Research Center for Medical Sciences
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

Regulation of Th2 responses by different cell types expressing the interleukin-31 receptor
Interleukin-31 (IL-31) is a recently identified cytokine produced by Th2 cells that is involved in the development of atopic dermatitis-induced skin inflammation and pruritus. Its receptor, IL-31RA, is expressed by a number of cell types, including epithelial cells, eosinophils, and activated monocytes and macrophages. To date, however, the regulation of Th2 responses by distinct cell types and tissues expressing IL-31RA has not been well studied. In contrast to observations indicating that IL-31 is actively involved in the promotion of Th2-type diseases, others suggest that IL-31-IL-31R signaling negatively regulates Th2-type immune responses.
On the basis of these previous findings, we assumed that Th2 immune responses are specifically regulated by different types of cells or tissues expressing the IL-31 receptor. To examine whether the reported exacerbated Th2-type response in IL-31RA KO mice has tissue specific mechanisms, we investigated the antigen-specific Th2 responses in IL-31RA-deficient mice administered an allergen nasally or intraperitoneally.
After nasal administration of Cry j 2, IL-31RA-deficient mice showed lower Cry j 2-specific CD4+ T cell proliferation, Th2 cytokine (IL-5 and IL-13) production, and Th2-mediated (IgE, IgG1, and IgG2b) antibody responses than WT mice. In contrast, IL-31RA-deficient mice administered Cry j 2 intraperitoneally showed stronger Th2 immune responses than WT mice.
The present study indicates that IL-31R signaling positively regulates Th2 responses induced by nasal administration of an allergen but negatively regulates these responses following intraperitoneal administration. Collectively, the data suggest that regulation of Th2 immune responses might be dependent on tissue-specific cell types expressing IL-31RA.

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 con-

ventional immunotherapy for the treatment of immunoglobulin E-mediated allergic diseases. In the previous study, a blinded, randomized, placebo-controlled trial employing oral immunotherapy with 80 g of steamed pack rice for cedar pollinosis was performed for 20 weeks. Thus, oral administration of the rice was found to be a safe therapy without side effects. The aim of this study was to investigate whether oral immunotherapy with small dose of the transgenic rice seed is effective to induce oral tolerance in patients with Japanese cedar pollinosis. Double blinded, randomized, placebo-controlled trial employing oral immunotherapy with 5 g or 20 g of steamed pack rice for cedar pollinosis was performed for 8 weeks. Twenty-one subjects were enrolled and divided into 3 groups that ate 5 g or 20 g of transgenic rice or normal rice.
No major adverse effects were observed in either group during treatment. Allergen-specific T-cell responses were evaluated. The ratio of allergen-specific T cells proliferative responses to 7Crp peptide, Cry j 1, and Cry j 2 were significantly lower in subjects who ate transgenic rice than in subjects who ate normal rice. 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. Taken together, oral immunotherapy with small dose of the transgenic rice was expected to be an effective treatment for cedar pollinosis.
Current clinical studies are being conducted to evaluate the clinical efficacy of oral immunotherapy with small dose of the transgenic rice.

Development of vaccination to induce CTLs against tumor specific antigens
Vaccine that raises specific cytotoxic T cells against tumors or pathogens is the convincing approach to overwhelm these diseases. By the past study, we have developed a new liposome based adjuvant to induce CTL by just mixing protein antigens and adjuvant before the administration. In order to apply this vaccine to cancer, further analysis was carried out, and this vaccine induced Th1 shifted immune response efficiently, but it was difficult to induce CTL against cancer. To prime CTL induction, we compared the several candidates of suicide gene therapies (SGTs). With SGT against colon tumor, efficient tumor vaccine was acquired to reject one million tumor cells implantation. Also, it was confirmed that the cryo-immunization of tumor expression OVA as a reporter induced specific CTLs. Using these results, we are developing a vaccine to induce CTLs to suppress the recurrence of tumors.

Publications

Saito S, Aoki A, Arai I, Takaishi S, Ito H, Akiyama N, Kiyonari H. Regulation of Th2 responses by different cell types expressing the interleukin-31 receptor. *Allergy Asthma Clin Immunol.* 2017; **13**: 23.