



Molecular and Clinical Basis of IgE-mediated Allergy

Martin Mempel, M.D. (Department of Dermatology and Allergy Biederstein, Technical University Munich, Munich, Germany)

While many aspects of allergy remain a mystery to investigators, there exists a relatively clear understanding of the processes leading to Type-1 hypersensitivity. The molecular mechanisms that drive IgE-mediated allergy oppose those of anergy and vice versa, which explains why specific immune therapy (SIT) is the only causative treatment for Type-1 allergy. How SIT actually works is best described in conjunction with an overview of allergy from a biochemical perspective.

Type-1 hypersensitivity begins with sensitization, which is caused by exposure to an allergen. The allergen or antigen, such as dust mite, metal ion or pollen grain, is taken up by dendritic cells in the mucosal or skin tissue where it is processed and transported to a draining lymph node by the antigen-specific presenting cells. Within the lymph node, the antigen is presented to naive T-cells (Figure 1), which can react to the antigen in one of three ways: 1) no reaction—occurring mainly under the influence of IL-12 secreted by antigen-presenting cells; 2) differentiation of T-cells into Th1 cells—occurring under the influence of IFN- γ and IL-2; or 3) differentiation of T-cells into Th2 cells—occurring under the influence of IL-4, the actual origin of early IL-4 secretion being unknown, although it may be secreted by CD4+ T, NKT or mast cells.

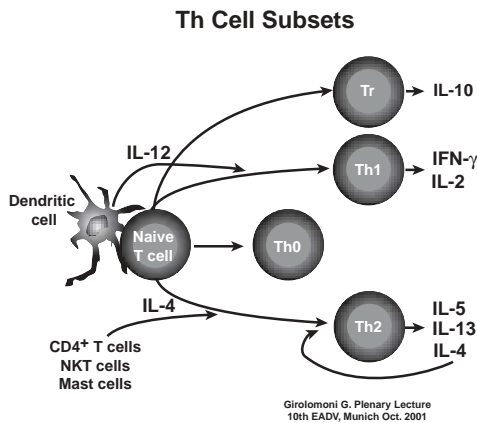


Figure 1.

Th1 differentiation leads to the homing of these cells to skin tissue throughout the body, and Th1 cytokines induce IgG2a, IgG3 and IgG4 production. Conversely, differentiation into Th2 cells leads to the induction of the humoral immune response, which results in the production of specific IgE. This occurs through direct contact between the Th2 and B-cells (also antigen-specific presenting cells), which activates the Th2 cells to secrete IL-5, IL-13, IL-6 and IL-4. The influence of these cytokines, along with the costimulatory effects of the CD 40 ligand/CD 40 axis, initiate the conversion of resting B-cells from IgM-bearing cells to proliferating specific IgE-producing plasma cells (Figure 2).

Th2-cells give rise to IgE-producing plasma cells

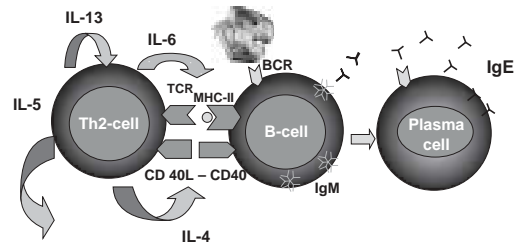


Figure 2.

In a sensitized individual, the mast cells are loaded with specific IgE. As soon as an antigen is recognized and bridged with the IgE molecules, degranulation of the mast cells takes place, releasing primarily histamine and serotonin into the surrounding area. In addition, TNF α is produced, which recruits more IgE-laden mast cells to the tissues, compounding the reaction.

While drugs, such as H1 blockers and corticosteroids, address allergy symptoms, SIT is the only causative treatment for Type-1 hypersensitivity, as it induces anergy in allergic patients. Repeated immunization with doses of antigen have been shown to induce IL-10 production, a crucial cytokine for T-cell anergy. IL-10 blocks both the Th1 and Th2 responses, including Th2 cytokine production, which leads to IgE production (Figure 3). SIT therapy appears to switch IgE production in allergic individuals to that of IgG (Figure 4). This therapeutic response is primarily due to IL-10 and may possibly be attributable to TGF- β as well. Studies indicate that the model just described is highly applicable to bee and wasp allergies, and data suggest that it applies to food allergies as well. It has not been well evaluated, however, for pollen and other environmental allergies.

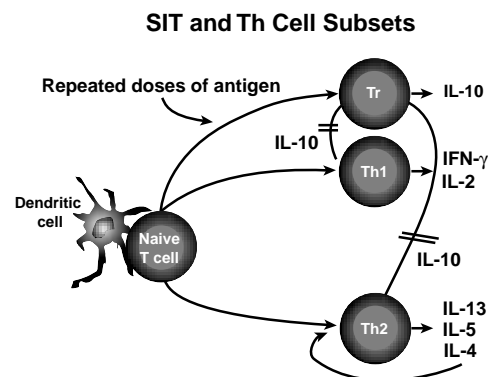


Figure 3.

Immunoblots using patient sera demonstrate the shift in immunoglobulin production after SIT therapy. In a bee allergy patient, for example, immunoblots prior to SIT therapy indicated virtually no IgG production and a strong IgE pattern (Figure 5). After therapy, an immunoblot following a sting challenge indicated that the patient's immunoglobulin profile had changed to equal amounts of IgE and IgG, primarily IgG4.

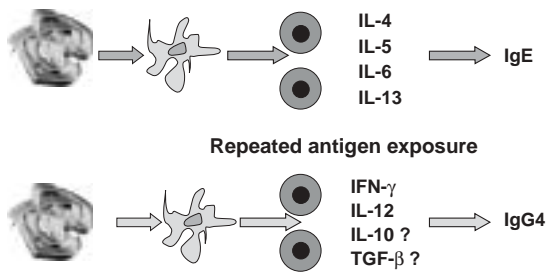
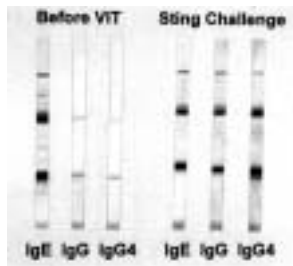


Figure 4.



VIT – Venom immune therapy

Figure 5.