Degradation-Regulatable Architectured Implantable Macroporous Scaffold for the Spatiotemporal Modulation of Immunosuppressive Microenvironment and Enhanced Combination Cancer Immunotherapy

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The presence of immunosuppressive cells such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) in residual tumors after surgery is known to be related to high recurrence of tumors which are more resistant to therapeutic interventions compared with the primary ones. Herein, a degradation-regulatable architectured implantable macroporous scaffold (Dr-AIMS) is designed to control the immunosuppressive tumor microenvironments (TMEs) as well as to activate T-cell-based antitumor immunity. The Dr-AIMS is fabricated by the combination of stable “bulk” material (methacrylate-modified hyaluronic acid) and hydrolytic-labile “sacrificing” component (methacrylate-modified oxidized hyaluronic acid) with varied blending ratios such that the degradation can be regulated from 10 to 28 days in vivo. The Dr-AIMS is loaded with PTX (depleting cancer cells and TAMs), R837 (activating antigen presenting cells and inhibiting MDSCs functions) and combined immune checkpoint blockade molecules (anti-CTLA-4 and anti-OX40 mAbs, invigorating T cells function) and is implanted as postsurgical treatment in 4T1 breast tumor model. In vivo results suggest the sustained and localized supply of immunomodulatory drugs from Dr-AIMS facilitates the depletion of MDSCs and M2-like macrophages simultaneously within the tumor tissues, enhances the infiltration of DCs and effector T cells into tumor, and systemic antitumor immunity is generated with reduced dose.

1. Introduction

Surgical resection still remains as the most common and effective therapeutic intervention for patients with solid tumors, and half of the cancer patients choose surgery as a cure strategy.[1] However, the residual or incompletely removed tumor cells after surgery always result in relapse and poor outcomes.[2] Cancer immunotherapy, explored as an alternative modality to eradicate tumor lesions by enhancing host immune system, has recently been emerged and developed rapidly with outstanding clinical benefits.[3] Since immunotherapy showed promising results in several types of cancers (e.g., melanoma, non–small cell lung cancer, esophageal carcinoma, and hepatocellular carcinoma) when treating minimal tumor burden, postoperative cancer immunotherapy seems to be appealing for the treatment of residual tumors.[4] However, the low-response rate of cancer immunotherapy in solid tumor patients should be explained by the impaired trafficking and expansion of effector lymphocytes in the tumor microenvironments (TMEs).[5] Heterogeneous immunosuppressive cell types, such as myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Treg) in tumor tissues inhibited the efficiency of cancer vaccines and the lytic activities of effector T cells for eliminating neoplastic cells.[6] Irrespective of whether the suppression activity requires cell-cell contacts or regionally secreted molecules, the immunosuppressive cells should be regulated locally to avoid the unwanted systemic side effects.[7] Moreover, dose-dependent systemic toxicities of chemotherapeutic drugs, immune-stimulating molecules, and immune checkpoint blockade molecules have been observed in clinical practices. Emphasized by recent studies, local immunomodulation seems to induce more efficient therapeutic effects, even with low-dose treatments, while systemic administration requires increased drug doses for enhancing the treatment efficacy that ultimately result in systemic toxicity.[8] Several research studies managed to acquire systemic anticancer responses by delivering immune modulators intratumorally with 10-fold lower doses compared to intravenous or intraperitoneal administration.[9] However, repeated and frequent drug administration remain a challenging problem.

Recently, the use of scaffolds as localized drug delivery platforms has been explored to enhance the therapeutic potential of chemotherapeutic drugs, vaccines and adoptive cell transfer as well.[10] Specifically, biodegradable and biocompatible materials have been attracted as promising sources for scaffold fabrication because