ASIAN JOURNAL OF PHARMACEUTICAL SCIENCES 11 (2016) 585–595

HOSTED BY

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajps

Review

External-stimuli responsive systems for cancer theranostic

Jianhui Yao, Jingxian Feng, Jun Chen *

Key Laboratory of Smart Drug Delivery, Ministry of Education, School of Pharmacy, Fudan University, 826 Zhangheng Road, Shanghai 201203, China

ARTICLE INFO

Article history:
Received 30 March 2016
Received in revised form 13 May 2016
Accepted 3 June 2016
Available online 15 June 2016

Keywords:
Nanotechnology
Stimuli-responsive
Light
Magnetic field
Ultrasound
Theranostics

ABSTRACT

The upsurge of novel nanomaterials and nanotechnologies has inspired the researchers who are striving for designing safer and more efficient drug delivery systems for cancer therapy. Stimuli responsive nanomaterial offered an alternative to design controllable drug delivery system on account of its spatiotemporally controllable properties. Additionally, external stimuli (light, magnetic field and ultrasound) could develop into theranostic applications for personalized medicine use because of their unique characteristics. In this review, we give a brief overview about the significant progresses and challenges of certain external-stimuli responsive systems that have been extensively investigated in drug delivery and theranostics within the last few years.

1. Introduction

Based on advances in nanotechnologies and insight into the pathology of cancer at the cellular and molecular levels, a large sum of well-tailored nanoscale carrier platforms have been developed such as liposome, dendrimer, polymer nanoparticle and inorganic nanoparticles made of iron oxide, quantum dots, gold or other metal frameworks. (Fig. 1)

Nanotechnologies hold numerous advantages in drug delivery field including their ability to incorporate payloads with different solubility into carriers [1], improve the *in vivo* pharmacokinetic (PK) process of drugs [2], enhance their stability and longevity in the blood circulation with or without additional structure modifications [3] and modify the carriers with targeting ligands on their surface for tissue or cell-specific delivery to minimize side-effects [4]. Among myriads of successful applications, stimuli-responsive "smart" nanocarriers have emerged as a promising nanotechnology in comparison with conventional nanoscale materials as a result of their unique stimuli-responsive nature. In addition, compared with various internal cues in the microenvironment of cancer, triggers from outside offered better spatially and temporally controllable features for activation and release of the loaded cargoes.

* *Corresponding author.* Key Laboratory of Smart Drug Delivery, Ministry of Education, School of Pharmacy, Fudan University, 826 Zhangheng Road, Shanghai 201203, China. Tel.: +86 021 51980066; fax: +86 021 51980066.
E-mail address: chenjun@fudan.edu.cn (J. Chen).

http://dx.doi.org/10.1016/j.ajps.2016.06.001

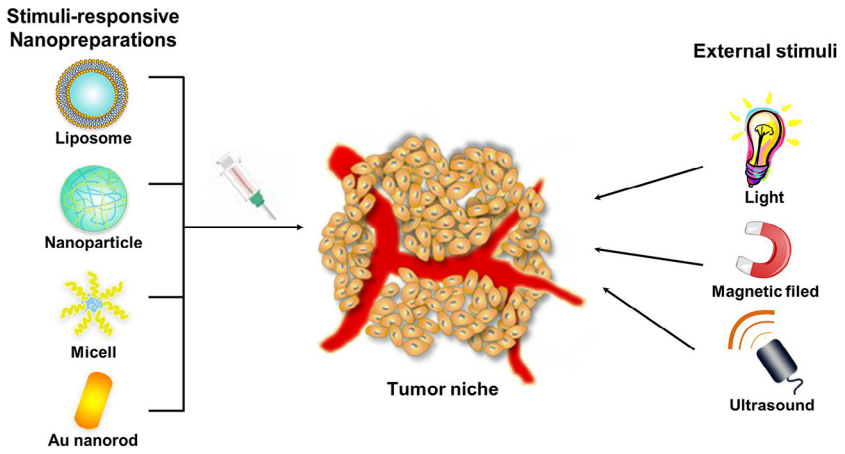

Fig. 1 – Schematic illustrations summarized various external stimuli employed for responsive nanosystems following systemic administration of different nanopreparations.

This review aims to discuss such novel nanomaterials that can be responsive to external stimuli, which have been exploited for cancer therapy and simultaneously can be used for diagnosis. In the interest of brevity, this review does not elaborate equally important internal stimuli and other fields that have not been widely studied yet, thus, the external stimuli we single out are light, magnetic field and ultrasound. Not only can they be used for fabricating stimuli-responsive systems but can potentially integrate therapy and imaging into single platform for theranostic applications which indicate a promising future in the forthcoming personalized medicine.

2. General concepts of stimuli-responsive system

The working mechanisms of stimuli-responsive systems are always alike: after injecting intravenously (or other administration mode like intraperitoneal injection), nanocarriers would leak through neovascular and accumulate at the tumor lesion via passive targeting (enhanced permeability and retention effect) or active targeting (i.e. based on the receptor-ligand affinity principle, exploiting folic acid-modified nanocarriers to actively bind to folic acid receptor over-expressed tumor cells so that could improve nanocarriers accumulation in tumor site), then, delivery systems can be activated by single or several specific triggers from inner or outer body and release the bioactive cargoes in the intended sites.

Specific triggers could be roughly divided into two categories: The first part is termed “intrinsic-stimuli” since they are local stimuli within the tumor microenvironment. As sophisticated as tumor, the microenvironment of pathological site have certain peculiar attributes compared with healthy one and these peculiarities could be used to design internal-stimuli sensitive delivery system. For example, pH-sensitive nanocarries have been applied continually to construct responsive systems for drug delivery since they can stabilize the integral particle at physiological pH during circulation in vasculature but release payloads while the system reaching tumor site and triggered by the lower pH value of the tumor microenvironment [5]. Thus the payloads just release specifically within the tumor site and reduce the unwanted side effect [6]. Other intrinsic stimuli such as temperature, redox, and enzyme activity have been exploited extensively in biomedical research as well.

There are a number of other parameters beyond the inner body which are termed as “external stimuli” including magnetic fields, ultrasound, light, etc. Compared with the “internal-stimuli” that make use of characteristics within tumor microenvironment like lower pH value, higher temperature as mentioned above, the external stimuli responsive systems could intrinsically or introduce contrast agents to visualize the accumulation of nanoparticles in the target tissues, cells or organelles and then activate the nanocarriers out of body by light or other triggers at desired time. Therefore, the controlled release is more spatiotemporal and has higher potential for clinical applications.

All in all, the primary principles of responsive delivery system could be described as follow: upon exposing to specific stimuli from the interior or exterior, their chemical composition or physical structure would undergo a given transformation that induces the release of payloads or activation of prodrugs and reacting in a controllable way.

3. Light responsive systems

Since 1994 the first photosensitizer has been approved by the U.S. Food and Drug Administration (FDA), and the advent of photo-responsive therapy has made an inspiring impact on the field of cancer therapy owing to its non-invasiveness and spatiotemporally controllable ability.

Once exposed to irradiation in specific wavelength range directly, photosensitizer molecules would absorb the energy from light and turn into highly unstable state, then transfer energy to surrounding oxygen molecules, generate reactive oxygen species (ROS) to damage nearby biomolecules, or convert absorbed energy into heat, raising local temperature [7] or the energy would be released by emitting photons that possess