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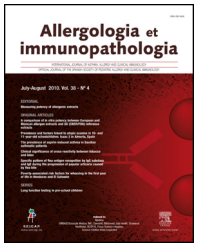

REVIEW

Allergen-specific immunotherapy: Update on immunological mechanisms

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Abstract Immunotherapy selectively modulates the allergen-specific immune response. It involves the gradual administration of increasing amounts of allergen for the purpose of inducing protective immunological changes and it is the only curative approach for specific type I allergy.
Aim:

- Description of the allergic inflammation.
- Comprehension of the early cellular changes after specific immunotherapy has been initiated.
- Exposure of the mechanisms involved in tolerance induction by regulatory T cells (Treg) with the inhibition of the Th2 responses.
- Comprehension of IL-10 and transforming growth factor-β (TGF-β) roles.
- Explanation of specific IgE, IgG and IgA changes.
- Description of the suppression of inflammatory responses during immunotherapy.

Introduction

Treatment of allergic diseases consists in allergen avoidance and the use of pharmacotherapy. This includes antihistamines, corticosteroids, antileukotrienes and beta-2 agonists[1]. Although effective at controlling symptoms and

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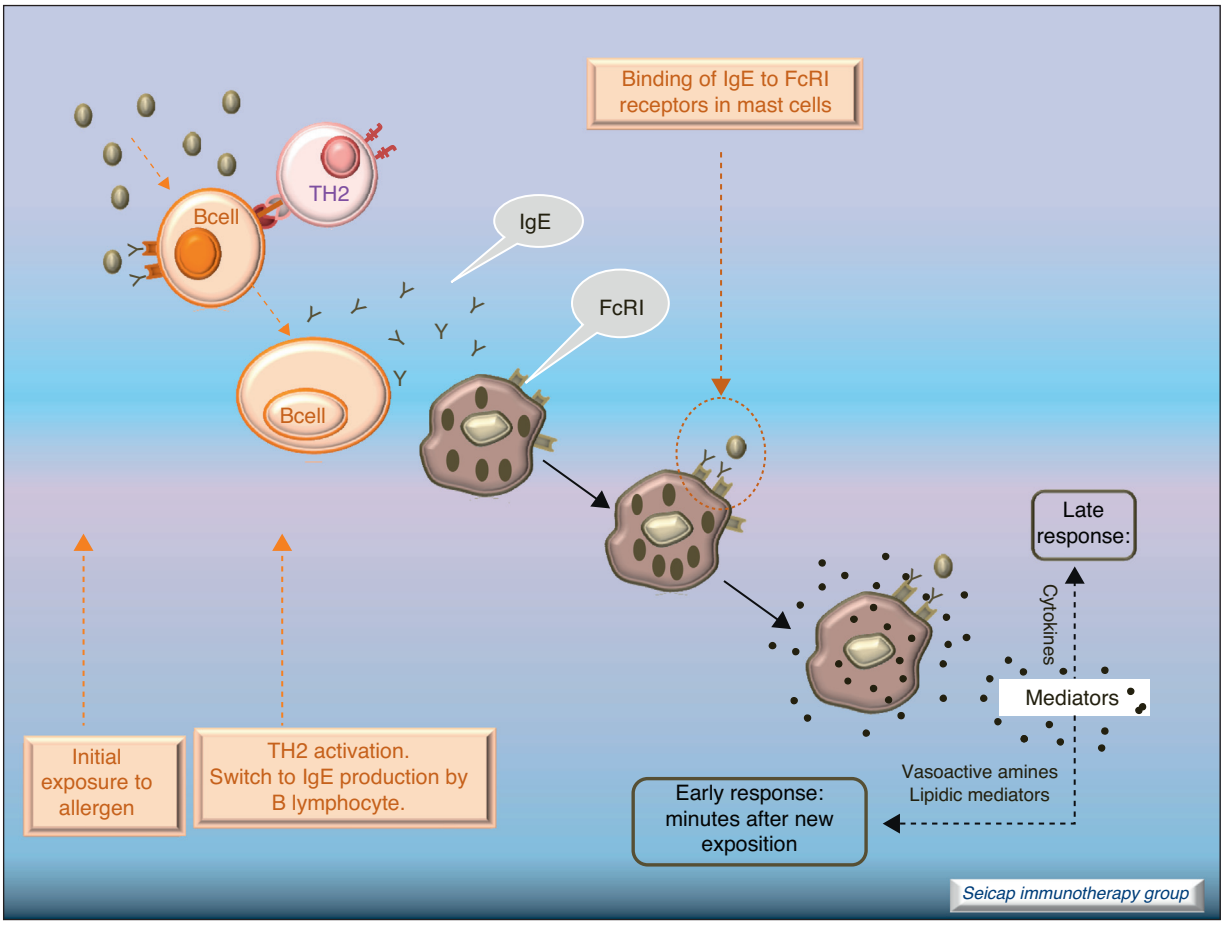

Figure 1 Allergic inflammation. Previous exposure to allergen: generation of IgE antibodies; binding of IgE to receptors in mast cells. Re-exposure: biphasic response.

inflammation, these treatments can have side effects if used for a long time. In patients, where it has been demonstrated and documented that symptoms appear on exposure to specific allergens, allergen-specific immunotherapy (SIT) should be indicated. This treatment selectively modulates the allergen-specific immune response.

Allergen-specific immunotherapy involves the gradual administration of increasing amounts of allergen for the purpose of inducing protective immunological changes. SIT is currently the only treatment that alters the abnormal immune response underlying allergic disease. It is the only curative approach for specific type I allergy.[2] Unlike pharmacotherapy, allergen immunotherapy provides long-term clinical benefits. These include long-term disease remission, prevention of new atopic sensitisations, and a reduction in disease progression from rhinitis to asthma.[3]

Since the first use of SIT in the early 20th century (a hundred years ago), a large amount of clinical trials have been published. These studies have led SIT to emerge as an evidence-based treatment with the knowledge of some of its mechanisms of action.[4]

Allergic inflammation

After a previous exposure to an allergen in susceptible individuals, IgE antibodies are generated. These antibodies bind to high affinity IgE Fc receptors on blood basophils and mucosal tissue mast cells. On reexposure to the specific allergen, a biphasic response is elicited.[1] Allergic patients, who are challenged with the antigen implicated in their allergic inflammation, often respond with this biphasic reaction. There is an early phase (peak at 15–30 min after allergen exposure) with the release of mediators from local tissue mast cells and circulating basophils. These mediators include histamine, kinins, prostaglandin D2, cytokines, chemokines and leukotrienes. Their function is the recruitment of cells to the zone leading to the arrival of inflammatory cells that include eosinophils, T lymphocytes and additional basophils which release specific inflammatory mediators (late phase, 6–12 h after allergen exposure). Thus, the mechanisms that contribute to the allergic inflammation persist. Fig. 1.

Most of the allergens which contact the respiratory mucosa are cleared by the physical barrier. Some will penetrate the epithelium and will be captured by antigen presenting cells, especially immature dendritic cells (DC). In healthy individuals this results in the induction of tolerance.[5] In atopic individuals, this initial encounter results in the switch of T-cells to Th2 cells. Specific IgE bound to low affinity IgE Fc receptors on DC play a role in facilitating allergen uptake.[1] This allergen-loaded DC arrives to lymph nodes where they present processed allergen as peptides to T cells with allergen-specific receptors.