosis; targeted delivery; nanomaterials; multimodal synergistic therapy

1. Introduction

Cancer, medically termed malignant neoplasia, represents a heterogeneous class of pathological conditions characterized by uncontrolled cellular proliferation that can disrupt physiological functions in any anatomical system [1]. Cancer seriously threatens people's lives and health. It has emerged as a critical public health challenge both in China and globally, with incidence and mortality rates remaining high for several years [2]. The occurrence and development of cancer are influenced by multiple factors, starting with cells within the body losing their normal regulatory mechanisms [3]. Every organ in the human body is composed of cells, which, under normal physiological conditions, undergo orderly cellular processes, namely proliferation, differentiation, and apoptosis, carrying out normal metabolism to maintain human health and life activities [4]. When some physical, chemical, or biological carcinogens appear and act on the human body, they influence cells to undergo mutations, thereby generating abnormal cells that would not occur under normal circumstances. These are called tumor or cancer cells [5]. The malignant proliferation of cancer cells is uncontrollable, and when it develops to a later stage, cancer metastasis will occur. This further increases the difficulty of cancer treatment [6]. However, extensive clinical research demonstrates that early cancer detection coupled with prompt therapeutic intervention can substantially decrease disease-specific mortality rates.

According to the literature, existing tumor diagnosis techniques are mainly divided into immunological examination [7] and clinical imaging diagnosis [8]. Immunological examination is mainly a method of detection that utilizes the specific binding ability of antibodies and antigens. Because it can use chemiluminescent substances, enzymes, and isotopes to amplify and display signals of the tested object, it is often used to detect trace substances such as hormones or proteins. On the other hand, the methods of clinical imaging diagnosis are relatively diverse and mainly include digital radiography (DR) [9], nuclear magnetic resonance imaging (NMRI) [10], computed tomography (CT) [11], and ultrasound examination [12]. However, X-rays are radioactive; during examination, a large number of normal tissues and organs are exposed to X-ray radiation, which greatly increases the risk of deformity and cancer. Furthermore, examination results obtained from clinical imaging diagnosis often indicate that the disease has reached the middle or advanced stage. At this point, whether control or treatment is taken for the disease, the effect is minimal, resulting in an extremely high mortality rate [4]. Therefore, definitive diagnosis in the nascent phases of oncogenesis forms the cornerstone of successful treatment strategies.

The current traditional tumor treatment methods include chemotherapy (broad-spectrum killing of tumor cells through cytotoxic effects) [13], radiotherapy (inducing DNA damage through ionizing radiation) [14], immunotherapy (stimulating the host immune system to achieve precise killing) [15], surgical treatment (a core approach for local control of solid tumors) [16], and hormone therapy (such as aromatase inhibitors that block estrogen precursor enzymes that produce estrogen to exert anti-tumor effects [17]). Among them, surgical treatment has been applied in the field of oncology for the longest time and can be used in clinical practice for non-metastatic solid tumors [18]. However, surgical treatment is costly, and completely removing tumor cells is challenging. Residual tumor lesions or circulating tumor cells (CTCS) [19] may cause metastatic recurrence through the blood and lymphatic systems [20]. Radiotherapy is a local therapy for treating tumors through radiation. Although it has only a history of several decades, it has developed rapidly. Its therapeutic effect mainly depends on the radiosensitivity of tumor tissues, and the performance of different tumor cells after irradiation varies greatly, resulting in unstable treatment outcomes. On the other hand, as a primary therapeutic

modality for malignant tumors, drug chemotherapy has been shown to significantly prolong survival duration and improve clinical outcomes. Common chemotherapy drugs include doxorubicin [21], paclitaxel [22], camptothecin [23], and cisplatin [24], among others. However, due to the non-targeting nature of chemotherapy drugs, they can indiscriminately attack normal cells and tumor cells, thereby causing serious toxic side effects. Therefore, exploring more efficient and less toxic treatment methods has become an important direction in current cancer research.

Recent advances in nanotechnology have facilitated its extensive integration into oncological applications, particularly revolutionizing site-specific drug delivery for oncology [25]. The encapsulation of chemotherapeutic agents within engineered nanoparticles enables tumor-specific drug delivery, simultaneously minimizing systemic toxicity while achieving enhanced drug accumulation at malignant sites for improved therapeutic outcomes. Nevertheless, the complexity, diversity, and heterogeneity inherent to the tumor microenvironment frequently hinder single therapies from attaining the intended therapeutic efficacy. Therefore, multi-mode collaborative therapy is gradually becoming a new trend in cancer treatment [26,27]. This review examines the physicochemical properties and functional characteristics of prevalent nanomaterials while evaluating current applications of nanomedicine in oncological diagnostics and therapeutics (Figure 1).

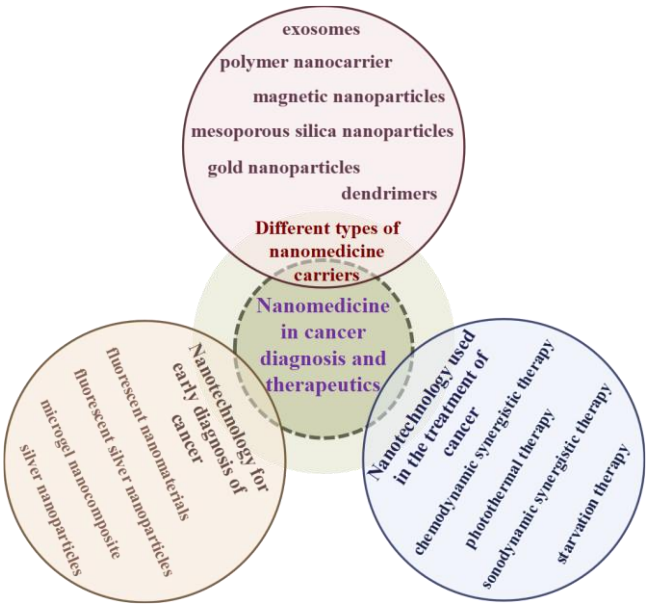

Figure 1. Framework diagram of nanomedicine application in cancer diagnosis and treatment.

2. Different types of nanomedicine carriers

Numerous organic and inorganic nanocarrier systems have been extensively engineered to enable precise cancer detection and targeted therapeutic delivery. Multifunctional nanomaterials not only significantly enhance therapeutic effects but also offer distinct benefits in addressing the resistance of aggressive tumors to single-modality therapies [28,29]. Nanocarrier materials leverage their pronounced enhanced permeability and retention (EPR) effect [30] to facilitate targeted accumulation within tumor tissues and cells, substantially improving localized drug enrichment. Moreover, these materials enable precise drug dosing and site-specific delivery to designated tissues or cellular

locations, thereby enhancing therapeutic outcomes while minimizing adverse effects [31,32].Based on the above discussion, the types and characteristics of multifunctional nanomaterials vary. When choosing them, one needs to comprehensively consider factors such as their physical and chemical properties, biocompatibility, drug loading capacity, and functional modifiability. To facilitate a clear comparison, Table 1 lists several common types of multifunctional nanomaterials and their main characteristics and applications in cancer treatment. Through precise engineering design, these materials can significantly enhance the tumor-targeted accumulation mediated by the EPR effect and achieve controlled drug release and the synergy of multiple treatment modes, thereby providing key tools for overcoming tumor resistance and improving treatment efficacy.

Table 1. Comparison of various multifunctional nanomaterials used in cancer treatment.

Types of nanomaterials	Characteristics	Types of disease	Mechanism of efficacy	Ref
Magnetic nanoparticles	High electrical conductivity, large specific surface area, and excellent dispersibility.	Pancreatic cancer	Enhance the binding force of nanomedicines to cancer cells and effectively inhibit the progression of pancreatic cancer.	[37]
Gold nanoparticles	Surface plasmon resonance, low toxicity, and biodegradable.	Cervical cancer	It can locally enhance the radiation dose, exert a stronger killing effect on cancer cells, play a "sensitization" role, and improve the therapeutic effect.	[41]
Mesoporous silica nanoparticles	High specific surface area, large pore volume, and high solubility.	Colon cancer	It can enhance hydrophobicity and bioavailability and precisely adjust the pore size to release the loaded drug molecules effectively.	[48]
Dendrimers	A highly branched, three-dimensional, symmetrical, and precisely structured architecture.	Triple-negative breast cancer	It enhances the tumor-targeting efficiency and anti-proliferative effect, providing higher tumor suppression.	[54]
Polymer nanocarrier	High drug loading capacity, diverse drug loading methods, and controllable drug release kinetics.	Liver cancer and prostate cancer	Polymer degradation and stimulus-responsive bond breakage achieve long-lasting, sustained release, thereby enhancing therapeutic efficacy and reducing toxicity.	[61]
Exosomes	Low immunogenicity, highly efficient active targeting, and excellent biocompatibility.	Parkinson's disease	It significantly reduced the level of oxidative stress, increased the survival rate of neurons, prolonged the half-life of the drug at the same time, maintained the biological activity of the drug, and thereby improved the therapeutic effect.	[68]

2.1. Magnetic nanoparticles

Magnetic nanoparticles (MNPs) have attracted extensive attention from scientists from all fields due to their superior chemical and physical properties [33]. MNPs exhibit notable performance benefits and cost-effectiveness; they not only exhibit high electrical conductivity, large specific surface area, excellent dispersibility, and low production cost but also high magnetic susceptibility and superparamagnetism, meeting the requirements of various applications. Therefore, in the past decade, MNPs have been successfully utilized in the development of numerous miRNA sensing platforms [34]. Among them, Fe_3O_4 nanoparticles have become the preferred magnetic nanomaterials for preparing biosensors due to their easy production, good biocompatibility, and superparamagnetism. They are widely used in numerous fields such as protein solidification, biomedicine, catalysis, environmental protection, magnetofluidics, and data storage [35]. Pang et al. [36] reported a biosensor based on magnetic nanomaterials. The DNA probe labeled with the Raman marker Cy3 (Cy3-DNA) was immobilized onto the Fe_3O_4@Ag surface, causing the rough Fe_3O_4@Ag surface to induce a distinct SERS signal. Upon introduction of the target miRNA, the immobilized complementary DNA probe facilitates specific hybridization, leading to the generation of DNA/RNA heteroduplex structures. DSN enzyme selectively cleaves the DNA strand within the DNA/RNA heteroduplex, triggering release of Cy3-labeled DNA fragments from the Fe_3O_4@Ag nanocomposite surface, thereby resulting in a decrease in Raman signal intensity. At this time, the target miRNA released from the double-stranded body can continue to bind to the next Cy3-DNA probe, thereby achieving cyclic splicing and signal amplification. Following signal amplification, magnetic separation was performed to concentrate the sample. The Cy3-labeled DNA fragments are subsequently removed through washing, and the SERS signal is measured. The magnetic enrichment of Fe_3O_4@Ag nanocomposites under Raman laser excitation significantly enhanced detection sensitivity, allowing the identification of early-stage cancer biomarkers and enabling precise diagnostic capabilities. Gao and colleagues investigated a two-stage sequential delivery approach employing gemcitabine (GEM) for targeted therapy in pancreatic cancer [37]. This two-stage strategy begins with the administration of metformin (MET) to degrade the dense stromal matrix. The underlying mechanism involves MET-induced activation of the AMPK pathway in PANC-1 cells, leading to downregulation of the profibrotic cytokine TGF-β and subsequent inhibition of pancreatic stellate cell (PSC) activity. The suppression of PSC-mediated filamentous proliferation enhanced the delivery of functionalized magnetic nanoparticles and substantially improved the binding force of nanomedicines to cancer cells (Figure 2). Results demonstrate that this approach effectively suppresses the progression of pancreatic cancer.

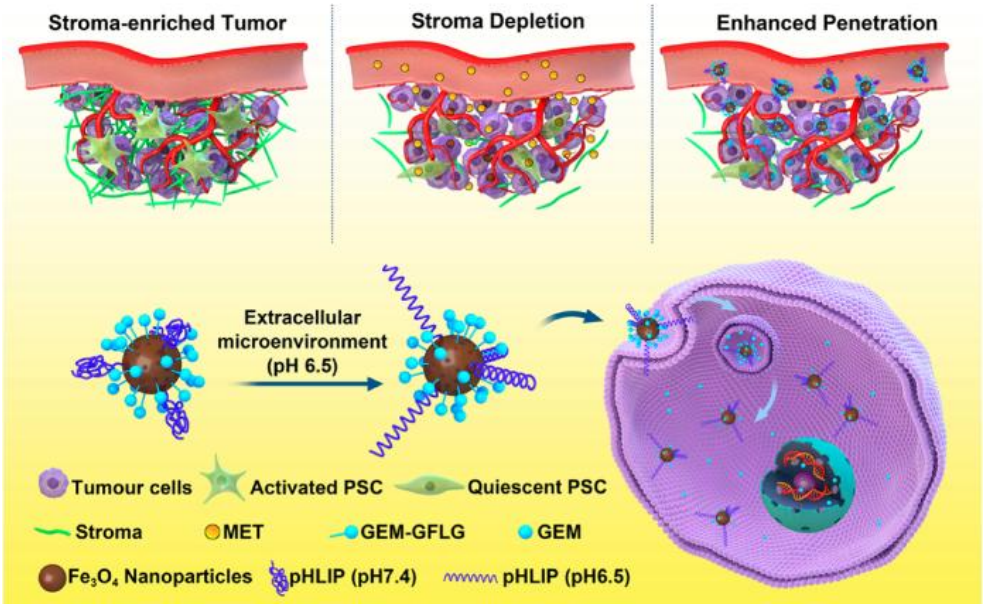

Figure 2. Experimental schematic diagram of MET-induced matrix depletion [37].

2.2. Gold nanoparticles

Nanostructured gold materials, including gold nanoparticles (AuNPs) and atomic gold clusters, have become pivotal in biosensing development owing to their exceptional surface plasmon resonance (SPR) effects and remarkable molar extinction coefficients, enabling ultra-sensitive detection platforms. Colorimetric analysis based on AuNPs, without the need for advanced instruments, provides an efficient, economical, and convenient approach for miRNA detection [38]. AuNPs play a significant role in the preparation of sensing substrates, capturing probes by binding the target through Au-S bonds. When the target miRNA is present, this target can trigger the aggregation of AuNPs, thereby causing the AuNPs solution to gradually change from red to purple. Persano et al. [39] developed an innovative miRNA detection platform combining 1) isothermal enzymatic amplification for target multiplication, 2) AuNP-based colorimetric readout via sequence-specific hybridization, and 3) magnetic particle-assisted separation, achieving high sensitivity in complex biological matrices. The Li research group [40] has developed a highly sensitive miRNA detection method assisted by AuNPs amplification through isothermal exponential amplification reaction (EXPAR). Zhong et al. [41] developed a novel target-activated, light-driven 3D DNA walker based on a gold nanoparticle framework. This system employed pyrene-containing DNase analogues to achieve sensitive miRNA detection. The target miRNA activates the 3D DNA walker, triggering the release of its walking arm. Under ultraviolet (hv) irradiation, the pyrene-modified DNAzyme on the walking arm repeatedly cleaves disulfide bonds in the substrate chain, leading to the recovery of the fluorescence signal and enabling sensitive miRNA detection (Figure 3).

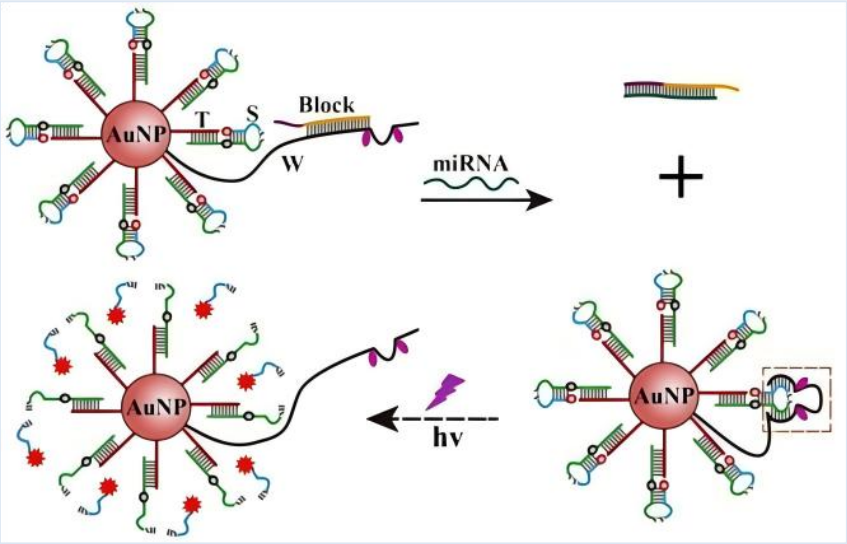

Figure 3. Schematic diagram of miRNA-activated light-driven 3D DNA Walker nanomachine [41].

2.3. Mesoporous silica nanoparticles

Mesoporous silica nanoparticles (MSNs) have garnered significant interest for drug delivery and biomedical applications owing to their high specific surface area and large pore volume [42]. The versatile functionality of MSN surface chemistry, both within its internal pores and on its external surface, has driven the development of novel multifunctional MSNs. Additionally, due to its unique mesoporous scaffold, MSN can easily load chemotherapy drugs and replace organic solvents, addressing the low solubility of chemical drugs in aqueous solutions [43]. Zhang et al. [44] found that mesoporous silica could enhance the dissolution and bioavailability of hydrophobic telmisartan (TEL) after oral administration (Figure 4). The results show that, compared with the coarse powder of TEL, the dissolution rate of MSNs loaded with TEL is significantly increased. Compared with the commercially available product Mecasin, the relative bioavailability of MSNs loaded with TEL was 154.4% ± 28.4%, confirming that the MSN platform can effectively load drugs and improve their bioavailability. Compared with other inorganic nanoparticles, MSN has a unique nanoporous structure, and its pore size can be precisely adjusted by regulating parameters such as template agent, surfactant concentration, pH value, and solvent during the synthesis process [45]. This controllable pore size characteristic enables MSN to achieve controllable degradation, thereby effectively releasing the loaded drug molecules [46]. In addition, as a promising stimulus-responsive drug delivery system, the surface of MSN can be modified with various functional groups. These chemical modifications can respond to specific stimulus signals (such as pH, temperature, or light), thereby achieving precise controlled release of drugs [47]. Li et al. [48] constructed intelligent pH/H_2O_2 sensitive chiral MSNRs. Specifically, phenobarbital nanol ester (PBAP) was grafted onto CMSRS-NH_2 to synthesize H_2O_2-sensitive chiral MSNRS (PCMSR). Doxorubicin (DOX) was then loaded into the nanopores of the PCMSRs, yielding drug-loaded nanoparticles (DOX-PCMSRs). In this system, DOX serves a dual function: it is a source of H_2O_2 and acts to kill tumor cells. After full drug loading, the nanoparticles were coated with a CD-modified hyaluronic acid (HA-CD) conjugate to provide active tumor targeting and enhance biocompatibility. This coating minimized premature drug leakage in healthy tissues and promoted specific accumulation within tumor sites.

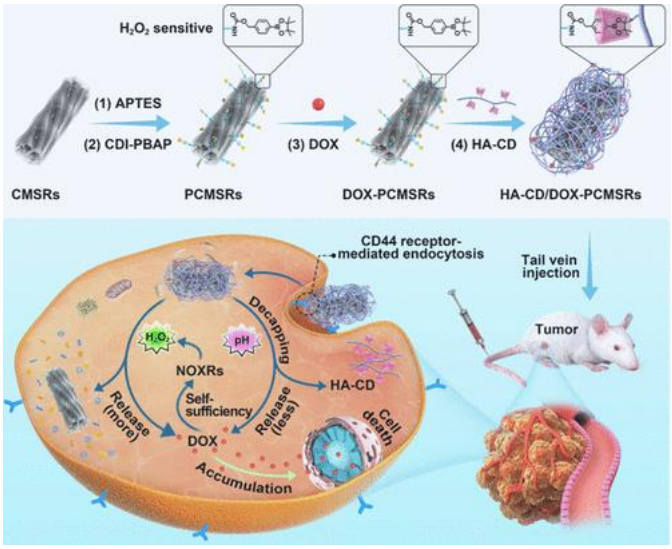

Figure 4. Schematic diagram of HA-CD/DOX-PCMSRs nanoparticle synthesis and its application in cells [48].

2.4. Dendrimers

Dendrimers are highly branched three-dimensional polymers constructed through precise synthesis. Their unique spherical topological conformation and monodisperse properties (size range 1–100 nm) [49] make them an important research object for nanodrug carriers. This molecule can be precisely regulated in terms of the number and spatial distribution of surface functional groups through the gradual assembly of natural or synthetic monomers (such as nucleotides, amino acids, or sugars), forming a nanoscale architecture with uniform molecular weight and regular structure [50]. Different from the random branching characteristics of traditional polymers, dendritic macromolecules adopt the stepwise convergent synthesis method. Through iterative reactions, the branching units are expanded layer by layer, thereby achieving programmable design of molecular generations, internal cavity volume, and surface functional groups. Research shows that its advantages, such as multivalent binding ability, monodisperse characteristics, controllable diameter of 1.5–14.5 nm, and surface modifiability [51], provide an innovative solution for breaking through the technical bottlenecks of traditional drug delivery systems.

Since their introduction in the early 1990s, dendrimer-based nanocarriers have faced challenges in achieving spatially and temporally precise drug release [52]. To address this issue, Rompicharla et al. [53] conjugated the poorly water-soluble anticancer drug paclitaxel to the surface of G4 polyamidoamine (PAMAM) dendrimers, followed by pegylation and subsequent biotin labeling. Compared with free drugs, the G4-paclitaxel-PEG-biotin conjugate exhibited significantly enhanced penetration into both cellular monolayers and tumor spheroids, resulting in improved cytotoxicity and greater tumor-inhibitory efficacy. Similarly, Liu et al. [54] identified a high-affinity peptide ligand—epidermal growth factor receptor binding peptide 1 (EBP-1)—via screening and conjugated it to a PAMAM dendrimer for the targeted delivery of encapsulated doxorubicin (Figure 5). This bifunctional nanocarrier demonstrates enhanced tumor-targeting efficiency and potent antiproliferative activity, leading to significantly improved tumor suppression in triple-negative breast cancer (TNBC).

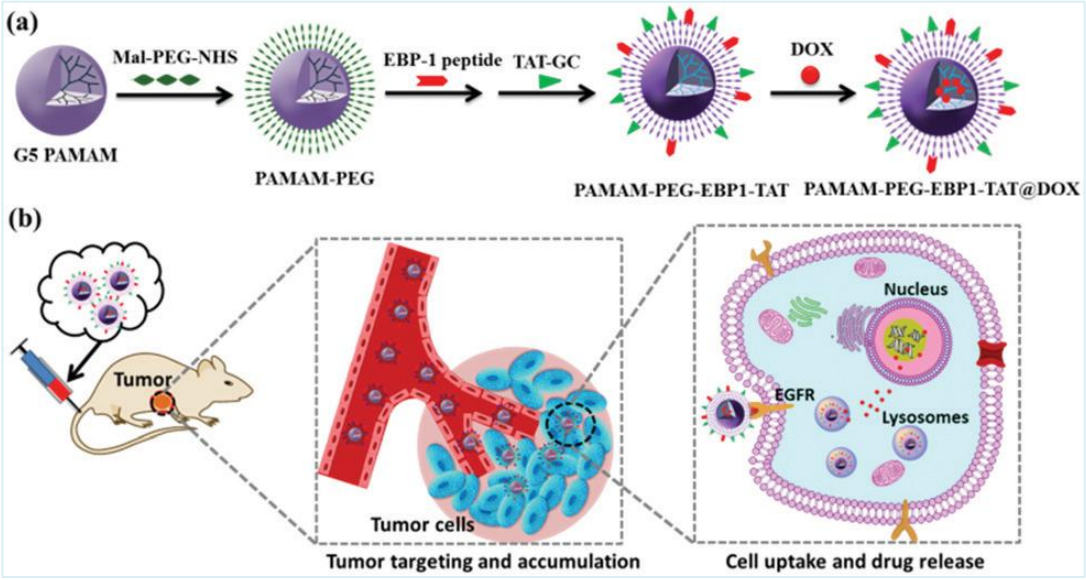

Figure 5. Schematic diagram of the synthesis of PAMAM-PEG-EBP1-TATA@DOX dendrimer polymer and its anti-triple-negative breast cancer treatment effect [54].

2.5. *Polymer nanocarrier*

PNCs are a type of solid colloid delivery system constructed based on biodegradable polymers, with a particle size range typically ranging from 10 to 1000 nm. They mainly include two structural categories: matrix type (nanospheres) and reservoir type (nanocapsules) [55]. In the nanosphere system, the drug is distributed in the continuous polymer phase through physical embedding or surface adsorption. Nanocapsules, on the other hand, achieve drug loading by encapsulating liquid nuclei (oil phase/water phase), and their core-shell structure is precisely regulated by polymer membranes. The preparation process of PNCs covers two major technical routes: 1) solvent-driven self-assembly methods (such as nano-precipitation, dialysis, and supercritical fluid technology) and 2) in situ polymerization techniques (including emulsion polymerization, interfacial polymerization, and controlled radical polymerization) [56].

In 1969, Speiser and his team first proposed the concept of polymer nanoparticles for drug delivery. Synthetic polymers—including polyglycolic acid (PGA), polylactic acid (PLA), polylactic acid-glycolic acid copolymer (PLGA), polycaprolactone (PCL), and polymethyl methacrylate (PMMA)—along with natural polymers, such as chitosan, alginate, gelatin, collagen, dextran, heparin, and albumin, are widely utilized in biomedical applications. PLGA-based nanoparticles have become a preferred material for polymeric nanocarriers owing to their excellent biocompatibility and tunable drug release profiles. By modulating the lactide:glycolide (L:G) ratio and molecular weight of PLGA, key properties such as hydrophobicity, biodegradation rate, and drug release kinetics can be precisely controlled [57]. Gumus Derelioglu et al. [58] studied the influence of the L:G ratio varying from 70:30 to 90:10 on the release of mitomycin C and found that with the increase of glycolic acid content, the release amount and release rate of the drug significantly increased.

Functional modification can endow PNCs with environmental response characteristics, enabling programmable drug release at the lesion site. Typical strategies include 1) ligand-targeting modifications (such as galactosamine-mediated hepatocyte targeting), which can increase the uptake

rate of tumor cells by 3–5 times, and 2) integration of stimulus-response units (such as pH-sensitive bonds and ROS-responsive groups) [59]. The polydopamine-galactosamine nanosystem constructed by Zhu et al. [60] increased drug accumulation in liver cancer cells by 4.2 times and raised the tumor suppression rate to 78% through the endocytosis pathway mediated by the asialoglycoprotein receptor. Tangthong et al. [61] constructed functionalized polymer nanoparticles for prostate cancer theranostics by incorporating gold nanoparticles, water-soluble chitosan, and Lys-Lys 3 peptides. This nanosystem specifically targets the overexpressed gastrin-releasing peptide receptor in prostate cancer cells and demonstrates synergistic targeting and cytotoxic effects in both PC-3 and LNCaP cell lines. This study offers a novel template-based synthesis strategy for developing functionalized polymer nanocarriers, demonstrating significant potential for application in cancer theranostics.

2.6. *Exosomes*

Exosomes are nanoscale, cell-secreted extracellular vesicles enclosed by a lipid bilayer, typically measuring 40–100 nm in diameter and exhibiting a buoyant density ranging from 1.13 to 1.19 $g \cdot mL^{-1}$ [62,63]. In 1981, Trams et al. [64] first proposed the concept of "exosomes", discovering that they possess 5'-nucleotidase activity and are widely present in the secretions of various cells. Exosomes are secreted by a wide range of normal cell types, including endothelial cells, mesenchymal stem cells (MSCs), and various immune cells. As pluripotent stem cells, MSCs exhibit not only self-renewal capacity and multi-lineage differentiation potential but also the ability to adapt to the tumor microenvironment and secrete substantial quantities of exosomes [65,66]. Exosomes, with their small size, excellent biocompatibility, and low immunogenicity, can effectively evade the phagocytic action of mononuclear macrophages and penetrate the vascular wall and extracellular matrix. Compared to synthetic nano-drug delivery systems such as liposomes, exosomes are endogenous nanovesicles with inherently superior biocompatibility and reduced immunogenicity. Their surface is rich in diverse proteins that facilitate receptor-mediated endocytosis with target cells. This optimizes drug internalization, enhances intracellular delivery, and ensures stable transport in the bloodstream, significantly improving overall delivery efficiency [67]. In addition, exosomes exhibit intrinsic targeting properties and a remarkable capacity to cross biological barriers, making them ideal drug delivery carriers suitable for the delivery of gene drugs, traditional Chinese medicine, and Western medicine. For instance, Haney et al. [68] found that catalase encapsulated in exosomes could significantly reduce the level of oxidative stress in Parkinson's disease models and increase the survival rate of neurons. Meanwhile, loading catalase onto exosomes not only prolongs the half-life of the drug and maintains its biological activity but also resolves its issues of easy inactivation and rapid degradation, thereby significantly enhancing therapeutic effects.

3. Nanotechnology for early diagnosis of cancer

Cancer does not occur overnight; instead, its formation requires a series of evolutions. Its occurrence and development mainly go through three stages: the ultra-early stage, the early stage, and the middle and late stage, which respectively correspond to molecular carcinogenesis, cellular carcinogenesis, and tissue carcinogenesis [69,70]. Studies have shown that the best time to prevent cancer is during the period of molecular carcinogenesis. The earlier cancer lesions are detected, the earlier intervention can be made, the greater the probability of the cancer being treatable, and the higher

the survival rate [71]. However, early symptoms of most cancers are rather concealed and hard to detect. The absence of reliable detection methods often results in delayed diagnosis, causing patients to miss the optimal window for treatment. In the early stages of cancer, certain endogenous substances that indicate the presence and progression of tumors can serve as tumor biomarkers [72]. According to literature reports, miRNA expression profiles differ significantly between cancerous and normal cells, and serve as a key regulatory factor in tumorigenesis and cancer progression [73,74]. Consequently, miRNAs represent a highly promising category of biomarkers with considerable potential for early cancer diagnosis.

The recent advancement of nanotechnology has opened new avenues for identifying cancer in its initial phases. Because of their nanoscale dimensions, exceptional surface-area-to-volume characteristics, straightforward functionalization, and precise structural controllability, nanoparticles have been extensively exploited in the engineering of nanodevices for early cancer diagnostics. A wealth of research has validated the efficacy of these strategies for diverse applications in biosensing and bioanalysis [75]. Guo's research group [76] constructed a highly sensitive electrochemical sensor utilizing a microgel nanocomposite for miRNA-21 detection, which was effectively employed to measure serum miRNA-21 expression in breast cancer patients during pre-treatment and post-recovery phases. Shi's research group [77] engineered three fluorescent nanomaterials characterized by narrow emission bands and substantial Stokes shifts to serve as signaling probes. These probes enabled the construction of a dual-ratio fluorescent sensing platform operating under single-excitation yet generating triple-emission signals for the parallel quantification of the breast cancer biomarkers miRNA-21 and PTK7. When tested on serum samples from breast cancer patients and healthy individuals, the system exhibited consistently strong performance with clear clinical potential. Salahandish et al. [78] fabricated a label-free nanobiosensor with high sensitivity by integrating an architecture comprising silver nanoparticles, polyaniline, and nitrogen-doped functionalized graphene for detecting the breast cancer–associated biomarker miRNA-21. They applied this nanoprobe to the analysis of blood samples, and the results demonstrated high repeatability.

Silver nanoclusters (AgNCs) have emerged as a promising class of signal transducers, garnering significant research interest owing to their high biocompatibility, excellent photostability, and tunable fluorescence properties. In contrast to gold nanoparticles (AuNPs), DNA-templated AgNCs eliminate the need for covalent conjugation with external indicators. Once these AgNCs approach sequences rich in guanine, they "lit up", enhancing fluorescence hundreds of times. The Zhang group [79] employed a DNA-template synthesis approach to generate fluorescent silver nanoclusters (AgNCs), creating a novel label-free and conjugation-free molecular beacon (MB) probe for multiplexed DNA detection. First, part of the sequence of the DNA template chain is locked by the hairpin structure of the molecular beacon (P1/P2) to prevent the formation of fluorescent silver nanoclusters. When the target substances (T1/T2) are added, the hairpin structures P1/P2 can specifically recognize them. Under the rule of base complementary pairing, their configuration changes, and the hairpin structure is opened, forming a DNA double-stranded structure; at the same time, a part of the DNA template sequence is released. At this time, this part of the sequence combines with Ag^+ in the reaction system. Fluorescent silver nanoclusters are synthesized through one-step reduction. Due to the presence of different target sequences, fluorescent silver nanoclusters with green fluorescence signals and orange fluorescence signals are designed to achieve dual detection of target DNA molecules. This solution is simple to operate, has a low cost, and can accurately detect multiple target molecules by using common spectrophotometers. Therefore, the fluorescent MB probe based on AgNCs can provide a potential

alternative platform for label-free/uncoupled analysis of target DNA.

4. Nanotechnology used in the treatment of cancer

In recent years, clinical treatment strategies have shown a significant trend of shifting from single therapy to combination therapy, with the aim of achieving better therapeutic effects through multi-modal collaborative treatment. Research shows that multimodal synergistic therapy not only integrates the advantages of single therapies but also generates a synergistic effect, and its therapeutic outcome is significantly better than that of single therapies or simple theoretical combinations [27]. This trend has emerged largely due to the heterogeneity of tumor tissues, which frequently harbor subpopulations of cancer cells resistant to particular treatments. As a result, monotherapy often fails to achieve satisfactory therapeutic outcomes. In contrast, multimodal synergistic therapy, by integrating the advantages of different therapeutic mechanisms, can enhance anti-cancer efficacy while reducing drug dosage, thereby effectively avoiding the toxic and side effects brought about by high-dose treatment [80]. Based on these advantages, the combination of nanotechnology and multimodal synergistic treatment has become an important research direction at present.To clearly illustrate the key carriers in this field, Table 2 compares the multi-functional nanosystems used for integrated cancer diagnosis and treatment. These nanosystems integrate diagnostic and therapeutic functions and mediate the synergistic effect of multiple treatment modes, effectively overcoming tumor heterogeneity and drug resistance. Figure 6 visually presents the typical mechanism of action of such nanomedicine-mediated combined therapy.

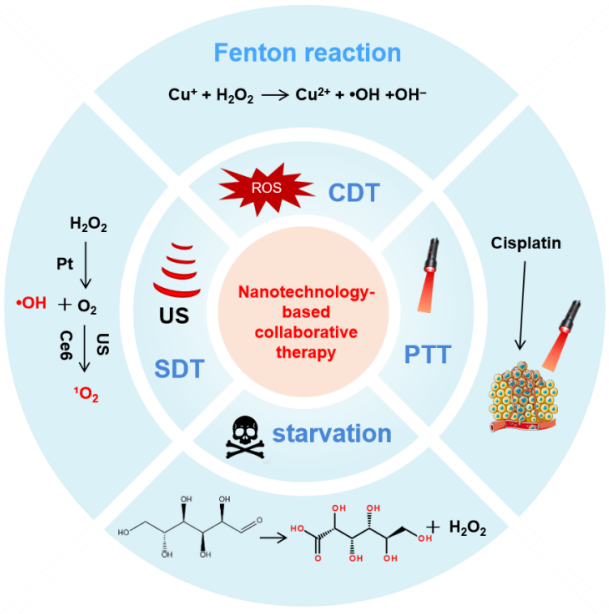

Figure 6. Schematic diagram of nanomedicine-mediated combined therapies for cancer.

Table 2. A variety of multi-functional therapeutic nanoplatforms for cancer theranostics.

Sequence	Nanomedicine types	Mechanism of efficacy	Inferences	Ref
1	Mesoporous silica nanoparticles	Can increase the hydrophobicity	Mesoporous silica nanoparticles platform can load drug effectively and improve bioavailability	[44]
2	Functionalized polymer nanoparticles composed of water-soluble chitosan, gold nanoparticles, and LyslLys 3 peptide	It can specifically recognize overexpressed gastrin-releasing peptide receptors	It provides a new template synthesis strategy for the development of functionalized polymer nanocarriers	[61]
3	Metal-organic skeleton nanomaterials	Fenton-like reaction	The combination of chemokinetic therapy and nanotechnology has high biocompatibility	[90]
4	DPtFIP nanoparticles conjugated by multiple small molecules	Folic acid targets and releases cisplatin, triggering photothermal therapy	The anti-tumor effect was further enhanced by the combination of hyperthermia and cisplatin	[97]
5	pH-responsive bionic nanocarriers	Promote endocytosis through receptor-mediated endocytosis to achieve targeted drug delivery	The integration of sonodynamic therapy with nanotechnological approaches has shown remarkable efficacy in suppressing tumor growth.	[106]
6	Nanoreactor for tumor metabolism regulation based on ZF-8	Cut off the tumor's energy supply	Starvation therapy based on nano-platforms can improve the therapeutic effect of tumors	[114]

4.1. Synergistic therapy based on chemodynamic therapy

Based on the above background, the combination of nanotechnology with combined therapy has become an important research direction. Nanocarriers can achieve the co-delivery of multiple therapeutic agents, ensuring consistency in their spatial and temporal distribution, which provides the possibility for achieving precise drug synergy at the tumor site [81].

Traditional cancer treatment methods, such as chemotherapy (using drugs like doxorubicin) and radiotherapy, have mechanisms closely related to the generation of ROS, inducing oxidative stress to kill cancer cells [82–84]. However, as these therapies lack tumor specificity, they not only attack cancer cells but also cause damage to normal tissues, resulting in serious dose-limiting toxic side effects [85,86]. Therefore, how to precisely limit the killing effect of ROS to the tumor interior becomes a key scientific issue.

Chemodynamic therapy (CDT) is an emerging treatment strategy designed to achieve this precise attack. CDT utilizes Fenton or Fenton-like reactions to convert the over-expressed H_2O_2 in the tumor microenvironment (TME) into more toxic hydroxyl radicals ($\bullet OH$) [87,88]. Theoretically, this endogenous reaction mechanism endows CDT with good tumor selectivity. However, the current

clinical application of CDT faces substantial challenges: its catalytic efficiency heavily relies on acidic pH and sufficient H_2O_2 substrates, while the actual H_2O_2 concentration in the body may not be sufficient to generate the •OH level required for treatment; at the same time, the high levels of antioxidant substances (such as glutathione) in tumors will quickly clear the generated ROS, significantly weakening its final efficacy [89].

To overcome these limitations, researchers are working to develop intelligent nanoplatforms. For example, Wang et al. designed an in situ convertible prodrug nanomedicine (ZnS/Cu_2S @ZIF-8@PVP) (Figure 7) [90]. This platform can trigger component recombination in the acidic tumor environment, generating Cu_2S nanodots with photothermal effects and simultaneously releasing Cu^+ ions for a Fenton-like reaction, thereby synergizing CDT with photothermal therapy (PTT). This study demonstrated that this combined strategy achieves effective tumor ablation in mouse models. Although this result provides a proof-of-concept for the combination of CDT with other therapies, its clinical translation prospects still need to be evaluated, including the long-term biological safety of the composite nanomaterials and the feasibility of large-scale production, which still require in-depth exploration.

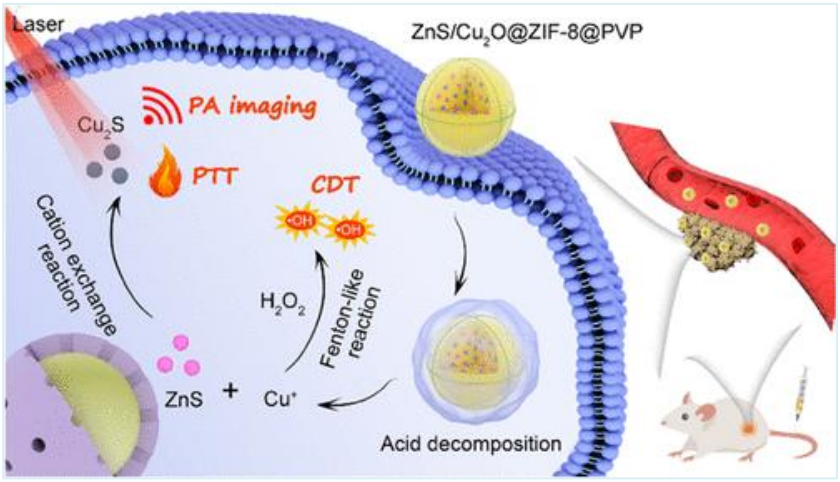

Figure 7. Schematic diagram of the synthesis of in situ convertible ZnS/Cu_2O@ZIF-8@PVP nanoparticles and their synergistic CDT/PTT anti-tumor effect [90].

4.2. Synergistic therapy based on photothermal therapy

PTT is a local physical therapy whose core mechanism lies in the generation of local high heat (typically 42–50 °C) through non-radiative relaxation processes in photothermal agents (such as noble metal nanomaterials) upon exposure to NIR, thereby selectively inducing tumor cell ablation [91,92]. Near-infrared light offers potential advantages for treating deep tumors due to its relatively deeper penetration ability (typically several centimeters) and lower tissue scattering [93,94]. Moreover, the thermal effect produced by PTT not only directly kills tumor cells but has also been proven to enhance the intratumoral penetration and internalization of chemotherapy drugs by promoting tumor vascular permeability and disrupting cell membrane integrity. It can also reversibly improve the tumor hypoxic microenvironment, thus laying a theoretical foundation for synergistic enhancement with other therapies such as chemotherapy, radiotherapy, and immunotherapy [95].

However, the clinical translation of PTT still faces a series of key challenges. First, its efficacy highly depends on the specific accumulation of photothermal agents in the tumor site and the precise irradiation of lasers, which limits its therapeutic effect on diffuse regions or those difficult to reach by the light path. Second, during the treatment process, off-site thermal damage may occur due to heat diffusion. More importantly, sub-lethal thermal exposure may induce heat shock proteins (HSPs) in tumor cells, thereby initiating a protective stress response, which may enhance tumor heat resistance and even cross-tolerance, potentially weakening the therapeutic effect [96].

To overcome these challenges, the design of intelligent nanosystems that can synergize PTT with other therapies has become a research hotspot. For instance, Guan et al. developed a large-molecule nanocomposite (DPtFIP) that simultaneously carries cisplatin prodrug and photothermal molecules (Figure 8) [97]. This study demonstrated that under near-infrared light irradiation, this system not only enables imaging-guided photothermal therapy but also significantly enhances the cytotoxicity of cisplatin through its thermal effect. Guan et al. attributed this synergistic effect to the increase in cell membrane permeability and the inhibition of DNA damage repair by heat.

Although this study provides a promising proof-of-concept for the PTT–chemotherapy combination strategy, its conclusion still needs to be carefully evaluated in more complex in vivo models. For example, the targeting efficiency of this nanosystem in the real tumor environment, long-term biological safety, and feasibility of large-scale production are all issues that must be addressed before its clinical translation. This case illustrates that the synergistic effect of PTT is not inevitable; its success highly depends on the precise control of the temporal and spatial effects of heat and drugs by ingenious nanoscale design and the effective inhibition of tumor adaptive resistance.

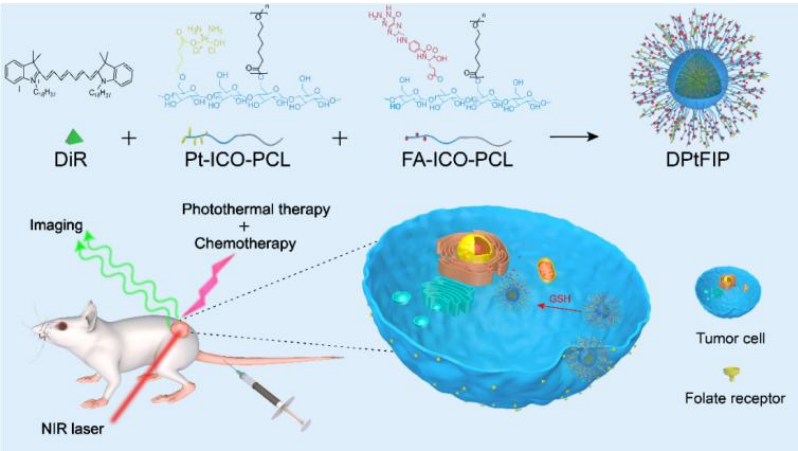

Figure 8. Schematic diagram of the synthesis of DPtFIP nanoparticles for GSH-responsive photothermal therapy and their synergistic chemotherapy applications [97].

4.3. Synergistic therapy based on sonodynamic therapy

Sonodynamic therapy (SDT) is a non-invasive treatment strategy that utilizes the excellent tissue-penetrating ability of ultrasound waves (typically > 10 cm) to activate the sonosensitizers enriched at the tumor site, thereby selectively killing cancer cells by generating ROS [98,99]. Compared to photodynamic therapy (PDT), which heavily relies on the penetration depth of light, SDT is considered to have potential advantages in treating deep or large solid tumors [100].

The core mechanism of SDT is that the sonosensitizers undergo energy transfer under ultrasound excitation, inducing the generation of ROS such as $^1O_2$ or •OH in the surrounding medium (such as oxygen or water), thereby causing oxidative damage to tumor cells [101,102]. However, the actual efficacy of SDT is limited by various factors. First, many traditional sonosensitizers, such as porphyrins and Ce6, face problems such as poor water solubility, insufficient in vivo stability, and limited enrichment efficiency at the tumor site, which directly affect the total amount of ROS generated and the specificity of the treatment [103,104]. Second, the efficiency of SDT is highly dependent on the oxygen concentration in the TME, and the universal hypoxia characteristic of tumors severely limits the ROS generation pathway using oxygen as a substrate. Third, the high levels of reducing substances in tumors, such as GSH, rapidly clear the generated ROS, forming a powerful antioxidant defense system, thereby weakening the final killing effect of SDT [105].

To address these challenges, the construction of multifunctional nanocarriers has become a key strategy to enhance the efficacy of SDT. For example, Wang et al. designed a pH-responsive biomimetic nanoplatform (CLP@HP-A) [106]. The innovation of this design lies in its synergistic treatment concept: on the one hand, the carrier achieves targeted delivery through endocytosis mediated by the galectin-3 receptor; on the other hand, the Pt component it carries has been reported to be able to catalyze the decomposition of endogenous H_2O_2 to generate oxygen, aiming to alleviate tumor hypoxia and simultaneously generate additional •OH. The authors claim that this "self-oxygenation" strategy, combined with the sonosensitizer Ce6, produces enhanced oxidative stress under ultrasound excitation, showing a synergistic anti-tumor effect in mouse models (Figure 9).

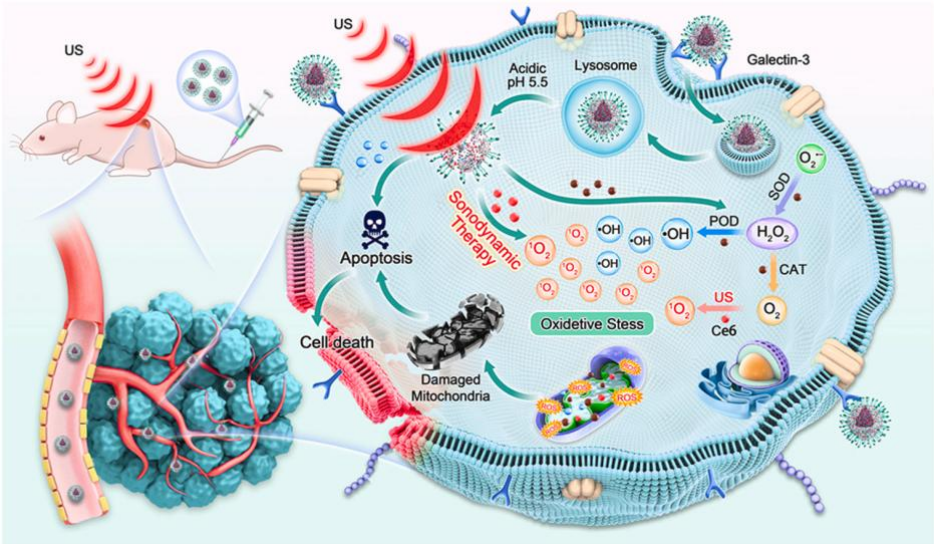

Figure 9. Schematic diagram of the preparation process of CLP@HP-A and its enhancement of sonodynamic therapy in a tumor microenvironment [106].

Nevertheless, the evaluation of this system and even such strategies still require caution. The success of this nanoplatform heavily relies on the collaborative working efficiency of its components in the complex in vivo environment, such as whether the catalyzed oxygen can precisely match the ultrasound dynamic process in space and time. At the same time, the long-term biological safety, the feasibility of large-scale production, and the universality in different tumor models of this composite

nanomaterial are still key issues that must be answered before moving toward preclinical trials. This case illustrates that although nanotechnology engineering is an important force driving the development of SDT, the claimed "synergistic enhancement" must be verified through more rigorous experimental design and more clinical-like models.

4.4. Synergistic therapy based on starvation therapy

The invasion and metastasis of malignant tumors are the main reasons for treatment failure. Intervening in their unique metabolic vulnerability, namely through starvation therapy, has become a promising strategy [107]. This strategy aims to cut off the energy source and biosynthetic raw materials of tumors by depleting key nutrients such as glucose or disrupting their vascular supply, thereby inhibiting their growth [108]. The theoretical basis of this method stems from the well-known Warburg effect, which states that many cancer cells tend to undergo rapid glycolysis even under aerobic conditions, a metabolic reprogramming that enhances their dependence on glucose and makes them more sensitive to glucose fluctuations in the microenvironment [109].

Glucose oxidase (GOx), as an enzyme that catalyzes the oxidation of glucose to produce gluconic acid and H_2O_2, is one of the key tools for implementing starvation therapy [110,111]. Theoretically, GOx can directly trigger "starvation" at the tumor site by consuming glucose, and the accumulation of its reaction by-product H_2O_2 can further cause CDT-like oxidative damage and exacerbate the acidity of the tumor microenvironment, thereby attacking the tumor in multiple ways [112].

However, the practical application of starvation therapy faces significant biological challenges. First, solid tumors themselves have high heterogeneity and insufficient perfusion, resulting in uneven nutrient distribution, making it difficult for the system-delivered GOx to uniformly and fully contact its substrates. Second, tumors have strong metabolic plasticity, and after glucose deprivation, they may activate compensatory pathways (such as glutamine breakdown or fatty acid oxidation) to maintain survival, thereby generating drug resistance [113]. More importantly, severe nutrient deprivation may select for more aggressive tumor cell subpopulations and exacerbate the immunosuppression of the tumor microenvironment, potentially hindering long-term control.

To overcome these limitations, researchers have designed complex nanosystems to achieve multi-pathway coordinated blockade. For example, Zhou et al. constructed a nanoreactor based on ZIF-8 (D/B/CQ@ZIF-8@CS), which simultaneously delivers 2-deoxy-D-glucose (2-DG), glucose transporter 1 inhibitor (BAY-876), and autophagy inhibitor chloroquine (CQ), aiming to comprehensively block the energy metabolism of tumors from multiple aspects of uptake–utilization–self-rescue [114]. This study demonstrated that this strategy effectively inhibited tumor growth in the 4T1 mouse model and enhanced the efficacy of anti-CTLA-4 immunotherapy by regulating lactate metabolism (Figure 10).

Although this study showcases a sophisticated nanosystem design, its clinical translation prospects still require cautious assessment. This complex scheme involving multiple inhibitors has issues, such as the temporal and spatial control of component release, potential off-target toxicity, and metabolic adaptation during long-term medication, which are major problems that must be addressed in the future. Therefore, although the nanosystem platform provides a new implementation method for starvation therapy, its ultimate efficacy still depends on whether we can effectively block the tumor's energy supply while effectively inhibiting its escape mechanism and avoiding global interference with the normal metabolism of the body.

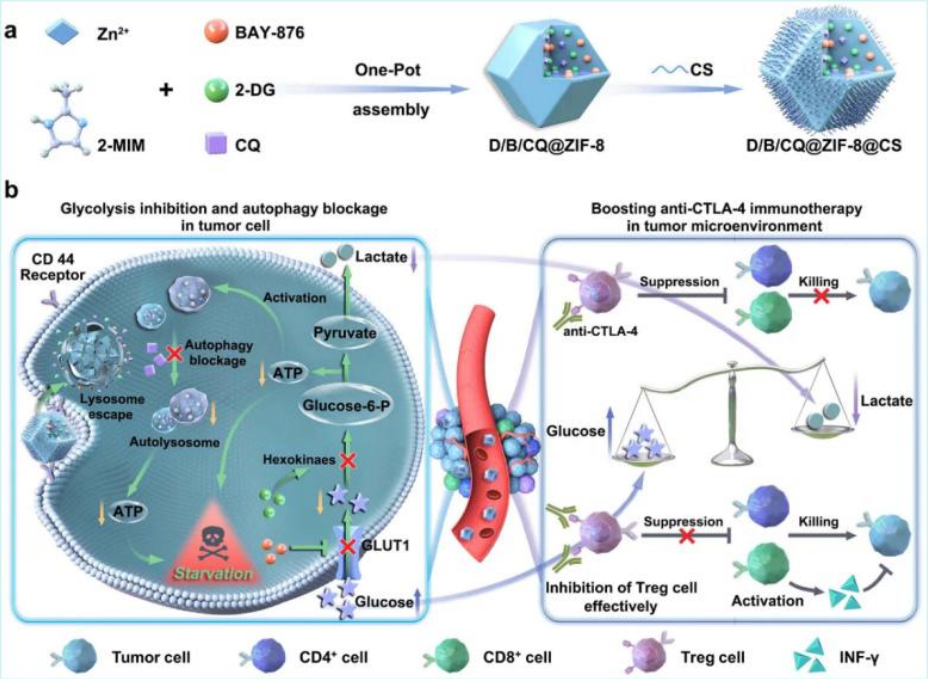

Figure 10. Schematic diagram of the synthesis of D/B/CQ@ZIF-8@CS nanoparticles and their application in anti-tumor therapy by regulating tumor metabolism [114].

5. Conclusions and prospects

Over the past few decades, significant progress has been made in the field of cancer nanomedicine, with its core advantage stemming from the precise control of the physical and chemical properties of materials. By encapsulating drugs, contrast agents, or gene therapy tools in nanocarriers of controllable size (typically 1–1000 nm), researchers can actively influence their in vivo biological behavior. For instance, by controlling the size of nanoparticles (10–100 nm, to take advantage of the enhanced permeability and retention effect) and surface charge (near-neutral, to extend the circulation half-life) and functionalizing their surfaces (such as grafting PEG or targeting ligands), the enrichment of therapeutic drugs in tumor sites can be significantly improved, and off-target toxicity to normal tissues can be reduced.

In the diagnostic field, nanomaterials, with their unique optical, electrical, and magnetic properties, are used to construct highly sensitive biosensors and novel contrast agents, providing powerful tools for the early detection and precise imaging of cancer. In the therapeutic aspect, nanocarriers not only enhance the solubility and stability of hydrophobic drugs but also demonstrate significant synergistic sensitization effects through organic integration with chemotherapy, radiotherapy, immunotherapy, and photothermal therapy, opening up new paths to overcome tumor drug resistance and metastasis.

However, the wide-scale translation of nanomedicine from the laboratory to the clinic still faces a series of fundamental challenges. First, delivery efficiency remains the biggest bottleneck; tumor heterogeneity leads to significant differences in the EPR effect among individual patients, and the complex tumor microenvironment (such as high interstitial pressure and dense matrix) severely hinders the deep penetration and uniform distribution of nanomedicines. Second, the biological complexity of

nanomaterials constitutes another major obstacle: the "protein corona" formed in vivo alters surface properties and targeting capabilities, and the long-term biological safety, potential immunogenicity, and clear in vivo clearance pathways still need systematic evaluation. Finally, the gap between large-scale production and clinical translation remains huge, including the complexity of synthesis processes, high costs, and batch-to-batch quality control issues, all of which severely restrict their large-scale clinical application.

Despite the challenges, the future development opportunities are equally clear. The next generation of nanomedicine research should focus on the following: 1) Developing intelligent response systems: designing “smart” nanocarriers that can sense and respond to specific signals in the tumor microenvironment (such as pH, enzymes, redox state) to achieve precise on-demand drug release. 2) Promoting cross-disciplinary integration: leveraging artificial intelligence and machine learning to integrate the physical and chemical parameters of nanomaterials with their in vivo biological behavior data to accelerate the rational design of new nanomedicines. 3) Building personalized treatment platforms: based on the specific molecular typing and microenvironment characteristics of patients' tumors, customizing personalized nanotherapy regimens to address the problem of tumor heterogeneity. 4) Addressing translational challenges: promoting the establishment of more clinically relevant new disease models and introducing considerations of large-scale production and regulatory science in the early stages of drug development.

In conclusion, the future of cancer nanomedicine is no longer limited to the development of new materials but lies in addressing the core bottlenecks in delivery efficiency, biological safety, and clinical translation with a critical engineering mindset. Through this cross-disciplinary collaborative innovation, nanomedicine is expected to ultimately fulfill its clinical promise and provide truly precise, efficient, and safe solutions for conquering cancer.

Author contributions

YQT and MZ jointly conceived the theme of this work; NTX performed data collection and literature analysis; MZ completed the draft writing and content integration; ZWZ and CML provided guidance on the review framework, revised the manuscript for academic rigor, and coordinated the final revision. All authors confirmed the final content and agreed to submit.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no conflict of interest in this paper.

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