

Development of allergen-specific immunotherapy of Japanese cedar pollinosis using solid-in-oil nanodispersions

孔, 慶靚

<https://hdl.handle.net/2324/4060140>

出版情報 : Kyushu University, 2019, 博士 (工学) , 課程博士
バージョン :
権利関係 :



氏 名 : 孔 慶靚 (KONG QINGLIANG)

論 文 名 : Development of allergen-specific immunotherapy of Japanese cedar pollinosis using solid-in-oil nanodispersions

(油中ナノ分散化技術を利用したスギ花粉症に対する免疫療法の開発)

論 文 内 容 の 要 旨

Japanese cedar pollinosis (JCP) is a type I hypersensitivity, which occurs when the immune system overreacts to cedar pollen, and affects the quality of life in persons of all ages in Japan. Allergen immunotherapy (AIT) is the only curative treatment for pollinosis patients by providing a sustained immunological and clinical tolerance to the cedar pollen. Subcutaneous immunotherapy and the sublingual immunotherapy treated with the allergen cedar pollen extract are two forms of AIT for JCP used in the clinical practice. However, low compliance and persistence for patients were reported in the clinical trials and real-life studies due to the side effects. Solid-in-oil (S/O) nanodispersions are oil-based dispersions of nano-sized particles with an antigen formed by coating it with hydrophobic surfactant molecules. They are expected to improve compliance and persistence for patients in different administration routes carrying the novel antigens. The aim of current thesis is to develop a safe, simple and effective AIT by administering transcutaneously or intranasally S/O nanodispersions loaded with the novel antigens, and thus, achieving the benefits of AIT rapidly and safely.

This thesis is composed of five Chapters, which are the general introduction in Chapter 1, the research achievements in Chapters 2 to 4, the general conclusion and future perspectives in Chapter 5.

In Chapter 2, the transcutaneous immunotherapy of JCP by using S/O nanodispersions carrying a mixture of T cell epitope peptides was developed and investigated. S/O nanodispersions carrying T cell epitope peptides showed a spherical structure with a mean diameter of 190 nm when dispersed into the oil. The quantitative and qualitative analysis of *in vitro* permeation results demonstrated the effective permeation of T cell epitope peptides into the skin. Moreover, an *in vivo* study using a mouse model of pollen allergy indicated that S/O nanodispersions loaded with T cell epitope peptides had a similar therapeutic effect compared with that of subcutaneous injection. The levels of serum total IgE, allergen Cry j 1-specific antibody IgE and cytokines secreted by splenocytes were inhibited in mice treated with S/O

nanodispersions carrying T cell epitope peptides compared to that of the control group.

Considering genetic differences in the T cell receptors in JCP patients, the modified allergen is applicable to all JCP patients due to its whole T cell epitopes information. To avoid the risk of side effects caused by the pollen extract, the allergen pollen extract was conjugated to galactomannan (PE-GM) to mask IgE-binding epitopes. The modified allergen PE-GM was used as the antigen in Chapter 3. S/O nanodispersions enhanced the skin permeability of both PE and PE-GM. The modification of PE by GM improved the uptake of PE by dendritic cells and showed an enhanced type 1 T helper immunity and a reduced type 2 T helper immunity in the pollinosis mouse model. A modulation of the immune response was observed by the transcutaneous administration of the S/O nanodispersions loaded with PE-GM, achieving a similar therapeutic effect compared with that of the injection method.

In Chapter 4, inspired by the marketed intranasal flu vaccine, the immune effect of an intranasal delivery of S/O nanodispersions was evaluated. The oil-based formulations based on S/O technology exhibit potential as intranasal vaccine carriers due to their high viscosity and adjuvant effects. In *in vivo* nasal absorption experiments, S/O formulations were associated with comparatively longer retention of antigen in the nasal cavity, and *in vivo* immunization induced strong mucosal and systemic immune responses. Histopathology analysis indicated that S/O nanodispersions did not modify the nasal epithelium or cilia, suggesting the non-toxicity of the carrier. These results indicate the potential of intranasal vaccination using S/O nanodispersions for future vaccination.

In Chapter 5, the main contents of this thesis were summarized and future perspectives regarding the development of AIT by using S/O nanodispersions were presented.