

Immunologic mechanisms of specific immunotherapy

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Specific immunotherapy (SIT) with allergen extract is currently the only available specific treatment of allergic diseases. The immune response to bee venom (BV) provides an especially suitable model to study the human antigen-specific regulatory mechanisms of IgE and IgG4 antibody production and of SIT. BV phospholipase A₂ (PLA) is the major allergen/antigen of BV. Whereas the normal BV response is characterized by high IgG4 antibody contents, allergics to BV normally show elevated serum levels of IgE anti-PLA. We have investigated the immunologic mechanisms of SIT with whole BV (BV-SIT) and with peptides representing immunodominant T-cell epitopes of the PLA allergen (PLA-PIT). In successful SIT, patients developed a state of specific anergy against PLA after 2 months that was directed specifically to the T-cell recognition sites of the allergen. In particular, the specific proliferative T-cell and entire cytokine responses were suppressed.

The induction of anergy in Th2 cells was associated with alterations in the TcR signaling pathway. In APC-free systems, which lack accessory molecule activation, anergic T cells showed increased levels of basal tyrosine phosphorylation and abrogation of p56^{lck} and ZAP70 kinase activity. In both BV-SIT and PLA-PIT, the antigen-specific proliferative and cytokine responses decreased within 1 month. Simultaneously, IL-10 increased and reached maximal levels after specific anergy was fully established. The addition of a neutralizing anti-IL-10 antibody re-established the cytokine and proliferative responses in T cells, indicating that IL-10 was directly involved in anergy induction. Intracellular IL-10 staining suggested an autocrine mechanism by IL-10 secreted from specific T cells in the induction phase of anergy. APC and bystander T cells producing IL-10 may, rather, maintain the anergic state.

The suppressive effect of IL-10 probably results from inhibition of the CD28 costimulatory signaling pathway.

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The suppressed proliferative and cytokine responses of anergic T cells could be reconstituted by *ex vivo* neutralization of endogenous IL-10, indicating that this cytokine is actively involved in the development of anergy. Interestingly, the full capacity of IFN- γ and IL-2 secretion and proliferation was activated by cytokine treatment with IL-2 or IL-15. In contrast, specific stimulation with IL-4 recovered the Th2 cytokine profile. Thus, microenvironmental cytokines recover and regulate T cells from SIT-induced anergy. IL-2 and IL-15 can induce distinct Th1 and Th0 cytokine patterns associated with normal immunity, whereas IL-4 reactivates Th2 cells, supporting the persistence of the allergic response.

While peripheral anergy was demonstrated in specific T cells, the capacity of B cells to produce specific IgE and IgG4 antibodies was not abolished. In fact, specific serum

levels of both isotypes increased during the treatment. However the increase in specific IgG4 was more pronounced and the ratio specific IgE:IgG4 decreased significantly. Moreover, IL-10 differentially regulates antigen-specific IgE and IgG4 antibody synthesis. It is a potent suppressor of IgE synthesis, and it simultaneously increases IgG4 production.

Induction of specific anergy in peripheral T cells by IL-10 and reactivation of distinct cytokine patterns by cytokines from the tissue microenvironment are key events in the immunologic mechanisms of SIT. Specific IL-10-induced anergy in T cells develops in both SIT and PIT. The reactivation of anergic T cells by certain cytokines suggests the decisive role of the immunologic microenvironment, modulating specific cytokine responses by T cells and thereby influencing the success or failure of SIT.

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