Modular nanomaterials for instructing therapeutic immune responses against cancer and autoimmune disease

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ABSTRACT SUMMARY

Cytokines and cell-based immunotherapies have shown significant early clinical promise in the treatment of both pathologic tolerance and cancer. For example, IL-2 therapies have shown benefit in the treatment of both metastatic melanoma as well as type 1 diabetes. However, a review of the literature shows that two factors are driving a significant unmet need in the clinical use of immunotherapies. First, the toxicities of cytokine therapies are often exacerbated by the need for frequent/high dosing due to short half-lives and serum protease-mediated degradation. Second, cancer and inflammatory microenvironment can thwart a therapeutic immune response by a number of mechanisms. Here we present two case examples supporting the use of rationally engineered biodegradable nanomaterials for in vivo modulation of immune responses in vivo against cancer and for induction of tolerance in autoimmune disease.

INTRODUCTION

In immune competent individuals, antigen-specific CD4+ T lymphocytes play a critical role in the immune system’s ability to discriminate between “self” and “non-self” – these cells help maintain the balance between tolerance to host tissues versus immunity against foreign pathogens. Naïve CD4+ T cells are quiescent until activation occurs through the interaction of cognate antigen with the T-cell receptor (TCR). Newly activated lymphocytes then develop along discriminatory pathways of differentiation to become either immune effector or immune suppressor cells. The phenotypic outcome is regulated by the T cell microenvironment, which includes: the strength of TCR signaling, concurrent binding of co-stimulatory or inhibitory ligands, and the composition of the cytokine milieu. CD4+ T cells therefore represent an intriguing checkpoint for therapeutic intervention: cellular differentiation and subsequent immune function can be controlled by manipulation of these signaling pathways. Specifically, the cytokine milieu has been shown to be critical for orchestration of lineage development towards effector T cell (Teff) or regulatory T cell (Treg) phenotypes. There already exists an unmet need for technologies to improve the delivery of drugs and cytokines and a number of strategies are currently under investigation. Modular nanosystems that can both deliver to target cells and provide a favorable microenvironment for therapeutic immune responses to develop represents an innovative approach to directly improve the efficacy of clinically-relevant therapies. Here we discuss two examples demonstrating the promise of these tools for immunotherapy.

EXPERIMENTAL METHODS

The tools we use are biodegradable nanoparticles composed of lipids or fatty acids on the surface and Polyethylene glycol-Poly(lactide) polymers cores. These are established clinical polymers that can be loaded with a variety of cytokines or drugs and surface-
Activation of immunity in Cancer[1]: We evaluated the effects of IL-2 and TGF-β antagonist monotherapies to enhance the antitumor responses against B16 melanomas. For these studies weekly intratumoral administration of soluble SB alone failed to delay tumor growth[1]. A similar null effect was observed when both soluble SB and IL-2 were co-administered in weekly doses (Fig. 2a). The nanolipogel encapsulated SB administered individually (nLG-SB) significantly delayed tumor growth resulting in mice with smaller tumors after one week of therapy (Fig. 2b). Although nanolipogel encapsulated IL-2 administered individually (nLG-IL-2) did not significantly delay tumor growth (Fig. 2a), the tumor masses at one week were significantly smaller than tumors obtained from mice in the control group (Fig. 2b). These results are in accord with prior studies demonstrating the efficacy of sustained release of either IL-2 or small molecules inhibiting TGF-β signaling over pulses of these agents for enhancement of antitumor response. When comparing all treatment groups, the most striking and significant reduction in both tumor growth rate and survival was observed in the mice receiving simultaneous sustained delivery of TGF-β inhibitor (SB) and IL-2 (Figs. 2a and 2c)[1].

CONCLUSION
Our working hypothesis is that nanomaterials can be used to target specific immune cell subsets and provide the appropriate microenvironment for continued tolerance in autoimmunity or immune activation in cancer. Towards addressing this hypothesis, developed promising tools that can function as stimulating or tolerogenic agents for cytotoxic lymphocytes and as agents that inhibit the tumor microenvironment’s ability to suppress the immune response.

REFERENCES