Acta Pharmacologica Sinica (2017) 38: 735–737
 1671-4083/17
www.nature.com/aps

Editorial

Cancer nanobiotechnolgy

Yong-zhuo HUANG*, Ya-ping LI

Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

Acta Pharmacologica Sinica (2017) 38: 735–737; doi: 10.1038/aps.2017.48

Advanced drug delivery techniques have been applied in cancer therapy to improve treatment outcomes and reduce adverse effects, and already achieved promising progress. In particular, nanobiotechnology plays an increased important role in combating cancer. Nano drug delivery systems can improve the pharmacokinetics profiles and tumor biodistribution of the antitumor drugs and their intracellular delivery; in addition, the drug instability and water insolubility problems can be solved by encapsulation into the nano systems.

Ideal delivery of antitumor drugs should maximize drug accumulation at tumors while minimize the unwanted drug exposure to normal tissues, thus executing cytotoxicity specifically in cancer cells and sparing normal cells[1]. In the recent decades, nanotechnology-based targeting delivery has been generally believed as the most promising method to achieve this ultimate goal of pharmacotherapy. The nano drugs make use of the enhanced permeability and retention (EPR) effect, with the tendency to accumulate more in tumors owing to their leaky vasculature and poor lymphatic drainage than in normal tissues, a so-called passive targeting phenomenon. The EPR effect, however, remains wide variation among different tumor models and different stages of the cancer progression[2]. Therefore, active targeting strategies have been employed to further improve the tumor delivery efficiency.

There are three major strategies commonly applied for active targeting. One is modification of the nanosystems with targeting ligands that can specifically bind with the overexpressed receptors on the tumor cell membrane. Peptide ligands have been widely used in tumor-targeting nano drug delivery due to their superiority in several aspects compared to the antibodies, as summarized in Ham and Shin's article[3]. First, the relatively small size that is favorable for retaining the bioactivity of the modified drugs (especially the protein drugs); second, availability of multivalency; third, reduced antigenicity. Shin's work was to fuse the tumor-homing F3 peptide to the protein toxin gelonin to increase the tumor uptake. Zhang and Wu *et al*[4] developed a dual-targeting hybrid nanoparticles for codelivery of doxorubicin (DOX) and mitomycin C (MMC). The polymer-lipid hybrid nanoparticles were modified by the $\alpha_v\beta_3$ integrin-binding RGD peptide, thus achieving a from-tissue-to-cell dual targeting, because both the angiogenic tumor vascular endothelium and invasive breast cancer cells overexpress $\alpha_v\beta_3$ integrin. Sun and Huang *et al*[5] designed a from-cell-to-mitochondria dual-targeting delivery system by using the G13-C12 peptide targeting galectin-3 that is highly expressed on the PC-3 human prostate cancer cells and then redistributes to the mitochondria. Kang and Huang *et al*[6] used the mannose-mediated tumor targeting liposomes for overcoming drug-resistant colon cancer. They discovered that the drug-resistant HCT8/T cancer cells and tumor tissues highly expressed mannose receptors (CD206), which thereby could serve as a potential target for tumor drug delivery.

Another strategy is to design a tumor microenvironment-responsive nanosystem by which drug release or activation is site-specific. The tumor microenvironment is a promising target for drug delivery, in which the acidic pH, elevating redox, and upregulated proteases are the most commonly used stimuli for triggering cellular uptake, drug release, or reactivation. MW Chen and coworkers[7] applied the redox-responsive micelles consisting of the α-tocopheryl succinate-based polyphosphoester copolymers with disulfide linkage for tumor cell-preferential release of PTX. The dissociation of micelles resulted in release of α-tocopheryl succinate that is an inhibitor of P-glycoproteins, thereby facilitating reversal of PTX resistance. Wang and Li *et al*[8] used the versatile disulfide cross-linked micelles (DCMs) platform to develop the nano-formulations of docetaxel and bortezomib (DTX-DCMs and BTZ-DCMs) for combination therapy.

In addition, the tumor microenvironment-responsive designs can develop into a macromolecular prodrug strategy for improving tumor-specific action. Cheetham and Cui *et al*[9] described a protocol for molecular design and synthesis of the self-assembling peptide-drug amphiphiles containing the redox-cleavable disulfide bonds, and revealed the significant influence of the number of the conjugated drug molecules and

*To whom correspondence should be addressed.
E-mail yzhuang@simm.ac.cn

the peptide sequence on the formation of the self-assembly nanostructure. Sun and Li *et al*[10] developed a redox-responsive polymeric prodrug system for programmable codelivery. The lipophilic immune checkpoint inhibitor NLG919 molecules were conjugated with the hydrophilic polymer via redox-sensitive linkage, thus forming the polymeric micelles. The physically encapsulated DOX was released rapidly once entering the tumor cells, while the covalently linked NLG919 was cleaved from the polymeric backbone in response to the elevating levels of GSH at a relatively slow rate. Lee and Kim *et al*[11] reported a facilely prepared formulation of nano self-assembly for polymer-DOX delivery. The pPBA-DOX nanocomplex was not only sensitive to the acidic pH, triggering DOX release via the low pH-hydrolyzed phenylboronic ester bond. Of interest, the PBA moiety could interact with the sialylated epitope in cancer cells, enabling the ligand-mediated uptake. Moreover, the pPBA bears strong negative charge that facilitates the prolonged circulation half life and thus promote EPR effect-associated passive targeting.

The third one is to use the physical targeting methods (eg, external magnetic guidance and ultrasound). Cui and Wang *et al*[12] prepared a magnetic PLGA nanoparticles modified with transferrin, in which the superparamagnetic nanoparticles and PTX were co-encapsulated. Dual targeting delivery can be achieved under the magnetic field direction and transferrin receptors-mediated specific uptake by the cancer cells. Photodynamic/photothermal therapy can also be considered as a physical targeting method because a photosensitizer or a photothermal agent is inactive unless triggering by laser. Shim and Oh *et al*[13] used the claudin 4-binding peptide-modified graphene oxide nanosheets, on which the photosensitizer chlorin e6 was loaded onto the nanosheets via interaction with the claudin 4-binding peptide. The combination therapy can be carried out via the graphene-induced photothermal effect and chlorin e6-induced ROS production.

Moreover, the application of cancer vaccination and tumor imaging and diagnosis has also been included in this thematic issue. A recombinant vaccine consisting of an immune-tolerant elastin-like polypeptides, iTEPs, and the CTL peptide antigen was characterized by the self-adjuvant function and was able to induce strong antigen-specfic CTL response, as reported by MN Chen's group[14]. Chen and Cai *et al*[15] introduced an intrinsic radiolabeling technique for preparing the ^{45}Ti-mesoporous silica nanoparticles ([^{45}Ti]MSN) based on the strong interaction between ^{45}Ti and the deprotonated silanol groups (-Si-O-). The PEGylated [^{45}Ti]MSN showed the promise in PET imaging.

Drug resistance and metastasis are the major formidable hurdles against effective therapy. Nanotechnology-based delivery strategy for combating drug resistance and metastasis has attracted great attention, and become a spotlight topic. There are four articles addressing the hurdles in this thematic issue[4, 6, 7, 16]. For example, Zhong and Zhang *et al*[16] reported that the cabazitaxel-loaded polymeric micelles were efficiently delivered to the tumor sites, resulting in a 71.6% inhibition of tumor growth and a 93.5% reduction of lung metastases.

Last but not least, in this thematic issue, we include five review articles to address the cutting-edging topics of cancer nanotechnology. Shim and Oh *et al*[17] gave an up-to-date summary on a star technology — gene editing and the key issues of CRISPR/Cas9 delivery strategies, as well as the regulatory perspective for gene editing-based therapy and its translation from bench to bedside. Luan and Sun *et al*[18] outlined the application of the engineering exosomes as delivery carriers. Qian, Shen and Gu *et al*[19] provided a comprehensive review on the conjugated polymer nanomaterials for *in vivo* imaging, photo-based therapy, and drug delivery. Mangal and Zhou *et al*[20] addressed the nanotechnology-based pulmonary delivery for lung cancer chemotherapy, revealing the promise of local delivery via inhalation routes for providing high drug accumulation in lung while reducing the systemic drug exposure. Wu and Wang *et al*[21] described the recent advances in peptide nucleic acid (PNA) biotechnology for cancer detection and therapy, and introduced the nanoparticulate PNA for drug delivery.

Researches on cancer nanotechnology have been booming in the past two decades. Nanomaterials and nanosystems have been widely applied in a broad spectrum of oncology. However, considering the complication of the *in vivo* environments and dynamics, it is still not much known about the nano delivery mechanisms and bio-interfacial interaction between the nano drugs and the body at either cellular or tissue level. Therefore, the mechanistic interpretation will promote the clinical translation in cancer therapy.

The traditional Chinese Dragon Boat Festival is around the corner. We thus select a cover with illustration of dragon boats, representing the drug-loaded carriers for tumor targeting delivery. Happy Dragon Boat Festival!

References

1 Huang Y, Jiang Y, Wang H, Wang J, Shin MC, Byun Y, *et al*. Curb challenges of the "Trojan Horse" approach: Smart strategies in achieving effective yet safe cell-penetrating peptide-based drug delivery. Adv Drug Deliv Rev 2013; 65: 1299–315.

2 Prabhakar U, Maeda H, Jain RK, Sevick-Muraca EM, Zamboni W, Farokhzad OC, *et al*. Challenges and key considerations of the enhanced permeability and retention effect for nanomedicine drug delivery in oncology. Cancer Res 2013; 73: 2412–7.

3 Ham SH, Min KA, Shin MC. Molecular tumor targeting of gelonin by fusion with F3 peptide. Acta Pharmacol Sin 2017; 38: 897–906.

4 Zhang T, Prasad P, Cai P, He C, Shan D, Rauth AM, Wu XY. Dual-targeted hybrid nanoparticles of synergistic drugs for treating lung metastases of triple negative breast cancer in mice. Acta Pharmacol Sin 2017; 38: 835–47.

5 Sun W, Li L, Li LJ, Yang QQ, Zhang ZR, Huang Y. Two birds, one stone: dual targeting of the cancer cell surface and subcellular mitochondria by the galectin-3-binding peptide G3-C12. Acta Pharmacol Sin 2017; 38: 806–22.

6 Kang XJ, Wang HY, Peng HG, Chen BF, Zhang WY, Wu AH, Xu Q, Huang YZ. Codelivery of dihydroartemisinin and doxorubicin in mannosylated liposomes for drug-resistant colon cancer therapy. Acta Pharmacol Sin 2017; 38: 885–96.

7 Chen FQ, Zhang JM, Fang XF, Yu H, Liu YL, Li H, Wang YT, Chen MW. Reversal of paclitaxel resistance in human ovarian cancer cells with

redox-responsive micelles consisting of α-tocopheryl succinate-based polyphosphoester copolymers. Acta Pharmacol Sin 2017; 38: 859–73.

8 Wang XS, Kong DJ, Lin TY, Li XC, Izumiya Y, Ding XZ, Zhang L, Hu XC, Yang JQ, Gao SG, Lam KS, Li YP. A versatile nanoplatform for synergistic combination therapy to treat human esophageal cancer. Acta Pharmacol Sin 2017; 38: 931–42.

9 Cheetham AG, Lin YA, Lin R, Cui H. Molecular design and synthesis of self-assembling camptothecin drug amphiphiles. Acta Pharmacol Sin 2017; 38: 874–84.

10 Sun JJ, Chen YC, Huang YX, Zhao WC, Liu YH, Venkataramanan R, Lu BF, Li S. Programmable co-delivery of the immune checkpoint inhibitor NLG919 and chemotherapeutic doxorubicin via a redox-responsive immunostimulatory polymeric prodrug carrier. Acta Pharmacol Sin 2017; 38: 823–34.

11 Lee J, Kim J, Lee YM, Park D, Im S, Song EH, Park H, Kim WJ. Self-assembled nanocomplex between polymerized phenylboronic acid and doxorubicin for efficient tumor-targeted chemotherapy. Acta Pharmacol Sin 2017; 38: 848–58.

12 Cui YN, Xu QX, Davoodi P, Wang DP, Wang CH. Enhanced intracellular delivery and controlled drug release of magnetic PLGA nanoparticles modified with transferrin Acta Pharmacol Sin 2017; 38: 943–53.

13 Shim G, Kim MG, Jin H, Kim J, Oh YK. Claudin 4-targeted nanographene phototherapy using a *Clostridium perfringens* enterotoxin peptide-photosensitizer conjugate. Acta Pharmacol Sin 2017; 38: 954–62.

14 Dong S, Xu T, Wang P, Zhao P, Chen M. Engineering of a self-adjuvanted iTEP-delivered CTL vaccine. Acta Pharmacol Sin 2017; 38: 914–23.

15 Chen F, Valdovinos HF, Hernandez R, Goel S, Barnhart TE, Cai W. Intrinsic radiolabeling of Titanium-45 using mesoporous silica nanoparticles. Acta Pharmacol Sin 2017; 38: 907–13.

16 Zhong T, He B, Cao HQ, Tan T, Hu HY, Li YP, Zhang ZW. Treating breast cancer metastasis with cabazitaxel-loaded polymeric micelles. Acta Pharmacol Sin 2017; 38: 924–30.

17 Shim G, Kim D, Park GT, Jin H, Suh SK, Oh YK. Therapeutic gene editing: delivery and regulatory perspectives. Acta Pharmacol Sin 2017; 38: 738–53.

18 Luan X, Sansanaphongpricha K, Myers I, Chen H, Yuan H, Sun D. Engineering exosomes as refined biological nanoplatforms for drug delivery. Acta Pharmacol Sin 2017; 38: 754–63.

19 Qian CG, Chen YL, Feng PJ, Xiao XZ, Dong M, Yu JC, Hu QY, Shen QD, Gu Z. Conjugated polymer nanomaterials for theranostics. Acta Pharmacol Sin 2017; 38: 764–81.

20 Mangal S, Gao W, Li T, Zhou QT. Pulmonary delivery of nanoparticle chemotherapy for the treatment of lung cancers: challenges and opportunities. Acta Pharmacol Sin 2017; 38: 782–97.

21 Wu JC, Meng QC, Ren HM, Wang HT, Wu J, Wang Q. Recent advances in peptide nucleic acid for cancer bionanotechnology. Acta Pharmacol Sin 2017; 38: 798–805.