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Review

Peptide based immunotherapy: A pivotal tool for allergy treatment

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ABSTRACT

Immunotherapies with T-cell epitope peptides have shown a promising impact over allergic diseases as a potential therapeutic tool in in vitro and in vivo conditions. It is recognized as an effective treatment with long lasting clinical effects and subsequent reduction of the allergic inflammatory reactions. In this review, we have summarized the role of peptide based immunotherapy and emphasis has been given to the recent advancement in pollen, cat, hymenoptera venom, and food allergy.

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1. Introduction

Allergy is a serious, life threatening health concern due to the imbalances in the immune system provoked by environmental substances in the susceptible individuals. Immunoglobulin E (IgE) is the most important immunoglobulin involved in the allergic reactions. Most of the allergic reactions are IgE mediated or type I hypersensitivity reactions.

Abbreviations: IgE, Immunoglobulin E; MHC, Major Histocompatibility Complex; ASIT, Allergen Specific Immunotherapy; APCs, Antigen Presenting Cells; DCs, Dendritic Cells.

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Because of its quick onset type I allergic reactions are also known as immediate type hypersensitivity. Allergens are substances responsible for induction of allergy in the susceptible individuals. These substances belong to pollens, dust mites, molds, danders, foods, medicines etc. The mechanisms of allergic reactions involve the interaction between IgE and allergen that cause release of allergic mediators like histamine, prostaglandin D_2 and leukotrienes following a cascade of molecular events [1]. The symptoms of allergy can be mild to severe including allergic rhinitis, allergic conjunctivitis, abdominal pain, vomiting, diarrhea, asthma, anaphylaxis and sometimes death. About 30–40% of populations have been found to be affected by the different allergic diseases including allergic rhinitis, asthma, allergic conjunctivitis, eczema, and food allergy [2].

The prevalence of allergy is worldwide, but still a permanent cure for allergic reactions is not available except strict avoidance of the offending allergens and symptomatic treatment of any adverse effects from accidental exposures [3]. Several therapeutic approaches are under scanner for the treatment of allergic diseases [4]. Among these, one method that's gathering popularity for allergy treatment is peptide based immunotherapy. Peptide immunotherapy is the use of peptides containing allergen-derived immunodominant T-cell epitopes that hold therapeutic promise for allergic reactions [5]. In this review, focus has been made on the mechanism of immunotherapy, overviews of immunotherapy developed for the treatment of pollen, food, insect, bee venom, and cat allergens, as well as pros and cons of T-cell epitope peptides in immunotherapy and its future perspective.

2. Different types of immunotherapy

Immunotherapy has been carried out for many years in which one of the most popular methods that are widely accepted is Allergen Specific Immunotherapy (ASIT). The ASIT includes oral, sublingual, and epicutaneous immunotherapy according to their route of administration.

2.1. Oral immunotherapy

An oral immunotherapy method induces desensitization by regular ingestion of a small amount of allergen, which increases IgG production, suppresses IgE production and ultimately suppresses allergic sensitization. The oral route of immunotherapy was reported for the first time in the 1980s [6]. The oral immunotherapy is easily administrable, carries much lower risk of anaphylaxis and requires less time to achieve therapeutic effects. Oral immunotherapy with cow's milk has been reported to modify the levels of a number of specific antibodies including IgE and IgG4 [7]. Several studies advocated administration of a single allergen at a time but a recent study by Bégin et al. (2014) reported that at preliminary level oral immunotherapy using multiple allergens simultaneously may be given under well-equipped medical supervisions [8]. But in many cases, oral immunotherapy with a relevant allergen is found to be risky and several side effects have also been reported which need to be minimised for the betterment of the therapy [9–11].

2.2. Sublingual immunotherapy

Sublingual immunotherapy is another type of immunotherapy in that allergen extracts are given as drops under the tongue of susceptible patients. It is commercialized in several parts of the world including American, European and Asian countries. Several clinical trials have shown clinical efficacy of single allergen tablets (grass and ragweed) or extract solution (ragweed) at primary level [12]. In a clinical study related to sublingual immunotherapy of house dust mite it has been reported that twelve months of treatment with 500 and 300 index of reactivity (IR) can be efficacious and well tolerated [13]. Sublingual immunotherapy is found very efficacious in children as well as in adults but, the chances of side effects cannot be ignored if not handled properly [14].

2.3. Subcutaneous immunotherapy

Subcutaneous immunotherapy is very similar to sublingual immunotherapy but in this mode of immunotherapy allergen is administered under the skin. This therapy has proven its efficacy in allergic diseases. Side effects induced by subcutaneous therapy include itchiness, swelling, and redness at the site of injection, highest systemic reaction, such as generalized itching, upper airway itchiness, coughs, or a shortness of breath [15]. Further, during the course of subcutaneous immunotherapy local reactions are very common [16].

2.4. T cell epitope peptide based immunotherapy

Considering the side effects of the above mentioned immunotherapies, there is a need of a safer and efficacious approach to combat allergic reactions. The T cell epitope peptide based immunotherapy could be one option. In this therapy, soluble peptides containing allergen-derived immunodominant T-cell epitopes are used to treat allergic patients [17]. Due to the use of T-cell epitope peptides the chance of adverse effects reduced significantly. Therefore, among various therapeutic approaches, allergen specific immunotherapy with T cell epitope peptide has been reported to be one of the most appropriate immunotherapy methods available as of now [18].

3. Mechanism of action of T-cell epitope peptide

T cell epitope is the particular region of an antigen or allergen that is immunogenic as well as antigenic in nature. T cell epitopes are mostly proteinaceous in nature. When these proteins are engulfed by antigen presenting cells (APCs), they get degraded in the proteosomal complex into small peptide fragments. These fragments bind to the Major Histocompatibility Complex (MHC) as per their binding capacity. These MHC–peptide complexes gets recognized by T cells and T-cell epitopes. Despite this, additional secondary signals are also required for activation of T cell provided by co-stimulatory molecules expressed on APCs [1]. The binding of CD28 on T cells and its two ligands B7-1 (CD80) and B7-2 (CD86) on APCs is considered as key event for T cell activation [19]. The recognition of T cell epitopes responsible for immune reactivity is necessary for the immune mechanism in response to exposure of allergens. The activated APC presents processed allergen epitopes in an inflammatory context to allergen-specific T cells which further lead to allergic reactions [1]. The Allergen Specific Immunotherapy amplifies the cross-linking of allergen specific antibodies bound to the surface of APC resulting in the activation and upregulation of pro-inflammatory genes. For cross-linking of two IgE molecules, allergens should be at least bivalent that it contained a minimum of two epitopes. Fig. 1 demonstrated an outline of the mechanism by which T-cell epitope deciphers its anti-allergic potential. It induces anergy in T-cells and IgG production. IgG further inhibits IgE-facilitated allergen uptake by Dendritic Cells (DCs) and prevents IgE-mediated allergen activation of effector cells and subsequent release of allergic mediators that finally suppress allergic manifestations [20,21].

4. T-cell epitope peptide therapy in different allergies

Immunotherapy with T-cell epitope peptide has been reported in a variety of allergies like bee and wasp venom, grass pollen, house dust mites and food allergy [22–25]. Immunotherapy has been proven as a pivotal tool in the treatment of several allergic diseases. Immunotherapy with T cell epitope peptides of cat allergens, immunotherapy with chimeric human–cat fusion proteins, immunotherapy with T cell epitope peptides of bee venom, and oral immunotherapy with T cell epitope peptide of ovalbumin (OVA) will be disscused in the next section.