Functional Nanoparticles for Enhanced Cancer Therapy

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The conventional therapeutic approach is mainly based on chemotherapy, which has a series of side effects. Compared with traditional chemotherapy drugs, nanoparticle-based delivery of anti-cancer drugs possesses a few attractive features. The application of nanotechnology in an interdisciplinary manner in the biomedical field has led to functional nanoparticles achieving much progress in cancer therapy. Nanoparticles have been involved in the diagnosis and targeted and personalized treatment of cancer. For example, different nano-drug strategies, including endogenous and exogenous stimuli-responsive, surface conjugation, and macromolecular encapsulation for nano-drug systems, have successfully prevented tumor procession.

Keywords: functional nanoparticles ; cancer therapy ; nanotechnology

1. Introduction

Cancer has a high incidence and mortality rate worldwide [1]. The overall mortality rate of cancer is still as high as 20.2% [2]. Moreover, 19.3 million new cancer cases will occur annually by 2025 [3]. Treatment strategies for cancer mainly depend on the cancer type and the stage of the first diagnosis. Available treatment options for cancer include surgery, radiotherapy, chemotherapy, hormone therapy, immunotherapy, and gene therapy [4]. Among these options, the most common way to treat cancer and inhibit tumor recurrence is chemotherapy, which kills cancer cells with cytotoxic drugs. However, an adverse problem of most chemotherapeutic drugs is that they cannot target the cytotoxicity of tumor cells, resulting in multiple side effects and poor prognosis [5].

In 1986, two Japanese researchers first reported the enhanced permeability and retention (EPR) effect of nanoparticles in tumor tissues, which opened the door to the nano-drug strategy for cancer treatment [6][7]. A large number of subsequent studies showed that, compared with traditional chemotherapy drugs, the drug system based on a nano platform showed significant advantages, such as (1) adjusting the oil–water distribution index of drugs and improving bioavailability, (2) better stability of protein and peptide drugs, (3) targeted administration, (4) the release of drugs in precise doses and on demand, and (5) co-delivery of multiple drugs/diagnostic agents [8][9][10][11].

2. Functional Nano-Drug Delivery Platform

Nanotechnology has aroused great interest in cancer treatment because of its excellent solubility, targeting capability, therapeutic efficacy, and low toxicity compared with conventional agents [10]. A series of strategies focused on stimuli-responsive, surface conjugation with targeting ligands, large molecules, and so on offer attractive features and promote highly efficient use of cancerous therapeutic agents.

2.1. Stimuli-Responsive Nano-Drug Delivery Platform

2.1.1. pH-Responsive

Acidic TME caused by hypoxia and extracellular lactic acid accumulation is one of the most significant characteristics of solid tumors. In addition, different cell parts also show different pH values, in which mitochondria are alkaline (pH ~8.0), and lysosomes are acidic organelles (pH ~4.7). During drug delivery, the pH value of endosomes was observed to change from pH ~6.3 to 5.5 [12][13].

A kind of macrophage-membrane-coated nanoparticle (cskc-PPiP/Paclitaxel @Ma) was developed to release tumor-targeted chemotherapy drugs responding to the pH value of endosomes and showed an excellent therapeutic efficacy [14]. One study showed that green-emitting Zn_2 GeO_4: Mn^{2+} Pr^{3+} nanoparticles possessed good pH stimuli-responsive luminescent behavior [15]. In a recent study, doxorubicin-hydrazone bond-PEG-folic acid (DOX-hyd-PEG-FA) polymers coated on the surface of nano-graphene oxide could be decomposed at the same time and had good pH sensitivity and active tumor targeting [16].

One study revealed that a higher therapeutic effect was seen for melanoma cancer cells than non-pH responsive gold nanoparticles [17]. In a previous study, hydrophobic Curcumin (CUR) was combined with hydrophilic hyaluronic acid (HA) to form pH-responsive nanoparticles, which achieved enhanced treatment efficacy for cancer with good biosafety. The nanoparticle size was 89 nm, and the transmission electron microscope (TEM) image revealed that the morphologies of the nanoparticle were spherical, and the release rate of CUR was 73.5% at pH 5.0 [18]. Furthermore, chitosan, folic acid, and silver nanoparticles loaded with gemcitabine were prepared and had an excellent response to pH. A recent study also demonstrated the responsiveness of layered hydroxide (LDH) in the treatment of colorectal cancer. Under the slightly acidic condition of the tumor site, LDH nano tablets gradually degrade so that Ethylenediaminetetraacetic acid (EDTA) can realize the controllable release of acid reaction at the tumor site.

2.1.2. Redox-Responsive

It has been shown that tumor extracellular matrix is an oxidizing medium, while intracellular space is reduced, glutathione (GSH) are reductants widely present in the human body [19][20]. GSH-responsive hydrophilic PEG and hydrophobic poly (lactic acid co glycolic acid) (PLGA) copolymer were reported to improve therapy efficacy in lung cancer in vitro/in vivo. The nanoparticles were spherical with a diameter of around 200 nm and negative zeta potential [21]. Redox-responsive PEG with PTX NPs achieved a better treatment effect than free drugs in a breast cancer xenograft mouse model. TEM images revealed that the nanoparticles were spherical with an average size of 70 nm [22].

2.1.3. ROS-Responsive

Cancer cells are subjected to more and more oxidative stress, resulting in changes in metabolic activities and carcinogenic transformation [23][24]. In particular, the level of reactive oxygen species in tumor tissue is mainly higher, which is due to the accumulation of active molecules under hypoxia in tumor tissue [25].

Recent studies have shown that special enzymes that produce reactive oxygen species have very beneficial functions in the treatment of cancer [26]. Through the self-assembly of thioketal units, photosensitizers, and Chlorin e6, a kind of ROS-responsive nanoparticle was formed and showed excellent tumor penetration and satisfied therapeutic efficacy [27]. One previous study developed integrated nanoparticles composed of poly (ethylene glycol) and polymerized methacrylate monomer loaded with β-lapachone, which is responsive to tumor ROS [28]. A kind of heparanase modified with β-cyclodextrin (β-CD) grafted heparin co-loading with doxorubicin (DOX), ferrocene (Fc), and TGF-β receptor inhibitor (SB431542) was established and successfully inhibited breast cancer metastasis, under which ferroptosis induced by ROS was essential [29].

A nano-drug composed of arginine-glycine-aspartate (RGD) conjugated with cytotoxin epothilone Bis was sensitive to ROS, showing excellent tumor selectivity and anti-cancer effect in vitro/in vivo [30]. A new ROS-responsive micelle composed of poly 10-hydroxycamptothecin and PEG, which loaded dexamethasone, was constructed, revealing an ideal anti-tumor effect [31]. Recently, phospholipid-coated $Na_2S_2O_8$ nanoparticles that could generate new reactive oxygen species for in-situ generation of Na^+ and $S_2O_8^{2-}$ and then transform into toxic sulfate radical and hydroxyl radical ($\bullet SO_4^-$ and •OH) were prepared. Nanoscale metal-organic frameworks (nMOFs) have made much progress in radiotherapy, photodynamic therapy, and chemodynamic therapy via nMOFs-mediated ROS generation [32].

2.1.4. Hypoxia-Responsive

It is well-known that an incomplete vascular network and limited oxygen diffusion distance exist in solid tumors (200 μm). Hypoxia is a unique pathological feature for 50–60% of solid tumors [33][34][35].

Self-assembled hypoxia-reactive carboxymethylglucan nanoparticles (CMD NPs) were established to promote the selective release of hydrophobic drugs in tumors [36]. Manganese dioxide nanoparticles (MnO_2 NPs) toward hydrogen peroxide (H_2O_2) for the simultaneous production of O_2 and regulation of pH were proposed to prevent tumor hypoxia and inhibit tumor growth and proliferation of breast tumors [37].

One previous study reported a platform composed of hyaluronic acid (HA)-stabilized CuMnOx nanoparticles (CMOH) and indocyanine green (ICG) for hypoxic tumor therapy and their thermally amplified catalytic activity and TME regulation ability [38]. One study reported a kind of PEG-camptothecin(CPT)-2-(piperidin-1-yl)ethyl methacrylate nanoparticle, which was hypoxia-responsive and showed tumor-suppressed effect [39]. Moreover, one study reported a hypoxia-responsive nanovesicle could enhance the efficacy of sonodynamic therapy (SDT) by generating sufficient ROS in tumors. Furthermore, SEM/TEM images showed that the morphology of the nano-assemblies had a uniform vesicular structure with an average diameter of around 129 ± 16.3 nm [40]. A new type of polymer micelles to sense hypoxia in tumors was constructed, in which the drug was released and caused immunogenic cell death through chemotherapy and photothermal therapy, which was effective in the treatment of advanced breast cancer.

2.1.5. Enzyme-Responsive

Tumor tissue has diverse enzyme expression profiles, which is helpful in developing efficient enzyme-responsive nano-drug delivery systems and can realize the fascinating physicochemical properties of different materials on the nanoscale [41][42].

Recently, a microneedle comprised of an anti-programmed death-ligand 1 antibody (aPD-L1) and cold atmospheric plasma therapy was also reported to induce immunogenic tumor cell death [43]. Fe^{3+} ion and naturally derived tannic acid could form sorafenib NP, which could inhibit the GPX4 enzyme for ferroptosis initiation and eventually tumor elimination [44]. One study reported that legumain-responsive gold nanoparticles (AuNPs) could lead to enhanced accumulation of doxorubicin (DOX) and hydroxychloroquine at the glioma site of patients, possessing therapeutic efficacy [45]. As reported in a previous study, carboxylesterase-responsive folate-decorated albumins into a nanocluster (FHP) confirms that it was reported to be enzyme-triggered and effective for precise cancer theranostics [46]. Matrix Metallopeptidase 2(MMP-2) responsive and RGD-peptide-modified liposome consisting of pirfenidone (an anti-fibrotic agent) and gemcitabine (a chemotherapeutic drug) was effective in pancreatic stellate cells model in BALB/c nude mice [47].

2.1.6. Temperature-Sensitive

The temperature of tumor tissue is usually 1–2 °C higher than normal cells, which is called hyperthermia [48][49]. Temperature is beneficial as an external stimulus in nanoparticle design. Some advantages include low toxicity and better control of cancer drug dose and localization [50].

Some types of temperature-response carriers include liposomes, polymer micelles, dendrimers, etc. [51]. Thermoresponsive micelles based on PEG-[poly(caprolactone), PCL]-PEG loaded with phenylalanine ammonia lyase showed an excellent anti-tumor effect in colorectal cancer. The molecular weight and polydispersity of the polymer were 5392 and 1.345, respectively [52].

2.1.7. Ultrasound-Sensitive

As an external stimulus, ultrasound is popular in nano-drug research because of its non-invasive, non-ionizing radiation as well as easy adjustment of its tissue penetration depth and frequency [53]. Ultrasound can release drugs from responsive nanocarriers [54], which could increase the permeability of biological barriers by increasing the temperature to increase the absorption, release, and production of cavitation bubbles [55].

The liposome is a mature multifunctional drug delivery system. For example, under the stimulation of hyperthermia caused by ultrasound, a temperature-sensitive liposome achieved complete regression of breast cancer in mice [56], which was also applied in a human breast cancer xenograft mouse model and achieved a good effect [57][58][59]. As reported in one previous study, focused ultrasound sonication with microbubbles (MBs) could improve delivery efficiency and significantly enhance DOX accumulation [60]. What is more, low-dose focused ultrasound hyperthermia significantly enhanced the pegylated liposomal doxorubicin delivery into brain tumors and showed a promising anti-tumor effect [61]. Liu et al. showed that a nanoreactor was designed by immobilizing catalase in the large opening of mesoporous organosilicon nanoparticles (MOS). The immobilized enzyme catalyzes the decomposition of H_2O_2 into O_2 molecules in a controlled manner, even when compared with 10 μm bubbles can also be produced continuously when incubated with H_2O_2. The bubbles generated in situ significantly enhanced the echo contrast and acted as cavitation nuclei, reducing the ultrasonic dose required for evident coagulative necrosis to 80 W. TEM images revealed a spherical shape with a diameter of 140 nm.

2.1.8. Magnetic Field-Sensitive

As a safe type of stimulus, magnetic fields are prevalent in nano-drug delivery in the therapy of tumors [62]. Besides treatment, magnetic field-sensitive nanoparticles were also used in diagnostic imaging [63]. A recent study used targeted magnetic carriers to deliver the DOX into the bladder wall, which caused more significant accumulation and provided site-specific delivery of drugs [64]. One recent study revealed that biomimetic magnetic Fe_3O_4-SAS@PLT nanoparticles were effective in curing non-inflamed tumors for ferroptosis with immunotherapy [65]. Magnetic field-induced hyperthermia could be used in the nano-drug treatment of bladder cancer in a hyperthermia-responsive manner [66][67][68].

2.1.9. Light-Sensitive

Light-responsive nanoparticles are popular for their convenient use at different wavelengths, such as ultraviolet (UV) [69], visible [70], and near-infrared (NIR) [71]. Nowadays, UV is widely used in functional nanoparticle design. Compared with UV, the deeper penetration of NIR is effective for deep tissue therapy [72].

Light-controlled drug delivery was first reported in 2010 [73]. The UV light irradiation could induce the burst release of hydrophobic NR molecules from the nanoparticle [74]. In another study, a copolymer system consisting of poly(ethylene oxide) (PEO) and poly(2-nitrobenzyl methacrylate) (PNBM) was sensitive to UV-light and led to the light-controlled release of payload drugs [73]. Compared with UV, infrared ranges from 600–900 nm, has deeper penetration, and is more effective in treating cancer in the deep part of the tissue. NIR-responsive systems are another main light-responsive system [75]. As an FDA-approved fluorescent dye, ICG is widely used in cancer therapy, which could absorb NIR light into heat [76]. Additionally, doxorubicin and ICG loaded in PLGA-based and dual-modality imaging guided chemo-photothermal nanoparticles showed faster release under NIR irradiation; this nanoparticle had a diameter of around 200 nm with good fluorescence stability. Doxorubicin release was stimulated by heat, and nanoparticle penetration of the tumor was improved after NIR irradiation, this research provided a promising strategy for early diagnosis and therapy for cancer [77].

2.2. Surface Conjugation with Targeting Ligands

The active target of cancer cells based on monoclonal antibodies, peptides, and aptamer has aroused significant interest in the field of targeting ligands [4].

2.2.1. Monoclonal Antibodies

Antibody-drug conjugates are monoclonal antibodies conjugated to cytotoxic agents [78]. Monoclonal antibodies (MAbs) are macromolecules widely used as targeting ligands to various types of nanoparticles, such as SPIONs [79], QDs [79], liposomes [80], and Au nanocages [81]. However, their bulky size and constant redundant region may limit their use. As reported in a previous study, nanoparticles formed by 2-methoxy-estradiol (2-ME) based on anti-human epidermal growth factor receptor 2 (HER2) antibody-modified BSA were validated in targeted cancer therapy; this system was prepared using the desolution method and was proven effective in retaining the immunospecificity of the anti-HER2 antibody for the targeted cancer therapy [82]. Furthermore, in a previous study, PTX was absorbed on graphene oxide nanosheets and then conjugated with vascular endothelial growth factor (VEGF) to form the targeted nanoparticles, which showed remarkable potential in photothermal controllable tumor treatment [83].

2.2.2. Peptides

Due to the bulky size of MAbs, peptides represent a viable targeting moiety with relative flexibility and overcome the disadvantages of using MAbs [84]. Peptide−drug conjugates (PDCs) are increasingly recognized in targeted drug delivery [85]. For example, RGD peptides were intimately connected with integrin [86]. Nanoparticles composed of RGD conjugation with superparamagnetic iron oxide nanoparticles (SPIONs) possessed better targeting affinity and specificity [87]. In one previous study, a biocompatible conjugate consisting of a fatty acid-substituted dextran decorated with cyclo[RGDfK(C-6-aminocaproic acid)] cRGDfK peptide could be used as a candidate for conventional PEG [88]. Recently, gemcitabine (GEM) and amphiphilic peptide conjugation were effective in breast cancer therapy, this system was formed via self-assembled behaviors, and the stability of GEM could be maintained during the circulation and accumulated in the tumor site, which broadened the application of GEM for breast cancer therapy [89]. Tumor vascular endothelial cells (tVECs) were targeted with cRGD-functionalized polyplex micelle loading anti-angiogenic protein encoding pDNA for anti-tumor activity in human pancreatic adenocarcinoma tumor-bearing mice by noting that tVECs abundantly express αvβ3 and αvβ3 integrin receptors [90][91]. Moreover, the application of cell-penetrating peptides (CPPs) based on nanoplatforms in cancer treatment has also been worth attention since their identification 25 years ago [92]. Nanoparticles could be functionally attached to CCPs to achieve good therapeutic efficacy. For example, a nanoparticle against CapG to a series of CPPs showed a good potential for metastasis in breast cancer [93].

2.2.3. Aptamers

Aptamers are complex three-dimensional structures composed of short, single-stranded, synthetic nucleic acid oligomers, DNA or RNA, with some good characteristics for their high affinity and specificity, easy synthesis, low molecular weight, and lack immunogenicity [94]. As ligands, conjugation of aptamers to nanoparticles has been reported in a series of previous studies [95]. The combined use of cisplatin in liposomes conjugated with aptamers has been reported where the nucleolins (NCL) were the target of aptamers. Aptamer-conjugated liposomes were formed by cholesterol incorporation and hydration, which showed strong anti-proliferative activity in breast cancer cells overexpressing NCL [96].

2.3. Large Molecules-Based Therapy

2.3.1. Nucleic Acid-Based Therapy

Nucleic acid-based therapy is a technology that transfers nucleic acids, including plasmid DNA, mini vector DNA, siRNA, etc., to the nucleus of diseased cells or tissues for the gene therapy of cancers [97][98][99]. Furthermore, gene therapy

focuses on the mutated genome of the tumor cells [100], aiming to restore instead of kill cells [101].

Poly(*N*-isopropylacrylamide) (PNIPAM) is the most extensively used in gene delivery systems [102]. The polyplex micelles consisting of PNIPAAm and therapeutic plasmid DNA (pDNA) could prolong blood circulation and suppress tumor growth in H22 tumor-bearing mice [103]. Nanoparticle-based delivery of small interfering RNAs (siRNAs) has also been reported to possess an anti-proliferative effect [104]. A biodegradable and redox-sensitive nanocarrier consisting of solid poly (disulfide amide) (PDSA)/cationic lipid core and a lipid-PEG shell for siRNA delivery was proven to have a good therapeutic effect [105]. Liposomes targeting the interleukin 12 (IL-12) gene in a non-viral manner could induce an immune response and achieve good therapeutic efficacy [106].

Additionally, thermosensitive nanocarriers have also been used in gene transfection.

2.3.2. Protein-Based Drug Delivery

Natural biological molecules usually form protein-based nanoparticles with biocompatible, biodegradable, and non-antigenic properties and can be functionalized with cell-targeting groups or ligands [107][108][109]. Gelatin is a protein obtained from the hydrolysis of collagen [110]. One previous study in dogs with bladder cancer revealed that gelatin nanoparticles loaded with paclitaxel (PTX) had a good therapeutic efficacy [111]. Drug molecules conjugated with proteins were used for cancer therapy [112]. Hollow mesoporous silica capsules have garnered significant attention as protein delivery vehicles [113]. For example, Fluorescein isothiocyanate (FITC)-labeled proteins were loaded into the nanoparticles to achieve efficient therapeutic efficacy [114], evidenced by several examples of protein delivery in liposomes [115]. Moreover, magnetic field-responsive protein conjugation nanoparticles were also reported to be an efficient system for brain tumors [116].

2.4. Others—Hydrogel

Hydrogel is a polymer with a three-dimensional, hydrophilic, and cross-linking network, capable of retaining a large amount of water or physiological fluids [117]. Injectable biodegradable hydrogels have broadened novel methods of cancer treatment [118][119].

In cancer therapy, hydrogels provide a platform for drug combinations. For example, an injectable DNA hydrogel assembled by chemo drug-grafted DNA in a previous study showed excellent anti-tumor efficacy and represented a promising adjuvant therapy in cancer treatment [120]. Additionally, thermosensitive PPZ hydrogel loaded with PEGylated cobalt ferrite nanoparticles showed a fantastic therapeutic efficacy in the breast cancer mice model [121]. Furthermore, a unique “Jekyll and Hyde” nanoparticle–hydrogel (NP-gel) hybrid platform was designed to load DOX, leading to a good anti-recurrence efficiency and low toxicity [122]. Based on the hyperthermia caused by ultrasound, a magnetic hyperthermia responsive hydrogel comprised of silk fibroin and iron oxide nanocubes was effective in the 4T1tumor-bearing mice model [123].

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