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EDITORIAL

Editorial of the special column on nanomedicines for tumor microenvironment modulation

The disease microenvironment describes the dynamic biological space surrounding diseased tissue or cells during the development and progress of a certain disease, which includes specific pH, enzymes, cytokines, extracellular matrix and stroma cells. In the past decade, disease microenvironment has been widely utilized as target or stimuli for specific drug delivery, for example, the enzyme- and pH-responsive tumor targeting delivery[1]. In recent years, researchers have paid more and more attention on the function of microenvironment in the development and progress of diseases, which could also act as a therapeutic target. Nanomedicines can specifically deliver one or several drugs into the diseased site, control the release of drugs in target cells or matrix, thus modulate the disease microenvironment, providing a new direction for the disease treatment[2]. Therefore, this thematic column focuses on the microenvironment of various diseases, and nanomedicines for microenvironment modulation to treat diseases.

Tumor immunosuppressive microenvironment greatly restricts the antitumor immunotherapy. Wang's goup[3] focuses on the abnormal glucose metabolism of tumor, summarize the complex interaction between tumor glucose metabolism-specifically metabolite transportation, glycolysis processes, and the immune microenvironment, and review the nanomedicine strategy to reprogram tumor glucose metabolism for enhancing immunotherapy. Among the modulating strategies, the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas (CRISPR-associated proteins) technology is one of the most powerful tools to directly modulate genome of target cells. Gong's group[4] provides a comprehensive overview of the development of CRISPR systems, vector technologies, and their applications in disease treatment, while also address the challenges encountered in clinical settings.

Except the reviews, several researchers report cutting-edge strategies to modulate microenvironment for tumor treatment. Zhang's group[5] reported a lipid-based CaO_2 and glucose oxidase loaded nanoparticle to disrupt calcium homeostasis and interfere with glycometabolism, thus successfully enhance tumor immunogenic cell death and boost antitumor immunotherapy. Ma and Peng's group[6] reported a metal sulfide of FeS and GSDMD plasmid coloaded nanoformulation to dual activate immunogenic PANoptosis and ferroptosis, as well as reprogram immunosuppressive effects *via* H_2S amplification, which significantly reshapes the immunosuppressive microenvironment and enhances antitumor immunotherapy with good metastasis inhibition. Pang and Peng's group[7] developed a pH-sensitive polycationic polymer-modified lipid nanoparticles system for the intravenous delivery of cyclic dinucleotides (CDN), enhanced the accumulation of CDN within the tumor, spleen, and tumor-draining lymph nodes, thus boosting the STING pathway of dendritic cells and repolarizing pro-tumor macrophages. Sun and Zhu's group[8] developed a glutathione-responsive nanoparticle to silence protein tyrosine phosphatase nonreceptor type 2 (PTPN2) and enhance immunotherapy efficacy by enhanced antigen presentation, increased T cell activation and M1-like polarization of macrophages. Xie and Jin's group[9] reported a submicronsized 4T1 cell membrane hybrid recombinant staphylococcal enterotoxin C2 (rSEC2) and paclitaxel dual-loaded liposomes, which can be delivered to lung metastasis for immunosuppressive microenvironment reversion and tumor cell apoptosis induction.

The microenvironment modulation strategy could also be used for other disease treatment. Chen's group[10] developed PD-1 bispecific killer cell engagers (BiKEs) to deplete activated immune cells expressing PD-1, and hence treat autoimmune diseases. Jiang, Sun and Luo's group[11] designed three self-degradable "gemini-like" ionizable lipids for the lipid nanoparticles preparation and siRNA delivery. After optimization, the mannose-modified LNPs effectively deliver siRNA to liver for the acute liver injury (ALI) and non-alcoholic steatohepatitis (NASH) treatment. Gao and Fu's group[12] developed an immunosuppressant TREM2-lowing antisense oligonucleotides (ASOs) and resveratrol co-loaded cationic liposome with acid-cleavable blood−brain barrier targeting peptide and microglia targeting peptide modification for Alzheimer's disease treatment, which could effectively

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restore the immune function of microglia and mitigate the immune stimulation to microglia. Similarly, Zhang and Gao's group[13] reported α-mangostin and β-site APP cleaving enzyme 1 (BACE1) siRNA coloaded lactoferrin-functionalized lipid nanoparticles to reprogram microglia and protect neurons, resulting in good Alzheimer's disease treatment outcome.

In summary, nanomedicine is a powerful tool for the disease microenvironment modulation and disease treatment. The deeply understanding of function of microenvironment in disease development may provide new target for nanomedicine design and disease treatment.

References

1. Xu Y, Xiong J, Sun X, Gao H. Targeted nanomedicines remodeling immunosuppressive tumor microenvironment for enhanced cancer immunotherapy. *Acta Pharm Sin B* 2022;**12**:4327−47.
2. Liu R, Luo C, Pang Z, Zhang J, Ruan S, Wu M, et al. Advances of nanoparticles as drug delivery systems for disease diagnosis and treatment. *Chin Chem Lett* 2023;**34**:107518.
3. Jiang C, Tang M, Su Y, Xie J, Shang Q, Guo M, et al. Nanomedicine-driven tumor glucose metabolic reprogramming for enhanced cancer immunotherapy. *Acta Pharm Sin B* 2025;**15**:2845−66.
4. Xu Y, Le H, Wu Q, Wang N, Gong C. Advancements in CRISPR/Cas systems for disease treatment. *Acta Pharm Sin B* 2025;**15**:2818−44.
5. Peng Q, Li X, Fang C, Zhu C, Wang T, Yin B, et al. Disrupting calcium homeostasis and glycometabolism in engineered lipid-based pharmaceuticals propel cancer immunogenic death. *Acta Pharm Sin B* 2025;**15**:1255−67.
6. Luo Y, Linghu M, Luo X, Li D, Wang J, Peng S, et al. Remodeling tumor immunosuppressive microenvironment through dual activation of immunogenic panoptosis and ferroptosis by H_2S-amplified nanoformulation to enhance cancer immunotherapy. *Acta Pharm Sin B* 2025;**15**:1242−54.
7. He Y, Zheng K, Qin X, Wang S, Li X, Liu H, et al. Intravenous delivery of STING agonists using acid-sensitive polycationic polymer-modified lipid nanoparticles for enhanced tumor immunotherapy. *Acta Pharm Sin B* 2025;**15**:1211−29.
8. Wang F, You H, Liu H, Qi Z, Shi X, Jin Z, et al. Silencing PTPN2 with nanoparticle-delivered small interfering RNA remodels tumor microenvironment to sensitize immunotherapy in hepatocellular carcinoma. *Acta Pharm Sin B* 2025;**15**:2915−29.
9. Yuan B, Zhang F, Yan Q, Wang W, Li Z, Du L, et al. Submicron-sized superantigen biomimetic liposomes with highly efficient pulmonary accumulation to remodel local immune microenvironment for cancer chemoimmunotherapy. *Acta Pharm Sin B* 2025;**15**:2900−14.
10. Naatz L, Dong S, Evavold B, Ye X, Chen M. Bispecific killer engager for targeted depletion of PD-1 positive lymphocytes: a new avenue for autoimmune disease treatment. *Acta Pharm Sin B* 2025;**15**:1230−41.
11. Wang Q, Wan B, Feng Y, Yang Z, Li D, Gao Y, et al. Self-degradable "gemini-like" ionizable lipid-mediated delivery of siRNA for subcellular-specific gene therapy of hepatic diseases. *Acta Pharm Sin B* 2025;**15**:2867−83.
12. Wei Y, Xia X, Wang X, Yang W, He S, Wang L, et al. Enhanced BBB penetration and microglia-targeting nanomodulator for the two-pronged modulation of chronically activated microglia-mediated neuroinflammation in Alzheimer's disease. *Acta Pharm Sin B* 2025; **15**:1098−111.
13. Xu Y, Ye X, Du Y, Yang W, Tong F, Li W, et al. Nose-to-brain delivery of targeted lipid nanoparticles as two-pronged β-amyloid nanoscavenger for Alzheimer's disease therapy. *Acta Pharm Sin B* 2025;**15**: 2884−99.

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