Division of Molecular Immunology

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General Summary

Our research interests have focused on the analysis of the basic immune system, which protects us from a number of diseases, and of immune disorders, such as hypersensitivity diseases and autoimmune diseases.

Research Activities

Repeated administration of interleukin 31 upregulates interleukin 31 receptor A in dorsal root ganglia and causes severe itch-associated scratching behavior in mice

We investigated the effects of repeated administration of interleukin (IL) 31 on itch-associated scratching counts (long-lasting scratching) and IL-31-related receptor messenger RNA expression in mice. Intradermal injection of IL-31 (100 and 300 ng/site) every 12 hours for 3 days significantly increased long-lasting scratching. Repeated administration of IL-31 also increased the expression of IL-31 receptor A (IL-31RA) and oncostatin M receptor beta in dorsal root ganglia (DRG). After the repeated administration of IL-31 was discontinued, IL-31RA expression decreased and reached the baseline level 2 days after the last dose of IL-31. Long-lasting scratching changed along with DRG IL-31RA expression. Moreover, IL-31-induced IL-31RA protein expression was confirmed with Western blotting analysis. These data suggest that IL-31 upregulates IL-31RA expression in DRG neuron cell bodies and that cutaneously injected IL-31-induced itching is enhanced by DRG IL-31RA expression in mice.

Evaluation of allergen-specific immune responses induced by oral immunotherapy with transgenic rice containing major T-cell epitopes of Japanese cedar pollen allergens in patients with cedar pollinosis

Oral immunotherapy with dominant T-cell epitopes is safer and more effective than conventional immunotherapy for the treatment of immunoglobulin E-mediated allergic diseases. However, for inducing oral tolerance the administration of high-dose antigens is required. Recent technical progress has allowed the production of transgenic rice that accumulates antigens at high concentrations. The aim of this study was to investigate whether oral immunotherapy with a transgenic rice seed containing a hybrid peptide (7Crp) comprising 7 human major T-cell determinants in Japanese cedar pollen allergens, Cry j 1 and Cry j 2, is safe and effective to induce oral tolerance in patients with Japanese cedar pollinosis. A blinded, randomized, placebo-controlled trial employing oral immunotherapy with 80 g of steamed pack rice for cedar pollinosis was performed for 20 weeks. Thirty subjects were enrolled and divided into 2 groups that ate transgenic rice or normal rice.

No major adverse effects were observed in either group during treatment. Allergen-specific T- and B-cell responses were evaluated. The ratio of allergen-specific T cells proliferative responses to 7Crp peptide, Cry j 1, and Cry j 2, which gradually increase in pollen season, were significantly lower in subjects who ate transgenic rice than in subjects who ate normal rice. On the other hand, the ratio of allergen-specific T cells proliferative responses to purified protein derivative antigen, which is used for the tuberculin skin test, did not differ between the groups. Furthermore, allergen-driven IL-5 and IL-13 were also significantly reduced in culture supernatants of peripheral blood mononuclear cells after subjects had eaten transgenic rice.

Adjuvant for inducing antigen-specific cytotoxic T lymphocytes via cross-presentation of cationic lipids

To elicit immune responses against tumors and viruses, vaccines that can induce antigen-specific cytotoxic T lymphocytes (CTLs) are most promising. However, administering protein antigens with commonly used adjuvants fails to induce antigen-specific CTLs. In this study, to obtain an adjuvant that could induce CTLs when protein antigens were used, we prepared cationic liposomes with dimethyldistearylammonium bromide. We assessed this adjuvant's efficacy by focusing on its activity to induce epitope-specific CTLs in mice with chicken ovalbumin protein in vivo.

This optimized adjuvant rapidly induced epitope-specific CTLs directed against protein antigens. The stability of dimethyldistearylammonium-containing liposomes was significantly improved by the addition of several reagents. In particular, the addition of some detergents improved the stability of liposomes after protein antigens and adjuvants were mixed. Furthermore, this adjuvant could efficiently induce CTLs simply by immediately being mixed with an antigen and without encapsulation. Without encapsulation, larger amounts of protein antigens were immunized than with encapsulation. The induction of CTLs was independent of Toll-like receptor ligand 2, 4, and 9 signaling and helper T cells. This adjuvant provided for strong CTL induction within 5 days in mice, and CTL induction was independent of the chicken-specific glycan structure. These induced CTLs also exhibited inhibitory effects against ovalbumin protein epitope-expressing tumors. With a single vaccine using an extract from B16 melanoma cells in conjunction with this adjuvant, melanoma growth and metastasis were significantly suppressed. Thus, this adjuvant should be useful for studies of CTL induction and for preparing T-cell vaccines against tumors with unknown MHC class I epitopes.

Publications

Arai I, Tsuji M, Miyagawa K, Takeda H, Akiyama N, Saito S. Repeated administration of IL-31 upregulates IL-31 receptor A (IL-31RA) in dorsal root ganglia and causes severe itch-associated scratching behaviour in mice. *Exp Dermatol*. 2015; **24:** 75-8.

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Saito S, Goto S, Yui N, Noda S. The feelings of mountain climbers-from the questionnaire in Yarigatake (in Japanese). *Nihon Sangaku Bunka Gakkai Ronshu*. 2015; **12:** 125-7.