International Vaccine Design Center

Division of Adjuvant Innovation (New Dimensional Vaccine Design Team)

新次元ワクチンデザイン系 アジュバント開発分野

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The laboratory is consisted of two groups working on vaccine and adjuvant lead by Ken Ishii and Jun Kunisawa, respectively to conduct novel research on vaccine immunology towards rational vaccine design. In FY 2023, we reported various papers related to immunology on vaccine and adjuvant R&D.

1. *TLR9 plus STING Agonist Adjuvant Combination Induces Potent Neopeptide T Cell Immunity and Improves Immune Checkpoint Blockade Efficacy in a Tumor Model.*

Immune checkpoint blockade (ICB) immunotherapies have emerged as promising strategies for the treatment of cancer; however, there remains a need to improve their efficacy. Determinants of ICB efficacy are the frequency of tumor mutations, the associated neoantigens, and the T cell response against them. Therefore, it is expected that neoantigen vaccinations that boost the antitumor T cell response would improve ICB therapy efficacy. The aim of this study was to develop a highly immunogenic vaccine using pattern recognition receptor agonists in combination with synthetic long peptides to induce potent neoantigen-specific T cell responses. We determined that the combination of the TLR9 agonist K-type CpG oligodeoxynucleotides (K3 CpG) with the STING agonist c-di-AMP (K3/c-di-AMP combination) significantly increased dendritic cell activation. We found that immunizing mice with 20-mer of either an OVA peptide, low-affinity OVA peptides, or neopeptides identified from mouse melanoma or lung mesothelioma, together with K3/c-di-AMP, induced potent Ag-specific T cell responses. The combined K3/c-di-AMP adjuvant formulation induced 10 times higher T cell responses against neopeptides than the TLR3 agonist polyinosinic:polycytidylic acid, a derivative of which is the leading adjuvant in clinical trials of neoantigen peptide vaccines. Moreover, we demonstrated that our K3/c-di-AMP vaccine formulation with 20-mer OVA peptide was capable of controlling tumor growth and improving survival in B16-F10-OVA tumor-bearing C57BL/6 mice and synergized with anti-PD-1 treatment. Together, our findings demonstrate that the K3/c-di-AMP vaccine formulation induces potent T cell immunity against synthetic long peptides and is a promising candidate to improve neoantigen vaccine platform.

2. *TLR4 agonist activity of Alcaligenes lipid a utilizes MyD88 and TRIF signaling pathways for efficient antigen presentation and T cell differentiation by dendritic cells.*

Alcaligenes faecalis was previously identified as

an intestinal lymphoid tissue-resident commensal bacteria, and our subsequent studies showed that lipopolysaccharide and its core active element (i.e., lipid A) have a potent adjuvant activity to promote preferentially antigen-specific Th17 response and antibody production. Here, we compared A. faecalis lipid A (ALA) with monophosphoryl lipid A, a licensed lipid A-based adjuvant, to elucidate the immunological mechanism underlying the adjuvant properties of ALA. Compared with monophosphoryl lipid A, ALA induced higher levels of MHC class II molecules and costimulatory CD40, CD80, and CD86 on dendritic cells (DCs), which in turn resulted in strong T cell activation. Moreover, ALA more effectively promoted the production of IL-6 and IL-23 from DCs than did monophosphoryl lipid A, thus leading to preferential induction of Th17 and Th1 cells. As underlying mechanisms, we found that the ALA-TLR4 axis stimulated both MyD88- and TRIF-mediated signaling pathways, whereas monophosphoryl lipid A was biased toward TRIF signaling. These findings revealed the effects of ALA on DCs and T cells and its induction pattern on signaling pathways.

Publication

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