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Nanoengineered Immune Niches for Reprogramming the Immunosuppressive Tumor Microenvironment and Enhancing Cancer Immunotherapy

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Cancer immunotherapies that harness the body's immune system to combat tumors have received extensive attention and become mainstream strategies for treating cancer. Despite promising results, some problems remain, such as the limited patient response rate and the emergence of severe immune-related adverse effects. For most patients, the therapeutic efficacy of cancer immunotherapy is mainly limited by the immunosuppressive tumor microenvironment (TME). To overcome such obstacles in the TME, the immunomodulation of immunosuppressive factors and therapeutic immune cells (e.g., T cells and antigen-presenting cells) should be carefully designed and evaluated. Nanoengineered synthetic immune niches have emerged as highly customizable platforms with a potent capability for reprogramming the immunosuppressive TME. Here, recent developments in nano-biomaterials that are rationally designed to modulate the immunosuppressive TME in a spatiotemporal manner for enhanced cancer immunotherapy which are rationally designed to modulate the immunosuppressive TME in a spatiotemporal manner for enhanced cancer immunotherapy are highlighted.

1. Introduction

Cancer immunotherapy has emerged as a potential *fifth therapeutic pillar*, along with chemotherapy, surgery, radiotherapy, and other targeted cancer treatments. Immunotherapy activates the innate and adaptive immune systems to cure diseases with the important features of potency, specificity, and memory.[1] By targeting the immune system instead of the tumor itself, cancer cells can be precisely recognized and destroyed in an antigen-specific manner. The most impressive characteristic of this therapy is that a long-term response can be realized through the memory of immune cells without collateral damage. One major breakthrough in *cancer immunotherapy* occurring in the past few decades was the development of chimeric antigen receptor (CAR) T cells via genetic modification of a patients' own *T cells* to specifically target tumor antigens.[2] This treatment has achieved prolonged complete remission and survival in patients with certain types of cancer.[3] In addition, immune checkpoint blockade (ICB) has demonstrated a notable long-term survival benefit in cancer patients with many types of solid tumors.[4] However, in spite of the astonishing results achieved to date, some problems remain unsolved, such as the limited number (≈20%) of patients responding to such treatments and the emergence of severe treatment-associated adverse effects.[1a,5] Additionally, increasing antitumor effector T-cell (T_{eff}) quality or quantity alone does not always correlate with treatment outcome.[6]

The tumor microenvironment (TME) is a determinant factor of the anticancer response and can confer resistance to immunotherapy. Tumors gradually develop several mechanisms to escape immune surveillance by a process called cancer immunoediting, which exerts a selective pressure in the TME, leading to tumor progression.[7] In recent years, several studies and clinical trials have attempted to target tumor escape pathways to completely eradicate malignant cells.[8] Overcoming obstacles in the suppressive TME is of vital importance for both delivering therapeutic agents and reviving T cell–based treatment. Therefore, modulating or reprogramming the immunosuppressive milieu is becoming fundamental for further enhancing the efficacy of cancer immunotherapy. There have been several good reviews of nanomaterial applications in cancer immunotherapy; however, they have mainly focused on the functional enhancement of antigen-presenting cells (APCs) or T cells.[9] Herein, we highlight recent advances in the reprogramming of the immunosuppressive TME with nanotechnology for improving cancer immunotherapy. We first review representative mechanisms that limit the global application of cancer immunotherapy. We then discuss the approaches studied to overcome the current limitations.

In this manuscript, the authors defined "nanoengineered immune niches" as the nanotechnology-based delivery or depot platforms of immunomodulatory drugs that target and reprogram the original TMEs for enhanced antitumor immunity.[10] With the better understanding of tumor microenvironment, synthetic nanoengineered immune niches have been developed, which involved interdisciplinary fields like cancer immunology, molecular biology, bioengineering, nanotechnology, and material science to optimize the therapeutic potential and reduce

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for modern cancer therapy. Although the major breakthroughs in *cancer immunotherapy* are ICB-based treatment and CAR T-cell therapy, the patient response rates to such creative treatments remain modest. Several preclinical studies and clinical trials have directed more attention toward the TME, which promotes various types of immunosuppressive factors to limit the therapeutic efficacy. Thus, smart strategies for modulating the TME to repolarize the immunosuppressive microenvironment toward one supporting antitumor immunity will be key technologies for overcoming the limitations of current immunotherapy. Combinations of ICB agents with other therapeutic modalities (e.g., cancer vaccines, chemotherapy, and radiation therapy) to modulate both immunostimulation and immunosuppression have generated good clinical outcomes. However, both the specificity and toxicity of combination therapeutic interventions also require consideration prior to successful clinical translation. In this respect, the spatiotemporal modulation of multiple arms of the immune response using robust and versatile engineered nano-biomaterial platforms is expected to inhibit the activities of immunosuppressive cells and to increase the activities of effector immune cells in a more precise manner, while minimizing the cytotoxic effects. In this progress report, we reviewed several nanoengineered immune niches that could enhance the therapeutic efficacy of cancer immunotherapy by utilizing the nanotechnology-based advantages in offering easy surface modifications with targeting ligands, efficient uptake by specific immune cells, and efficient delivery of immunologically active components to target sites. To enhance immunogenicity of tumors to antitumor immunity, the development of nanomaterials that can provide efficient delivery of tumor-specific antigen (i.e., neoantigens) and adjuvant or ICD inducers should be accomplished.[32–34,39] In the future, the tumor-specific antigen and immunomodulatory drugs targeting the suppressive factors can be loaded into the nanoengineered immune niches, based on the precise analysis of tumor cells and immunosuppressive factors in TME of cancer patient. By loading two or more immunomodulatory drugs targeting different protumoral signaling pathways in TME into these nanodelivery systems, synergistic effects of each therapeutic modality could be obtained. Although the combination approaches have shown enhanced therapeutic efficacy, a lot of side or toxic effects were also observed.[97,113] Therefore, the precise dose, order of treatment, and the administration routes should be carefully considered in the design of nanoengineered immune niches to maximize therapeutic outcomes, while minimizing cytotoxic effects. To facilitate the clinical translation of nanoengineered immune niches, it is also essential to consider key design principles with regard to material composition, in vivo degradation, and final fate of NPs to investigate the safety of these approaches, as well as controllable, reproducible, and scalable NP synthesis. Moreover, a well understanding of nano–bio interactions, systemic transport, and targeting of NPs to the TME will contribute to more safer and efficacious nanotherapeutics.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

antitumor immunity, cancer immunotherapy, immunosuppression, nanoengineered immune niches, tumor microenvironment

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