Acta Pharmaceutica Sinica B 2020;10(11):2016–2017

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

Acta Pharmaceutica Sinica B

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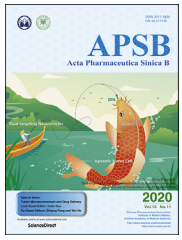

Editorial of Special Issue on Tumor Microenvironment and Drug Delivery

Drug delivery to treat cancer has attracted considerably and increasingly high attention. Several drug delivery systems are available in the market and many other promising candidates are currently under investigation[1]. However, the complex tumor microenvironment greatly influences drug delivery efficiency of these systems to tumors, while the tumor microenvironment can be leveraged to design smart drug delivery systems for improving tumor drug delivery. Therefore, knowledge about the tumor microenvironment and its impact to tumor drug delivery are critically important for improving the drug delivery efficiency to tumors.

In the theme issue, named tumor microenvironment and drug delivery, there are several original researches, reviews and letters in the area. As the guest editors, we would like to appreciate *Acta Pharmaceutica Sinica B* for providing us the opportunity to share the information and thank all authors for their contributions to this special issue.

Tumor microenvironment has several distinct characters, such as dense stroma, irregular vascular structure and many supporting cells, such as tumor associated macrophage (TAM) and cancer-associated fibroblasts[2]. TAM plays an important role in the tumor microenvironment. Han et al.[3] discussed the complex function and macrophages in tumor, and then summarized prospective macrophage-focused therapeutics strategies. Huang and Hu[4] focused on desmoplastic tumors with abundant stromal cells and extracellular matrix. They reviewed the latest advances in natural products inhibiting desmoplastic tumors by modeling CAF and highlighted their potential therapeutic capabilities for cancer treatment. Li et al.[5] summarized the function of tumor vasculature and the immune-vascular crosstalk in tumors. Then they proposed strategies towards tumor vascular normalization. Hypoxia and high level of hydrogen peroxide (H_2O_2) are characterized in the tumor microenvironment and they are significant obstacles for cancer therapy. Catalase, an antioxidant enzyme, allows for degradation of endogenous H_2O_2 and the resultant tumor reoxygenation. Zhang et al.[6] designed a deep-penetrated nanocatalase by coating catalase nanoparticles with PEGylated phospholipids membrane, aiming to alleviate tumor hypoxia and promote chemo-photodynamic therapy. Based on excessive hydrogen peroxide at tumor microenvironment and acidic microenvironment, Pan and Quan et al.[7] present a core–shell dual metal organic frameworks system loaded photosensitizer indocyanine green and chemotherapeutic agent doxorubicin for photothermal/photodynamic/chemotherapy.

Despite recent exciting advances in cancer therapy, the complicated immunosuppressive tumor microenvironment still impedes the clinical successes of currently available immunotherapy. In this regard, Pang and colleagues[8] highlighted the current understanding of the immunosuppressive tumor microenvironment and reviewed the emerging nanotechnology-related strategies to modulate the immunosuppressive cells within the tumor immune microenvironment for robust immunotherapeutic responses. Li and Burgess[9] discussed the main components of the biological microenvironment and the immunological microenvironments in tumors and highlighted recent advances in nanoparticle drug delivery systems towards targets within the tumor microenvironment to enhance cancer chemotherapy and immunotherapy. Hu et al.[10] were concentrated on relapse of acute myeloid leukemia (ALL) after allogeneic hematopoietic stem cell transplantation (allo-HSCT). They reviewed currently available and promising upcoming agents targeting leukemia cells and immune microenvironment for prevention and treatment of ALL relapse after allo-HSCT therapy. Primary bile acids could trigger natural killer T cell-based immunotherapy for liver cancer, but their application is restricted by the abundant expression of receptors across the gastrointestinal tract. Song et al.[11] developed nanoemulsion-loaded obeticholic acid for precisely manipulating liver sinusoidal endothelial cells and triggering natural killer T cell mediated cancer immunotherapy. As a result, the nanoemulsion successfully suppressed hepatic tumor growth and increased natural killer T cell populations inside tumor.

Metastasis is one of the leading causes of death. Hu et al.[12] first summarizes the targeting delivery strategies, including primary tumor targeting drug delivery, tumor metastasis targeting drug delivery and hijacking circulation cells. Then, as a promising treatment, the application of immunotherapy in tumor metastasis treatment is introduced, and strategies that stimulating immune response are reviewed, including chemotherapy, photothermal

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.2020.11.017

therapy, photodynamic therapy, ferroptosis, sonodynamic therapy, and nanovaccines.

The binding of ligand modified nanoparticles is affected by the microenvironment of tumor cells. Fluidic shear stress, which exists in blood circulation, may be a critical factor for binding with flowing tumor cells. Zhang et al.[13] developed dual-targeting nanovesicles with different $\alpha v\beta 3$-binding rates to achieve a "fast-binding/slow-unbinding" function. The dual-targeting nanovesicles showed efficient cellular uptake and antitumor effect both for static and dynamic tumor cells. In tumor metastasis mice model and leukemia mice model, the drug-loaded dual-targeting vesicles showed higher therapy efficacy than single-targeting ones. Zhang and Fu et al.[14] developed a locally injectable thermo-sensitive hydrogel using poly (*N*-iso-propylacrylamide-*co*-acrylic acid)-*g*-F68 copolymer to continuously release a Chinese medicine, triptolide, over time and kill the cancer cells *via* a "two-strike" effect. Conjugation of antibodies to drug carriers enables specific cancer targeting, however, the antigen recognition is always orientation-dependent. By using a molecular engineering technique, Oh and Shin et al.[15] developed a site-specifically anti-body-modified nanoparticles for target cell uptake and cancer therapy.

Tactical nanoparticle drug delivery systems are very promising to delivery gene products to cancer cells based on the difference between cancer and healthy cells. Therefore, Flavia C. Zacconi et al.[16] reviewed the recent advances in lipids- and polymers-based nanoparticles for siRNA delivery to the cancer cells and provided the necessary information about siRNA development.

We hope this theme issue would provide valuable information for readers to realize the complex functions of tumor microenvironment and the influence on drug delivery and tumor treatment. The focus on tumor microenvironment may provide new idea and strategy to improve tumor therapy.

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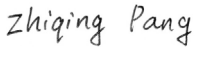

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