

Recent Advances of Multi-Stimuli-Responsive Drug Delivery Systems for Cancer Therapy



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Abstract

Chemotherapy remains as a major treatment modality for cancer nowadays however, it is often associated with toxicity issues. To solve this problem, constructing stimuli-responsive drug delivery system (DDS) which can deliver therapeutic agents and control the release of them in a smart manner is an effective way. Among them, multi-stimuli-responsive DDS has attracted enormous interest owing to their more precise release of drugs in complicated blood circulation and pathological environment. Thus, the main focus of this review is to highlight the progresses on the design of multi-stimuli-responsive DDS for cancer therapy in the past year.

Keywords: Drug delivery system; Stimuli-responsive; Cancer therapy

Introduction

Nowadays, cancer with an increasing morbidity at an alarming rate is still a major cause of death worldwide [1]. And the most common cancer treatment method is conventional chemotherapy which is based on highly potent anticancer drugs. However, the harmful side-effects due to the nonspecific uptake by normal tissues/organs limit their further applications [2]. To conquer these limitations, an effective way is to construction stimuli-responsive drug delivery system (DDS) which can deliver therapeutic agents and control the release of them in a smart manner [3].

One of the biggest advantages of an ideal stimuli-responsive DDS is the precise control of drug release in response to exogenous or endogenous stimuli. However, most of single or dual-stimuli-responsive DDSs are easily affected by complex external factors and suffered the problem of low release accuracy and some side effects [4]. To solve this problem, multi-stimuli-responsive DDSs have been developed for more precise release in complicated blood circulation and pathological environment [5]. In this mini review, we will summarize the progress and research efforts made by different research groups on designing and constructing multi-stimuli-responsive DDSs for cancer therapy in the past year.

Discussion

In the past year, polymers with unique sensitivity are mostly used for the construction of multi-stimuli-responsive

DDSs. For example, Wang's group [6] designed a triple-stimuli-responsive DDS based on graft copolymer assembly. The graft copolymer was consisted of thermo-responsive tetraethylene glycolyl poly (trimethylene carbonate) as backbone and light-sensitive poly(2-nitrobenzyl methacrylate) as side chain linked by an intervening disulfide bond. In aqueous solution, the polymer can self-assemble into micelle loading drugs. And the drug could be release respond to temperature, reducing agent and light. Analogously, Cao et al. [7] demonstrated a multi-stimuli-responsive nanogels for selective release of simultaneously encapsulated hydrophobic and hydrophilic cargos in a spatiotemporally controlled manner. The nanogel was composed of hydrophilic pH- and thermo responsive poly(2-(dimethylamino)ethyl methacrylate) and hydrophobic photocleavable o-nitrobenzyl linkage. The hydrophobic cargos were noncovalently encapsulated into lipophilic interiors of the nanogels, while the hydrophilic cargos were chemically linked to the nanogel precursor polymer poly(2-(dimethylamino)ethyl methacrylate) through a redox-cleavable disulfide junction. For these dual-loaded nanogels, hydrophobic cargos can be released in response to temperature, pH, and UV light, while the hydrophilic cargos can be released in response to redox reagent. Hu et al. [8] synthesized a core-crosslinked poly(thioether ester) (PTE) micelles with ROS-, GSH- and pH-sensitivity for intracellular drug delivery. PTE with abundant hydroxyl groups in the side chains were facilely synthesized

by the thiol-ene/thiol-epoxy polymerization of ethanedithiol (EDT) and glycidylmethacrylate (GMA). Then, poly (ethylene glycol) (PEG) and lipoic acid (LA) were grafted onto the PTE backbone to obtain PTE-g-PEG-LA graft copolymers, which were subsequently converted to core-crosslinked nanoparticles in aqueous media. The obtained core-crosslinked PTE-g-PEG-LA micelles could serve as drug delivery vehicle for effective loading of anticancer drug and triggered release of the loaded drug in response to various micro-environmental conditions (ROS-abundant, acidic or reductive environment) thosetypically existed in cancer cells. Similarly using polymer, Zhao's et al. [9] reported a multi-stimuli-responsive nanoparticles based on the co-assembly of a 3-arm star quaterpolymer with a near-infrared (NIR) photo thermal agent and chemotherapeutic compound. The nanoparticles can exhibit NIR light/pH/reduction-responsive drug release and intracellular drug translocation in cancer cells. Later, Li et al. [10] fabricated a pH, temperature and reduction multi-stimuli responsive polymeric microsphere via distillation-precipitation polymerization technique, with or without the hollow layer between their pH and reduction responsive poly(methacrylic acid) (PMAA) cores and temperature sensitive poly(N-isopropylacrylamide) (PNIPAM) shells. Owing to the middle hollow layer between their pH and reduction responsive PMAA cores and temperature sensitive PNIPAM shells, the PMAA/PNIPAM yolk/shell microspheres possessed the higher drug loading capacity and better tumor microenvironment-responsive controlled release performance. Most recently, Sui's et al. [11] synthesized a multiple stimuli-responsive SN38 prodrug, named PEG-S-S-SN38, by conjugating PEG (MW: 2000) and SN38 with disulfide bonds and carbonic ester linkages as linkers for efficient delivery of SN38. The amphiphilic PEG-S-S-SN38, with a high SN38 loading content, could self-assemble into nanoparticles and the release of SN38 was very slowly at physiological pH, while quickly in the presence of glutathione (GSH), esterase and H_2O_2 , all of which are abundant in the cytoplasm of cancer cells.

Apart from polymers, inorganic nanomaterial is also a good candidate. For example, Zhang's et al. [12] utilized a kind of NIR resonant material-hollow mesoporous copper sulfide nanoparticles (HMCuS NPs) to encapsulate doxorubicin (DOX). And the outer surface of HMCuS NPs was capped with multifunctional hyaluronic acid (HA) simultaneously as smart gatekeeper as well as tumor targeting moiety. In the tumor acidic lysosome, the enzymatic degradation of HA took off the protective capping, then NIR irradiation and acidic pH further enhanced the DOX release. Later, Timin et al. [13] designed a hybrid inorganic/organic capsules enabling multimodal triggering by physical (UV light, ultrasound) and chemical (enzymatic treatment) stimuli. The UV- and ultrasound response was achieved by a synergetic combination of TiO_2 and SiO_2 nanostructures which were in situ deposited into the polymer shell of microcapsules during sol-gel synthesis. At the same time, these hybrid capsules were consisted of degradable polypeptides and polysaccharides and thus could

be decomposed in response to enzymatic reaction. Most recently, our group [14] designed and prepared a triple-stimuli (reduced GSH, pH and light irradiation) responsive system based on cerium oxide nanoparticles (CeO_2 NPs) coated mesoporous silica nanoparticles (MSNs). Upon entering into cancer cells, both high concentration of intracellular GSH and low pH environment would reduce CeO_2 NPs to cerium ions, accompanied with the degradation of CeO_2 NPs and the conformational change of HP under light irradiation, the pore entrances were re-exposed and preloaded DOX are thus released from the nanocarrier, resulting in a contrast fluorescence enhancement. Meanwhile, 10_2 generated from HP for potential photodynamic therapy (PDT) upon light irradiation. In comparison, not much influence can be observed for normal cells.

Conclusion

Although multi-stimuli-responsive DDSs are remarkably superior over other DDSs for drug delivery, there also exist drawbacks currently limiting their practical application in the clinical setting. To realize their real applications in human bodies in future, several points need to be taken into consideration. First of all, enhancing the biodegradability of DDSs. Biodegradation should not only modulate the release of drugs for a desired period of time, but also enable the removal of the empty DDS after drug release. Secondly, making the size of DDSs less than 200nm in diameter. The ability to configure dimensions can facilitate cellular uptake of DDSs through a receptor-mediated endocytosis to cross cell membranes, thus significantly increasing their circulation time in blood. Thirdly, prolonging circulation in the bloodstream by surface modification of the DDSs, which will enhance the deliverable capability of DDSs to the diseased site, thus reducing the side effects.

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Conflict of Interest

The authors declare no competing economic interests.

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