DNA vaccine co-expressing Her2/ErbB2 antigen, fused with LAMP, elicits strong antitumor effects in vivo by increasing tumor infiltration with CD8+ T cells

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Abstract

DNA vaccine has emerged as an attractive immunotherapeutic approach against infectious diseases and cancer due to their fast, efficient design and validation. It remains, however, a challenge in clinical settings due to historically low levels of immunogenicity in humans.

In order to enhance the immunogenicity of DNA vaccines used as a cancer therapy, we have developed a nucleic acid platform, UNITE(TM) (Universal Intracellular Targeted Expression), which combines novel delivery methods and adjuvants that complement our lysosomal targeting technology. Fusing a tumor associated antigen (TAA) with the lysosomal Associated Membrane Protein 1 (LAMP1) -2, we can activate Ag specific CD8+ T cells by targeting the major histocompatibility complex II compartment. In this study, we selected ErbB2/Her2 as the cancer target because it is a broadly overexpressed and well-characterized oncoantigen.

Mice vaccinated with Her2-LAMP DNA demonstrate robust Her2-specific CD4+ and CD8+ T cells, in addition to antibody responses, which in turn have significant antitumor effect in murine breast and bladder tumor models. Moreover, we demonstrate that the Her2-LAMP vaccine promotes CD8+ T cell tumor infiltration to a greater degree than when compared to a traditional DNA vaccine without LAMP. In summary, we demonstrate that a UNITE(TM) nucleic acid vaccine can enhance antitumor immunity in vivo.

Introduction

• The platform of UNITE(TM)-VAX utilizes a plasmid DNA expressing TAAAs and LAMP to deliver TAAAs to the MHC II compartment, which potentially enhances both antibody generation and CD4+ T cell response.

• Based on our previous studies, we hypothesize that LAMP can rapidly prime and activate antigen-specific CD4+ T cells and these activated CD4+ T cells play an essential role for the function and infiltration of CD8+ T cells into tumor sites.

UNITE(TM) platform: Unique Mechanism of Action

A classic activation of CD4 T cells is initiated by APC cells to present Ag to MHC II molecule after taking up and processing extracellular Ag. LAMP DNA mediated activation of CD4 T cell can be achieved by APC cells processing endogenous Ag.

OVA-LAMP DNA vaccine rapidly activates Ag-specific CD4+ and CD8+ T cells in the draining LNs

LAMP DNA vaccine promotes tumor infiltration with antigen-specific CD8+ T cells

Therapeutic study: HER2-LAMP DNA vaccine significantly suppressed HER2-expressing breast tumor growth and improved survival

HER2-LAMP significantly promotes tumor infiltration with activated CD8+ T cells, upregulates T cell recruiting chemokines but also increases the expression of PD-L1

Prophylactic study: HER2-LAMP DNA efficiently protected mice from Her2-expressing breast tumor with Her2-specific T cells

Conclusions

• HER2-LAMP DNA vaccine elicits robust Her2-specific CD4+ and CD8+ T cell responses in vivo, which in turn have significant antitumor effect in murine breast tumor model.

• HER2-LAMP DNA vaccine significantly promotes tumor infiltration with activated CD8+ T cells suggesting LAMP benefits CD8+ T cell infiltration.

• The expression of PD-L1 in tumor microenvironment (TME) is upregulated with HER2-LAMP vaccine suggesting combination HER2-LAMP with PD1/L1 blockade could have the potential to increase the therapeutic effect.

References


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