学 位 論 文 の 要 旨

Application of Chitosan Preparations as Vaccine Adjuvants
(キトサン製剤のワクチンアジュバントとしての応用)

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Vaccines serve as vital tools in safeguarding humans and animals against diverse pathogens. Alongside the development of antigenic forms like attenuated and subunit vaccines, adjuvants play a pivotal role in enhancing vaccine efficacy. As a novel adjuvant material, our focus lies in chitosan nanoparticle and Pickering emulsion formats, probing their potential as adjuvants in (1) mammalian and (2) fish vaccines, with the aim of advancing vaccine technology for broader biomedical and veterinary applications.

(1) Acid-responsive immune-enhancing chitosan Pickering emulsion as an adjuvant in mammalian vaccine.

Chitosan was selected as the primary material for crafting chitosan nanoparticle-stabilized Pickering emulsion (CSPE). CSPE's inherent pliability allows it to undergo stress-induced deformation upon interacting with cell membranes, mimicking the flexibility observed in natural pathogens and thus facilitating efficient cellular uptake. In the acidic environment of lysosomes, the amino groups of chitosan molecules undergo protonation, thereby increasing their solubility in water. This transition of CSPE from particle stabilization to the stabilization of polymer chains results in swelling and the accumulation of protons, ultimately leading to the rupture of lysosomes. Experimental investigations assessing CSPE's effectiveness as an adjuvant revealed its proficiency in loading antigens, promoting endocytosis, and facilitating antigen cross-presentation. Furthermore, CSPE demonstrated its capability to recruit antigen-presenting cells to injection sites and enhance T cell activation, thereby amplifying both humoral and cell-mediated immune responses. In preventive and therapeutic tumor models for lymphoma and melanoma, CSPE exhibited notable inhibition of tumor growth and prolonged survival in mice. In summary, the evasion of antigenic lysosomes facilitated by the

transition in chitosan molecular states underscores the potential of CSPE to augment cell-mediated immunity. Thus, CSPE emerges as a promising candidate for a vaccine adjuvant, offering new avenues for enhancing vaccine efficacy and therapeutic outcomes.

(2) A mass-producible oral vaccine system based on chitosan and its derivative against Vibrio anguillarum in fish.

Fish mortality resulting from pathogen infections poses significant economic challenges for aquaculture. Vaccination stands out as an effective solution, and the addition of adjuvants enhances the immune protection provided by vaccines, even when slightly weakened. Chitosan emerges as an ideal adjuvant for oral administration due to its mucoadhesive and immunomodulatory properties. In this study, we introduced a composite adjuvant formulation and developed a chitosan-based oral fish vaccine formulation conducive to mass production. Subsequently, we explored a suitable immersion challenge model for flounder, incorporating attenuated Vibrio anguillarum. Additionally, we investigated the immunoprotective effects of chitosan and its derived adjuvants. Our findings revealed that the combination of N-[(2-hydroxy-3-trimethylamino)propyl] chitosan chloride nanoparticles and sodium alginate exhibited remarkable protective effects against the immersion challenge model involving Vibrio anguillarum. This underscores the potential of chitosan-based adjuvants in enhancing immune responses and mitigating pathogen-induced mortality in aquaculture settings.