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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 agonists work primarily through two mechanisms: antigen presenting cell (APC) engagement and enhancement followed by T cell co-stimulation.1-7 However, multiple TLR agonists, including TLR7/8 agonists, have displayed considerable toxicities upon systemic administration.2-4 As a result, we developed an APC mediated delivery system of TLR7 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 two 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

TLR agonists are essential components of successful cancer vaccines but have been primarily limited in safety and potency when used as single-agent immunotherapies.2,3-5-6 Tumor cells can express a wide variety of antigen-specific CD8+ T cells.

TLR agonists can be administered both systemically and locally to ensure sufficient antigenic and immune cell immune modulation at the tumor site. However, systemic delivery is often associated with toxicities that limit the potential of these molecules to be used in combination with other immunotherapies.7-8 Formulation optimization enabled high concentrations of two different TLR7 agonists, Resiquimod (R848) and Montelukast, to be loaded on both mouse and human T cells with extended release.

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 agonist 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 CDB 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 immunotherapeutic strategy.

References

3. Development D. Recent Advances in the Discovery and Delivery of TLR7 Agonists as Vaccine Adjuvants. Immunoكثريات. 2018:2 145-197

Acknowledgments

We would like to thank our Tongue colleagues for productive discussions and critiques.

B66

Presented at the 44th AACR, November 17, 2019, Boston, MA

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