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 led by Ken Ishii and Jun Kunisawa, advances rational vaccine design. In FY 2024, we reported various papers related to vaccine immunology, focusing on vaccines, mucosal adjuvant, and autoimmunity, contributing to safer, more effective immunotherapies and elucidating the mechanism of vaccine adjuvant.

1. 5,6-dimethylxanthenone-4-acetic acid (DMXAA), a partial stimulator of interferon gene (STING) agonist, competes for human STING activation.

We previously demonstrated that DMXAA acts as Th2 type adjuvant through IRF3-mediated innate immune activation. In addition to the adjuvant effect, DMXAA acts as anti-cancer drug through STING activation, but that effect was found in only mouse. Although DMXAA cannot fully activate human STING, DMXAA reached phase III in lung cancer clinical trials. However, the effect of DMXAA against human lung cancer is completely unknown. Here, we show that DMXAA is a partial STING agonist interfering with agonistic STING activation, which may explain its partial anti-tumor effect observed in humans, as STING was reported to be pro-tumorigenic for lung cancer cells with low antigenicity. Furthermore, we developed a DMXAA derivative-3-hydroxy-5-(4-hydroxybenzyl)-4-methyl-9*H*-xanthen-9-one (HHMX)-that can potently antagonize STING-mediated immune responses both in humans and mice. Notably, HHMX suppressed aberrant responses induced by *STING* gain-of-function mutations causing STING-associated vasculopathy with onset in infancy (SAVI) in *in vitro* experiments. HHMX treatment suppressed aberrant STING pathway activity in peripheral blood mononuclear cells from SAVI patients, and showed a potent therapeutic effect in SAVI mouse model by mitigating disease progression.

2. Tridecylcyclohexane in incomplete Freund's adjuvant is a critical component in inducing experimental autoimmune diseases.

Incomplete Freund's adjuvant (IFA) has been used for many years to induce autoimmune diseases in animal models, including experimental autoimmune encephalitis (EAE) and collagen-induced arthritis. However, it remains unclear why it is necessary to emulsify autoantigen and heat-killed *Mycobacterium tuberculosis* (HKMtb) with IFA to induce experimental autoimmune diseases. Here, we found that immunization with self-antigen and HKMtb was insufficient to induce autoimmune diseases in mice. Furthermore, IFA or one of its components, mineral oil, but not mannide monooleate, was required for the development of experimental autoimmune disease. Immunization with autoantigen and HKMtb emulsified in mineral oil facilitated innate immune activation and promoted the differentiation of pathogenic $CD4^+$ T cells, followed by their accumulation in neuronal tissues. Several water-soluble hydrocarbon compounds were identified in mineral oil. Of these, immunization with HKMtb and autoantigen emulsified with the same amount of hexadecane or tridecylcyclohexane as mineral oil induced the development of EAE. In contrast, immunization with HKMtb and autoantigen emulsified with tridecylcyclohexane, but not hexadecane, at doses equivalent to those found in mineral oil, resulted in neuronal dysfunction. These data indicate that tridecylcyclohexane in mineral oil is a critical component in the induction of experimental autoimmune disease.

3. Alcaligenes lipid A functions as a superior mucosal adjuvant to monophosphoryl lipid A via the recruitment and activation of $CD11b^+$ dendritic cells in nasal tissue.

We previously demonstrated that Alcaligenes-derived lipid A (ALA), which is produced from an intestinal lymphoid tissue-resident commensal bacterium, is an effective adjuvant for inducing antigen-specific immune responses. To understand the immunologic characteristics of ALA as a vaccine adjuvant, we here compared the adjuvant activity of ALA with that of a licensed adjuvant (monophosphoryl lipid A, MPLA) in mice. Although the adjuvant activity of ALA was only slightly greater than that of MPLA for subcutaneous immunization, ALA induced significantly greater IgA antibody production than did MPLA during nasal immunization. Regarding the underlying mechanism, ALA increased and activated $CD11b^+$ $CD103^-$ $CD11c^+$ dendritic cells in the nasal tissue by stimulating chemokine responses. These findings revealed the superiority of ALA as a mucosal adjuvant due to the unique immunologic functions of ALA in nasal tissue.

Publications

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