Immunologic Response with Venom Immunotherapy

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Allergen-specific immunotherapy (SIT) has been used as a desensitizing therapy for allergic diseases and may represents a curative and specific way of the treatment. The mechanism by which immunotherapy induces protection is associated with changes in the fine balance between allergen-specific regulatory T cells and TH2 cells, TH1 cells, or both. Histamine, originally considered a mediator of acute inflammatory and immediate hypersensitivity responses, has also been demonstrated to regulate antigen-specific TH1, TH2, and regulatory T cells, as well as related antibody isotype responses. Histamine enhances TH1-type responses by triggering HR1, whereas both TH1- and TH2-type responses are negatively regulated by HR2. Human CD4+ TH1 cells predominantly express HR1 and CD4+ TH2 cells predominantly express HR2, which results in their differential regulation by histamine. The significantly decreased value of the HR1/HR2 ratio in the placebo group indicates HR2 dominance during venom immunotherapy. The induction of a tolerant state in peripheral T cells represents an essential step in allergen-specific immunotherapy. Peripheral T cell tolerance is characterized mainly by suppressed proliferative and cytokine responses against the major allergens and its T cell recognition sites. It is initiated by autocrine action of IL-10 and/or TGF-b, which are increasingly produced by the antigen-specific T Regulatory (Treg) cells. Tolerized T cells can be reactivated to produce either distinct Th1 or Th2 cytokine patterns thus directing allergen-SIT towards successful or unsuccessful treatment. Treg cells directly or indirectly influence effector cells of allergic inflammation, such as mast cells, basophils and eosinophils. In addition, there is accumulating evidence that they may suppress IgE production and induce IgG4 and IgA production against allergens.

IL-10-mediated immunosuppressive functions of B cells have been described in murine models of autoimmunity, infection, and cancer. Patients treated for rheumatoid arthritis with the B cell depleting antibody rituximab who showed exacerbation of ulcerative colitis and development of psoriasis illustrate the relevance of immune regulatory functions of human B cells. Interestingly, an

increase in IL-10-producing B cells also occurs during ultra rush high dose allergen-specific immunotherapy of venom allergic individuals by bee venom (BV-SIT). Regulatory B cells expressing IL-10 suppress immune responses and the lack or loss of regulatory B cells leads to exacerbated symptoms in experimental autoimmune encephalitis, chronic colitis, contact hypersensitivity, collagen-induced arthritis and non-obese diabetic mouse models. Another B cell-related immune regulatory response restricted to humans is induction of non-inflammatory IgG4 antibodies, which is characteristic for high dose antigen tolerance models. Several molecules including CD25 and PD-L1 were upregulated in IL-10-producing B cells. Br1 cells potently suppressed antigen-specific CD4+ T cell proliferation whereas other B cells did not. Furthermore we demonstrate that human Br1 cells show selectively increased production of IgG4. B cells specific for the major bee venom allergen phospholipase A2 that were isolated from beekeepers had increased expression of IL-10 and IgG4. Human Br1 cells may regulate humoral and cellular immunological tolerance through suppression of T cells responses and production of anti-inflammatory IgG4 antibodies.

By the application of the recent knowledge in mechanisms of allergen SIT, more rational and safer approaches are a waiting for the future of prevention and possibly cure of allergic diseases.