Institute of DNA Medicine
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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

Pleiotropic function of interleukin-31

Interleukin (IL) 31 is a T-cell-derived cytokine that induces severe pruritus, hair loss, and dermatitis and is involved in allergic diseases, such as atopic dermatitis and bronchitis. To investigate the function of IL-31, IL-31 transgenic mice were created in our laboratory. In addition to scratching behavior and hair loss as reported previously, enhancement of the serum immunoglobulin (Ig) E level was observed in the IL-31 transgenic mice. Moreover, these pleiotropic functions were verified by the administration of IL-31 into normal mice. To further analyze the mechanisms of IgE production by IL-31, we are seeking factors enhancing T helper type 2 (Th2) cytokine production, focusing on the IL-31 receptor-expressing cells, such as keratinocytes, macrophages, and granulocytes. We found that activated M2 macrophages become target cells in the presence of IL-31 to promote Th2 cell differentiation.

Furthermore, to investigate the function and the locations of IL-31 or the IL-31 receptor, 2 strains of IL-31 or IL-31 receptor (IL-31R) knockout/*LacZ* knockin mice were generated. In *IL-31R*$^{+/lacZ}$ knockin mice 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside staining was limited to the hair matrix. To produce offspring with a genetic identity for the analysis of the pleiotropic functions of IL-31, the heterozygous mouse will be backcrossed 6 or more times into the C57B/6J genetic background.

A rice-based edible vaccine expressing Japanese cedar pollen allergens induces oral tolerance in Japanese monkeys with Japanese cedar pollinosis

Japanese cedar (*Cryptomeria japonica*: CJ) pollinosis affects more than 30% of the Japanese population and is, thus, one of the most common diseases in Japan. Furthermore, CJ pollinosis has been found to occur naturally in Japanese monkeys (*Macaca fuscata*), which show symptoms similar to those of human patients.

Plants have recently been recognized as a form of bioreactor for the cost-effective production of large-scale recombinant proteins. The edible tissue of plants further provide the significant benefit of being a simple method of mucosal delivery of vaccines without the need for complicated purification steps.

Our previous study showed that oral administration of transgenic rice seeds that have accumulated high concentrations of polypeptides derived from CJ pollen allergens to mice reduces their serum IgE levels and T-cell proliferative responses to CJ allergens, proving the efficacy of oral immunotherapy for the treatment of pollinosis.
In this study, the transgenic rice plants that had accumulated high concentrations of JC allergens were used for oral immunotherapy for CJ pollinosis in monkeys. Five monkeys with CJ pollinosis were fed once a day with 20 g of the rice seeds containing about 50 to 60 mg of allergens for 3 months. No side effects, such as urticaria, dyspnea, vomiting, and weight loss, were observed during immunotherapy. One and a half months after the start of feeding, proliferative responses of T cells to JC allergens in 4 of 5 monkeys were significantly inhibited compared with those in monkeys at the start of feeding. However, their T-cell responses to CJ allergens were restored 1 month after the end of feeding.
On the other hand, in healthy monkeys without CJ pollinosis, the side effects and the induction of immune responses to CJ allergens were not observed after oral administration of transgenic rice seeds.
These results indicate that oral immunotherapy with transgenic rice seeds is a safe and effective treatment for pollinosis.

Construction of a new anticancer strategy focused on glycosylation
We are developing a novel anticancer strategy that induces cytotoxic T cells against non-polarized cells represented by cancer cells, by enhancing MHC class I-restricted antigen presentation by inhibiting N-glycosylation.
Analysis of the N-glycosylation structure that controls the secretion of IL-31 showed that some structures of N-glycosylation were able to enhance MHC class I-restricted antigen presentation. On the basis of this finding, we are developing a new vaccine that induces cytotoxic T cells against cancer or viruses with artificial immature N-glycosylated proteins.

Publications

Watanabe M, Fujioka K, Akiyama N, Takeyama H, Manabe N, Yamamoto K, Manome Y. Conjugation of quantum dots and JT95 IgM monoclonal antibody for thyroid carcinoma without abolishing the specificity and activity of the antibody. *IEEE Trans Nanobioscience.* 2011; **10:** 30-5.

Iikura K, Katsunuma T, Saika S, Saito S, Ichinohe S, Ida H, Saito H, Matsumoto K. Peripheral blood mononuclear cells from patients with bronchial asthma show impaired innate immune responses to rhinovirus in vitro. *Int Arch Allergy Immunol.* 2011; **155** suppl 1: 27-33.