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Gemini nanoparticles-based quadruple therapy (GNQT) achieved effective tumor immunotherapy by comprehensive regulation of tumor microenvironment

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ABSTRACT

Even though immune checkpoint blockade (ICB) therapy has advanced cancer immunotherapy greatly due to its quick development, and scientists have also tried a variety of combination therapies to further amplify the therapeutic impact, the therapeutic outcome is still limited because of the complex immunosuppressive microenvironment of tumor tissue. To improve the antitumor effect of immunotherapy, developing more comprehensive and effective tumor microenvironment regulation strategy is necessary. In this work, we prepared Gemini NPs composed of drug-loaded nanoparticles DI NPs (Doxorubicin and Ibrutinib were simultaneously encapsulated by PLG-*g*-mPEG) and gene-loaded nanoparticles PPD NPs (pSpam1 and pshPD-L1 were simultaneously encapsulated by PEI1.8k-RT), and proposed a Gemini nanoparticles-based quadruple therapy (GNQT). Compared with triple therapy and four-drug combination therapy, GNQT demonstrated comprehensive modulation of the tumor microenvironment and had exceptional anticancer ability in melanoma model without obvious toxicity. In addition, by establishing a persistent immunological memory effect, GNQT could also successfully prevent tumor lung metastasis in mice. The GNQT proposed here provided new insights into tumor immunotherapy and had important implications for the research of preclinical antitumor immunotherapy.

Introduction

Cancer immunotherapy is a powerful tumor treatment strategy that has developed rapidly after traditional treatment methods such as radiotherapy and chemotherapy, shifting the paradigm for the development of tumor treatment strategy [1–7]. Cancer immunotherapy aims to control and eradicate tumors through activating or boosting the body's own immune system [1–4]. Although the rapid development of ICB therapy has brought great progress in cancer immunotherapy, and various combination therapies have been developed to further improve the therapeutic effect, the objective response rate of tumor patients is still limited [8–13]. Exploring the reasons for the low response rate of the body to immunotherapy and formulating more effective combination therapy strategies will bring benefits to more cancer patients.

The antitumor immune response can be roughly divided into the following steps: the release and presentation of tumor antigens, the education and activation of T cells in the draining lymph nodes, blood circulation-mediated invasion of T lymphocytes into tumor tissue, the distinct identification and elimination of tumor cells by T lymphocytes [14]. In these processes, antigen-presenting cells and tumor-infiltrating T lymphocytes play irreplaceable roles. However, to our knowledge, in immunosuppressive tumor microenvironment, the lack of immunogenicity and danger signals make it difficult for dendritic cells (DCs) to be recruited to tumor tissues and initiate immune cycles, and there are usually only few tumor-infiltrating T lymphocytes in most tumor types (for example, B16F10 melanoma) [15–18]. Besides, another challenge is the strong extracellular matrix (ECM) of tumor cells, which prevents medicines and immune cells from penetrating tumor tissues [19,20]. Even worse, suppressive

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