MEDDOCS Open Access Publisher

Journal of Nanomedicine

Open Access | Review Article

Application of responsive nano-drug delivery system in cancer therapy

***Liqun Yang*[1]*; *Zhipeng Hou*[2]**

[1]*Key Laboratory of Reproductive Health and Medical Genetics, National Health and Family Planning Commission, China*

[2]*Center for Molecular Science and Engineering, College Liqun Yang of Science, Northeastern University, China*

***Corresponding Author (s): Liqun Yang,**

Liqun Yang, Key Laboratory of Reproductive Health and Medical Genetics, National Health and Family Planning Commission, China

Email: yanglq@lnszjk.com.cn

Received: Dec 8, 2017

Accepted: Feb 20, 2018

Published Online: Mar 02, 2018

Journal: Journal of Nanomedicine

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Nano-drug delivery system; pH-responsive; Light-responsive; Temperature-responsive; Magnetic-responsive; Enzyme-responsive.

Abstract

In recent years, responsive nano-drug delivery systems have been extensively studied for cancer therapy due to their enhanced permeability and retention effect. In this review, we discuss recent advances in the development of responsive nano-drug delivery systems that are able to control drug biodistribution in response to specific stimuli, either exogenous (variations in temperature, magnetic field or light) or endogenous (changes in pH or enzyme concentration).

Introduction

As the most important and common treatment in cancer therapy, chemotherapy still faces many challenges such as poor tumor selectivity and multidrug resistance. In recent years, nanomedicine delivery systems have provided the new strategies to many limitations of conventional chemotherapy [1]. Nano-drug delivery systems have greater potential for multiple targeting functionalization, in vivo imaging, combined drug delivery, and other aspects compared to the traditional drug delivery systems [2]. Targeting drug delivery systems are driven by the incorporation of stimuli-responsive materials, enabling them to bypass the biological barrier and achieve targeted intracellular drug delivery [1]. Stimuli-responsive nano-drug delivery systems typically have two constructional approaches: one is that the nanocarrier material itself has a stimulus-responsive property and the other is stimuli-responsive group or molecule to modify the surface of the nanomaterial. A large variety of nanomaterials could respond to physical stimuli, chemical stimuli or biological stimuli. Herein we select several common response factors combined with specific examples to make a review and outlook of nano-drug delivery system in cancer therapy.

Responsive nano-drug delivery systems

Among these response materials, the pH-responsive materials are widely designed for use in nanomedicine delivery systems in cancer therapy. It is well known that many chemical bonds are not stable in strong acid or base systems. Based on this feature, pH-responsive polymers with acid-labile chemical bonds are usually designed to remain stable at physiological pH, but they will quickly degrade in the weak acid environment of tumor tissue resulting in drug targeting release. And these polymers ensure to retain their pH responsiveness after incorporation into nanostructures [2].

Cite this article: Yang L, Hou Z. Application of responsive nano-drug delivery system in cancer therapy. J Nanomed. 2018; 1: 1005.

Tu et al. developed a pH-responsive drug delivery system by PEGylating commercially available aliphatic dendritic polyester Boltorn H40. Based on its amphiphilic structure, the resulting star copolymer (H40-star-mPEG) with a hydrophobic H40 core and multiple hydrophilic mPEG arms self-assembles into a stable micelle in aqueous solution. The experimental results show that the drug release rate of DOX loaded micelles is greatly increased in acidic environment [3]. Heffernan et al. used a novel hydrophobic polymer-poly (1, 4-phenyleneacetone dimethylene ketal) (PPADK), which contains ketal bonds in its backbone to make polyketal nanoparticles. Under acidic conditions, the nanoparticles are hydrolyzed to low molecular weight hydrophilic compounds and the encapsulated therapeutic agent is released at an accelerated rate [4]. In addition, there is an interesting strategy for drug delivery under acidic condition [4]. Ke et al. incorporated sodium bicarbonate and anticancer drug (DOX) into PLGA hollow microspheres (HMs) by a double emulsion method. In an acidic environment, $NaHCO_3$ reacts with hydrogen ions to form CO_2 bubbles. The enlargement of the volume leads to the rupture of the microsphere wall and the rapid release of anticancer drugs [5].

When light strikes the material, it transfers some of the energy to the irradiated material, which can be used to change the polarity, structure, and configuration of the chemical bond, triggering the drug release mechanism. The general design idea is to passivate the target molecule with a photoactive protecting group, and the material undergoes photolysis reaction after light irradiation to activate the target molecule to complete the drug release. Karthik and coworkers constructed light-responsive nano-drug delivery systems using two new components: fluorescent carbon dots and a quinoline based photo trigger. They have developed fluorescent carbon dots tethered to a quinoline based photo trigger for regulated delivery of anticancer drugs. The photo regulated drug release ability of Qucbl-Cdots has been established by means of periodic exposure to light and dark conditions. Furthermore, Qucbl-Cdots were readily internalized inside the HeLa cells and showed precise control over the drug release to kill the cancer cells upon irradiation. However, the use of Qucbl-Cdots in in vivo studies is limited due to their absorbance below 500 nm [6].

When the temperature of the system changes, it can cause varieties in the volume, solubility and configuration of the temperature-sensitive material to trigger drug release. Temperature-responsive microgels were synthesized with poly N-isopropylmeth acrylamide (PNIPMAM; transition temperature=44 °C) as shell and with poly N-isopropylacrylamide (PNIPAM; transition temperature=34 °C) as core by Berndt and his copartners, and the response temperature can be adjusted by changing the shell /core mass ratio. The effect of mass ratio on the thermal behavior of spherical core-shell microgels was investigated [7].

Of course, it is also possible to control the targeted release of magnetic nanoparticles in the tissues of the patient through an external magnetic field. Magnetic drug delivery materials are usually made of metal or metal oxide nanoparticles, with organic substances such as fatty acids, polysaccharides or polymers wrapped to improve colloidal stability [8]. Ye et al. encapsulated inorganic imaging agents of super paramagnetic iron oxide nanoparticles (SPION), manganese-doped zinc sulfide (Mn: ZnS) quantum dots (QDs) and the anticancer drug busulfan in PLGA nanoparticles by an emulsion-evaporation method. Then the PLGA nanovesicles were prepared and the vesicles were used as nano-drug systems for anticancer drug delivery. Also, the degradation property of PLGA vesicles was investigated in vitro researches and the vesicle delivery ability to anticancer drugs was evaluated by in vivo animal experiments. The delivery system has high entrapment efficiency and sustained drug release capacity for lipophilic drug busulfan. Preliminary conclusions have been drawn that the delivery system has high encapsulation efficiency and sustained drug release capacity for lipophilic drug busulfan [9].

Enzyme response is the most common in biological stimulation. Enzyme-responsive nano-drug delivery systems are catalyzed and degraded by enzymes of specific tissues or cells (Eg tumor cells) upon entry into the human body, thereby triggering the release of the entrained drug. It can also serve to enhance the efficiency of drug delivery and reduce side effects. Thornton et al. attached the oppositely charged peptide chains to the polyethylene acrylamide gel particles. Enzymes can cleave peptide chains from gel particles on gel particles when the gel encounters thermophilic protease. The negatively charged portion of the peptide chain is cut off, leaving the cationic portion of the gel particles make a positive charge on the whole. The role of the same type of charge repulsion makes the gel burst to release the drug loaded [10].

Recent studies on dual-response nano-drug delivery systems have been increasingly available. Synergy between the two response stimuli allows for more precise regulation of the site and dose of drug release. Jaber and coworkers reduced the particle size of the nanometer drug $H_3PMo_{12}O_40$ to 15 nm by solvothermal method and synthesized Fe3O4 @SiO_2/poly (N-isopropylacrylamide) as a magneto caloric nanocarrier for the $H_3PMo_{12}O_40$ nano-drug. Then the release behavior of H3P-$Mo_{12}O_40$ nano-drug on the thermal response carrier was investigated in the AC magnetic field. The effects of drug particle size, loading and release medium temperature on the drug release were investigated. It can be concluded with the magnetic field strength, temperature and drug loading increased, the drug release rate would increase [11].

Challenges and Future Prospects

With the deepening of research on cancer therapy of nano-drug delivery system, it has been possible to achieve the targeted control of anticancer drugs, combined administration and prolongation of circulation time. This effectively reduces the damage caused by chemotherapy and traditional modes of administration to the human body and has broad application prospects in the field of biomedicine. However, most of the delivery systems still remain in the experimental phase. Such as the biocompatibility of nanocarrier materials, the toxicity of degradation products to human beings and the irreversibility of response process are all the problems to be solved. Thus, there is still a long way to go from the experimental stage to the clinical testing to the final popularization and application. Even so, nanomedicine delivery systems will certainly make even more major breakthroughs with the development of nanotechnology and biomedical technologies and the cross-cutting assistance in various academic fields.

Acknowledgements

This work was supported by was supported by the National Key R&D Program of China (2016YFC1000902), the National Science Foundation of China (51503093) and the Shenyang Science and Technology Bureau (F16-205-1-37).

Figures

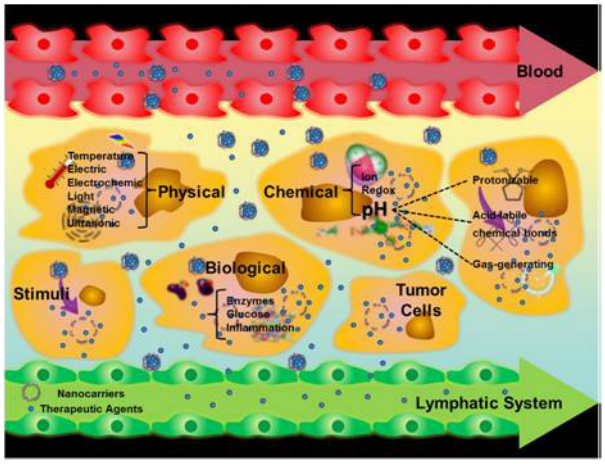

Figure 1: Nanocarriers enhance the permeability and retention of drugs in tumors. The figure shows the different stimuli that can be used to trigger drug-release from appropriately responsive materials in tumor cells.

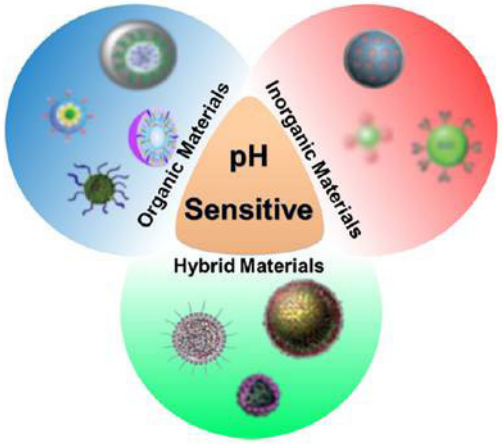

Figure 2: The three different classes of pH-sensitive nanomaterials for drug delivery in cancer research

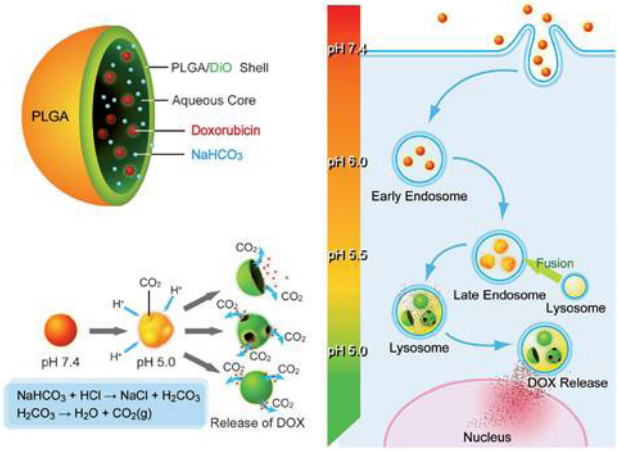

Figure 3: Schematic illustration of the structure of a PLGA hollow microsphere containing doxorubicin and the mechanism of drug release (left), as well as the intracellular trafficking and release of the drug from the pH-responsive microspheres(right).

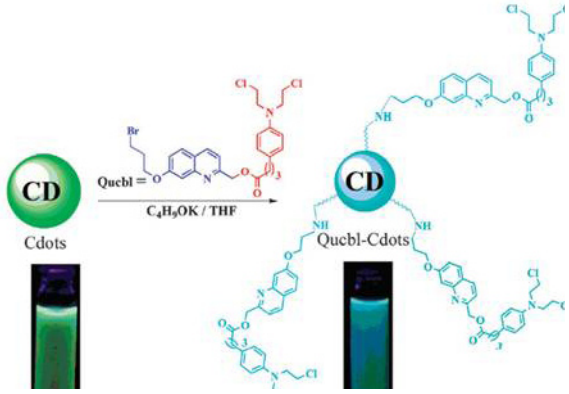

Figure 4: Synthesis of quinoline-chlorambucil loaded carbon dots (Qucbl-CDs).

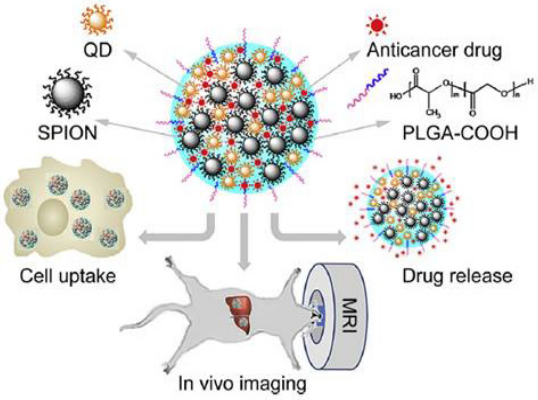

Figure 5: Schematic diagram showing the composition of PLGAeSPIONeMn: ZnS nanoparticles and their multiple applications.

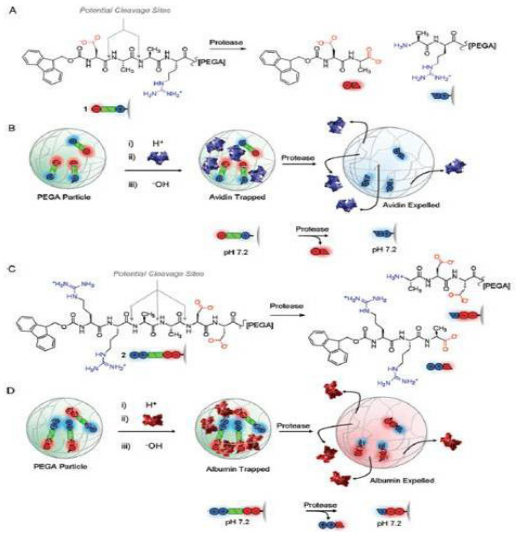

Figure 6: A) SThe peptide designed for the release of positively charged proteins was comprised of Fmoc–aspartatic acid–alanine–alanine–arginine, where the amide bond between the two alanine residues is particularly liable to cleavage by our target enzyme. B) Generation of positive charges by enzymatic cleavage of the bond between alanine residues allows protein molecules to diffuse through the polymer pores for payload release. C) Peptide designed for the release of negatively charged protein molecules. Two N-terminal arginine units are separated from two aspartic acid groups by two alanine residues. A single net negative charge remains on the particle following enzymatic hydrolysis. D) Exclusion of albumin from the negatively charged swollen particle occurs following hydrolysis of the bond between alanine residues.

References

1. Kanamala M, Wilson W R, Yang M, et al. Mechanisms and biomaterials in pH-responsive tumour targeted drug delivery: a review [J]. Biomaterials. 2016; 85: 152-167.
2. Liu J, Huang Y, Kumar A, et al. pH-sensitive nano-systems for drug delivery in cancer therapy [J]. Biotechnology advances. 2014; 32: 693-710.
3. Tu C, Zhu L, Qiu F, et al. Facile PEGylation of Boltorn® H40 for pH-responsive drug carriers [J]. Polymer. 2013; 54: 2020-2027.
4. Heffernan M J, Murthy N. Polyketal nanoparticles: a new pH-sensitive biodegradable drug delivery vehicle [J]. Bioconjugate chemistry. 2005; 16: 1340-1342.
5. Ke C J, Su T Y, Chen H L, et al. Smart multifunctional hollow microspheres for the quick release of drugs in intracellular lysosomal compartments [J]. Angewandte Chemie. 2011; 123: 8236-8239.
6. Karthik S, Saha B, Ghosh S K, et al. Photoresponsive quinoline tethered fluorescent carbon dots for regulated anticancer drug delivery [J]. Chemical Communications. 2013; 49: 10471-10473.
7. Berndt I, Popescu C, Wortmann F J, et al. Mechanics versus Thermodynamics: Swelling in Multiple-Temperature-Sensitive Core–Shell Microgels [J]. Angewandte Chemie International Edition. 2006; 45: 1081-1085.
8. Tietze R, Zaloga J, Unterweger H, et al. Magnetic nanoparticle-based drug delivery for cancer therapy [J]. Biochemical and biophysical research communications. 2015; 468: 463-470.
9. Ye F, Barrefelt A, Asem H, et al. Biodegradable polymeric vesicles containing magnetic nanoparticles, quantum dots and anticancer drugs for drug delivery and imaging [J]. Biomaterials. 2014; 35:3885-3894.
10. Thornton P D, Mart R J, Webb S J, et al. Enzyme-responsive hydrogel particles for the controlled release of proteins: designing peptide actuators to match payload [J]. Soft Matter. 2008; 4:821-827.
11. Jaber J, Mohsen E. Synthesis of Fe3O4@ silica/poly (N-isopropylacrylamide) as a novel thermo-responsive system for controlled release of H3PMo12O40 nano drug in AC magnetic field [J]. Colloids and Surfaces B: Biointerfaces. 2013; 102: 265-272.