Acta Pharmaceutica Sinica B 2022;12(9):3453−3455

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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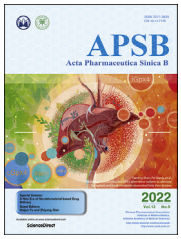

Editorial of Special Column on A New Era of Nanobiomaterial-based Drug Delivery

In the present era of nano/biomaterials, nanosized drug delivery systems (NDDS) have been extensively contributed to the advancement of nanomedicine[1]. Fundamental research is carried out on a diverse range of nano-biomaterials, such as liposomes, dendrimers, micelles and so on. However, nanobiomaterial-based delivery systems yet need to be further optimized to achieve convincing therapeutic performance[2]. Several approaches are underway to improve the targeting and tumor-penetrating potential of nanomaterials. Nanomedicine's delivery pathways into tumors in the context of tumor heterogeneity are of particular importance[3−5]. To systematically summarize the field and update the cutting-edge advances, this special column entitled 'A New Era of Nanobiomaterial-based Drug Delivery' is focused on emerging approaches and technologies to improve the performance of nanobiomaterial-based drug delivery systems for the treatment of various diseases, in particular cancer, autoimmune and infectious diseases.

Early and accurate delineation of tumor boundary are crucial in predicting patient survival rates and evaluating tumor microenvironment responses to radiation therapy and chemotherapy in both preclinical and clinical settings. In this collection, Wu et al.[6] discussed the strategies for accurately delineating tumor boundaries with chemotherapeutic nanomaterials. This review article would provide novel insights for delineating tumor boundaries and elongating survival rates of cancer patients via chemotherapeutic nanomedicine.

In the research study by Yang et al.[7], a tentative drug- or photosensitizer-free strategy was demonstrated by employing enzymatic self-assembly of the F-pY-T peptide. Upon dephosphorylation catalyzed by alkaline phosphatase overexpressed on cancer cells, the F-pY-T peptide sequence self-assembled to form nanoparticles, which were subsequently internalized. These peptide nanoparticles triggered ICD and elicited antitumor immune response by inducing mitochondria oxidative stress and generating reactive oxygen species in the tumor cells. The peptide nanoparticles were further combined with programmed death ligand 1 (PD-L1) blockade therapy.

Given the breakthrough of mRNA vaccines against COVID-19, lipid nanoparticle (LNP)-based drug delivery systems have become the most clinically advanced non-viral nanotechnology to deliver various biopharmaceutics including proteins, peptides and nucleic acids. To prompt the advance of LNP-based nanovectors, Xu et al.[8] summarized their efforts in the design, synthesis, characterization, evaluation, and optimization of combinatorial LNPs with novel structures and properties for the delivery of small- and macromolecular therapeutics.

To initiate drug release in specific tumor sites remains a challenging puzzle. To this end, Qian et al.[9] developed a multifunctional nanoparticle system (PCRHNs) by grafting reduction-responsive camptothecin (CPT) prodrug copolymer onto the Prussian blue nanoparticles, and then modified with cRGD ligand to recognize $\alpha_v\beta_3$ integrin and hyaluronic acid to bind CD44 receptor on the surface of tumor cells, respectively. The resultant dual-targeting nanoparticles exhibited glutathione (GSH)-activatable CPT release profile and excellent photothermal conversion efficiency. Furthermore, the nanoparticles were employed for photoacoustic imaging-guided chemo-photothermal therapy of breast cancer.

Apart from photothermal ablation therapy, microwave-assistant thermal ablation has also been exploited as a common therapy for clinical treatment of hepatocellular carcinoma (HCC). However, insufficient thermal ablation can leave tumor residues to cause recurrence. To this end, Liang et al.[10], D-mannose-chelated iron oxide nanoparticles were thus designed for microwave ablation-enforced tumor-associated macrophages (TAM) repolarization and combinatory therapy of HCC. Given minimal invasiveness, controllability, high efficiency, and strong specificity of photothermal ablation, Huang et al.[11] further demonstrated the application of indocyanine green-loaded liposomal nanoparticles for PTT of retinoblastoma.

To address the immunosuppressive tumor microenvironment and the heterogeneity of the tumor cells, Zhou et al.[12] reported a hybrid bacterium with tumor targeting and penetration, TAM polarization and photothermal conversion capabilities for improving antitumor immunotherapy. The hybrid bacteria with hypoxia targeting ability can effectively accumulate and penetrate the tumor tissues, polarized TAM into M1 phenotype to reverse the immunosuppressive tumor microenvironment.

Peer review under responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2022.08.002

The occurrence of intrinsic and adaptive immune resistance is the dominant reason for immunotherapy failure. To circumvent intrinsic and adaptive resistance to cancer immunotherapy, Yu et al.[13] engineered a bispecific prodrug nanoparticle for circumventing immune evasion of the tumor cells by targeting multiple immune resistance mechanisms. The prodrug nanoparticles integrating a BRD4 inhibitor JQ1 and an indoleamine-2,3-dioxygenase 1 inhibitor NLG919 *via* glutathione-liable disulfide bond. The bispecific prodrug can restore the antitumor immunity by abolishing inducible PD-L1 expression with JQ1 and suppressing tryptophan consumption with NLG919 in the tumor microenvironment.

Glioblastoma (GBM) is a primary aggressive brain tumor with high recurrence rate. The poor efficiency of chemotherapeutic drugs crossing the blood−brain barrier (BBB) is well-known as one of the main challenges for anti-glioma therapy. TAMs in glioma further thwarts the drug efficacy. To take the advantages of liposomes and solid nanoparticles, Li et al.[14] developed a lipid-small molecule hybrid nanoparticle (LPHNPs) for imaging and treatment in an orthotopic GBM tumor model. LPHNPs remarkably improved the drug-loading capacity and formulation stability against the physical encapsulation using conventional liposomes. LPHNPs display minimal system toxicity, enhanced potency of photodynamic therapy and visualization capacities of drug biodistribution and tumor imaging. Furthermore, the hybrid LPHNPs nanoparticle demonstrates excellent curative effects to significantly prolong the survival of mice with the orthotopic glioma, validating the potential of hybrid LNP system to improve drug delivery efficacy and potentiate cancer therapy.

To circumvent immunosuppressive microenvironment in GBM, Gao et al.[15] further reported a proteolytic targeting chimera (PROTAC)-integrated and substance peptide-modified nanotherapeutic. The PROTAC nanoparticles could target GBM by penetrating BBB and degrade bromodomain-containing protein 4 (BRD4) target. The nanoparticles regressed glioma tumor growth by inducing tumor cell apoptosis and modulating TAM-involved immune suppressive tumor microenvironment. To migrate adaptive cancer immune resistance of GBM, Xu et al.[16] reported a dual-targeting nanotheranostic for second near-infrared (NIR-II) fluorescence imaging-guided photo-immunotherapy of GBM.

Lysyl oxidase (LysOX) has been recently identified to play important role in the pathological processes of several acute and chronic neurological diseases. In the research study contributed by Luo et al.[17] demonstrated that LysOX promotes ferroptosis-associated lipid peroxidation in neurons *via* activating extracellular regulated protein kinase (ERK)-dependent 5-lipoxygenase (Alox5) signaling. Pharmacological inhibition of LysOX with β-aminopropionitrile (BAPN)-loaded amorphous calcium carbonate nanocarriers significantly blocks seizure-induced ferroptosis and thereby alleviates neuronal damage.

Helicobacter pylori accounts for global infection rate over 50%, and represents formidable challenges in clinical therapy due to its complex pathological microenvironment *in vivo*. To improve the eradication efficacy, Hu et al.[18] developed a versatile RHL/Cl-Ch-cal nanovesicle integrating cholesterol-PEG, calcitriol and antibiotic clarithromycin for multi-targeted therapy of *H. pylori* infection.

Mucosal vaccines can induce innate and adaptive immune response at the mucosal site to defense microbial infection and transmission. In the review article by Wang et al.[19] summarized the characteristics of mucosal barriers for effective mucosal vaccine delivery. The authors further discussed the strategies to overcome the mucosal barriers for engineering mucosal vaccines.

Finally, we would like to express our sincere gratitude to all the eminent contributors, who have made such significant contributions to this special column in *Acta Pharmaceutica Sinica B*, and would also like to extend our gratitude to all the peer-reviewers for their insights and thoughtful comments, which significantly improved the quality of this column. We also want to express our deep gratitude to Zi-Jie Liu for her remarkable efforts to coordination and the handling of this special column. It is our hope that all of the articles in this special column will be found helpful and useful to both established and new investigators in the field of nanomedicine and drug delivery.

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