Deep TLR Primed™ T cells induce potent anti-tumor activity without systemic toxicity

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Deep TLR Primed™ T cells induce potent anti-tumor activity without systemic toxicity

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Abstract

TLR7 agonists have been shown to augment immune responses in the tumor microenvironment (TME). The agonist work primarily through two mechanisms: antigen presenting cell (APC) engagement and enhancement followed by T cell co-stimulation.1-3 However, multiple TLR agonists, including TLR7/8 agonists, have displayed considerable toxicities upon systemic administration.4 To circumvent this problem, we developed a T cell mediated delivery system of TLR agonists that can target the TME and lymphoid organs to maximize efficacy while avoiding systemic toxicities. Torque’s Deep-Primed™ T cell technology enhances T cell function by tethering immune modulators to the T cell before adoptive cell transfer (ACT), and by using Torque’s multi-targeted T cell (MTC) platform that primes the T cells against multiple tumor antigens. Herein, we screened several liposomal formulations containing different TLR7 agonists for both in vitro agonist loading and release in mouse and human T cells followed by in vivo testing in a mouse melanoma model.

Introduction

Deep TLR Agonist

Abstract

TLR7 agonists have been shown to augment immune responses in the tumor microenvironment (TME). The agonist work primarily through two mechanisms: antigen presenting cell (APC) engagement and enhancement followed by T cell co-stimulation.1-3 However, multiple TLR agonists, including TLR7/8 agonists, have displayed considerable toxicities upon systemic administration.4 To circumvent this problem, we developed a T cell mediated delivery system of TLR agonists that can target the TME and lymphoid organs to maximize efficacy while avoiding systemic toxicities. Torque’s Deep-Primed™ T cell technology enhances T cell function by tethering immune modulators to the T cell before adoptive cell transfer (ACT), and by using Torque’s multi-targeted T cell (MTC) platform that primes the T cells against multiple tumor antigens. Herein, we screened several liposomal formulations containing different TLR7 agonists for both in vitro agonist loading and release in mouse and human T cells followed by in vivo testing in a mouse melanoma model.

Results

1. TLR agonists 1 and 2 are specific for TLR7

2. Optimal liposome formulation maximizes agonist loading and extends drug release

3. Deep TLR loaded T cells retain viability and extend TLR agonist release

4. Deep TLR Primed™ T cells increase cell expansion and tumor control in vivo

Conclusions

• Torque’s Deep TLR Primed T cells released a potent small molecule agonist of TLR7 over an extended period of time.

• Two TLR7-specific agonists capable of liposome encapsulation were identified.

• Formulation optimization enabled high concentrations of two different TLR7 agonists to be loaded on both mouse and human T cells with extended release.

• The optimal liposomal formulation enabled encapsulation of high concentrations of TLR7 agonists loaded onto MTCs with minimal effect on viability and proliferative capacity.

• Deep TLR Primed T cells remain viable and release TLR agonist slowly over 10 days.

• Deep TLR Primed T cell expansion exceeds that of CD8 T cells alone or co-administered with systemic TLR7 agonist.

• ACT with Deep TLR Primed T cells provides a novel avenue to leverage the immune stimulating potential of TLR agonists for superior anti-tumor efficacy while avoiding systemic exposure and toxicities - key current bottlenecks to successful TLR therapy.

• In the future, agonist delivery via Deep-Primed™ tumor antigen-specific autologous T cells could target a wide variety of tumors and their distant metastases, enabling a new immunotherapy strategy.

References


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