Invited review article

Spectrum of allergens for Japanese cedar pollinosis and impact of component-resolved diagnosis on allergen-specific immunotherapy

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Abbreviations:
CRD, component-resolved diagnosis;
ELISA, enzyme-linked immunosorbent assay;
IgE, immunoglobulin E;
JCP, Japanese cedar pollen;
OAS, oral allergy syndrome;
SIT, allergen-specific immunotherapy

ABSTRACT

The high prevalence of Japanese cedar pollinosis in Japan is associated with a negative impact on the quality of life of patients, as well as significant loss of productivity among the workforce in early spring, thus representing a serious social problem. Furthermore, the prevalence is increasing, and has risen by more than 10% in this decade. Cry j 1 and Cry j 2 were identified as the major allergens in Japanese cedar pollen (JCP), and in 2004, the existence of other major and minor allergens were revealed by a combination of two-dimensional electrophoresis and immunoblotting analysis. Allergenome analysis identified a chitinase, a lipid transfer protein, a serine protease, and an aspartic protease as novel IgE-reactive allergens in patients with JCP allergy. Thaumatin-like protein (Cry j 3) was shown to be homologous to Jun a 3, a major allergen from mountain cedar pollen. Isoflavone reductase-like protein was also characterized in a study of a JCP cDNA library. The characterization of component allergens is required to clarify the sensitizer or cross-reactive elicitor allergens for component-resolved diagnosis (CRD). Increasing evidence from numerous clinical trials indicates that CRD can be used to design effective allergen-specific immunotherapy. In this review, we summarize the eight characterized JCP allergens and discuss the impact of CRD and characterization of novel allergens on allergen-specific immunotherapy.

Prevalence of Japanese cedar pollinosis in Japan

Japanese cedar (Cryptomeria japonica) pollinosis is one of the most prevalent forms of seasonal rhinitis in Japan. Japanese cedar pollen (JCP) is released from the male flowers of Japanese cedar trees and levels are usually high from February to April in Japan. During this period, the forecasted levels of JCP in each Japanese geographic prefecture are broadcast with weather reports on a daily basis, and many people choose to wear face masks when they venture outside.1 Despite the high prevalence of pollinosis and huge interest in the conditions of JCP dispersal in recent decades, pollinosis was first reported in Japan in 1961 as an allergy to ragweed pollen.2 Subsequently, Japanese cedar pollinosis was discovered in the Nikko area of Tochigi prefecture in 1964.3 In the past half-century, JCP levels and the prevalence of pollinosis have increased dramatically.4 The results of a nationwide survey in 2001 using cross-sectional random sampling methods showed that the estimated prevalence of Japanese cedar pollinosis was 13.1%.5 The most recent survey conducted in 2008 revealed that the prevalence of pollinosis in the Japanese population had almost doubled to 26.5%.6 Pollinosis has a negative impact on quality of life;7 therefore, the recent increase in the prevalence of Japanese cedar pollinosis represents a significant social problem in Japan.

Japanese cedar and cypress are major constituents of Taxodiaceae family in Japan. Mountain red cedar, European cypress, and Rocky mountain junipers in Mediterranean countries and United States are also members of Taxodiaceae and Cupressaceae family.8–11 Patients allergic to pollen from a member of Taxodiaceae/Cupressaceae family shows allergic symptoms after...
inhaled pollen form another member of the family. Group 1, 2, and 3 allergens from pollen in the family cross-react among the polli-
nosis patients.

Sensitization with pollen allergens

Pollinosis is triggered by the invasion of the nasal and ocular mucosa by pollen grains. Many allergens with the capacity to bind immunoglobulin E (IgE) have been identified from many plant species and are registered on allergen databases. Some pollen-derived allergens are species-specific, while others are commonly identified in various plant species as enzymes or components of grasses, trees, vegetables, and fruits; these are known as pan-
allergens. Pollen grains readily access the aqueous phase of the nasal and ocular mucosal membranes, where they are hydrated. The hydrated pollen grain ruptures, releasing their cytoplasmic com-
ponents, including allergens, non-allergenic proteins, starch gran-
ules, and certain chemicals. Non-proteinous components, such as pollen cytoplasmic granules and pollen-associated lipid mediators, may act as adjuvants in the induction of antigen-specific type II helper T cell (Th2)-skewing immune responses to cytoplasmic and surface proteins of pollen during the sensitization phase. Some proteins also act as adjuvants in the induction of Th2 responses, accumulation of inflammatory cells, and activation of innate immu-

neces. These patients react mainly to gliadin. The patients with hydrated wheat protein-WDEAI sensi-
ticated into antigen-specific Th2 cells and follicular helper T cells (Tfh), while IL-33 alone induces group 2 innate lymphoid cells (ILC2), while IL-33 alone increases NH cell numbers. Activated ILC2 secrete large amounts of IL-5 and IL-
13, which promote the differentiation and activation of naïve CD4 T cells into Th2 cells and inflammatory effector cells. These reports strongly suggest that pollen contains proallergic natural adjuvants provoking type 2 immunity during the sensitization and elicitation phases of polli-
nosis (Fig. 1).

In addition to mucosal sensitization, the transcutaneous route may also be important for sensitization in dermatitis and food al-

ergy. In Japan, people who use facial soap containing hydrated wheat protein on a daily basis can develop wheat-dependent ex-
ercise-induced anaphylaxis (WDEAI) after the ingestion of wheat-containing food. These patients react mainly to γ1gliadin and α1gliadin from hydrated wheat protein contained in the product, while patients diagnosed with conventional wheat protein-
dependent WDE without using the product react strongly to α5-gliadin. The patients with hydrated wheat protein-WDEAI sensi-
tized by the soup showed more severe systemic allergic reactions

![Fig. 1. Schematic hypothetical model of sensitization with Japanese cedar pollen. Pollen protease-mediated damage to the epithelial cells of the nasal mucosa induces the production of cytokines such as IL-33, which in turn induces the migration and activation of inflammatory cells and innate lymphoid cells. Th2 cytokines from ILC2 and inflammatory cells induce naïve T cells to differentiate into Th2 cells following TCR stimulation by antigen-presenting cells. The antigen-specific Th2 cells and follicular helper T cells (Tfh) induce class-switch recombination of B cells to IgE-producing B cells and plasma cells. The antigen-specific IgE binds to FcεRI receptors on mast cell and basophils. Allergens from pollen cross tight junctions and bind to corresponding antigen-specific IgE, causing the release of inflammatory mediators, such as histamine and leukotrienes from effector cells. LTP, lipid transfer protein; IFR, isoflavone reductase-like protein; TSLP, thymic stromal lymphopoietin; DC, dendritic cell; Th0, naïve T cell; LTs, leukotrienes; ILC2, group 2 innate lymphoid cell; ECP, eosinophil cationic protein; MBP, major basic protein; Tfh, follicular helper T cell.](image-url)