

Allergen-specific immunotherapy: Power of adjuvants and novel predictive biomarkers

Allergen-specific immunotherapy (AIT) is a potent and precise immune tolerance-inducing treatment toward specific proteins. AIT is a successful, but long-term treatment, and therefore, it is very demanding for the patients. Moreover, there are patients who do not respond to this therapy and others who develop allergic symptoms after initial success of the treatment. Therefore, novel approaches are urgently needed to potentiate its efficacy (ie, new adjuvants), uncover unknown biological mechanisms, as well as discover the biomarkers of effective clinical response to AIT. If we do not fulfill these goals, we might face the deceleration of AIT development and significant decrease in its availability for the patients. Therefore, in this issue of the journal Gueguen et al¹ and Johnson-Weaver et al² present their approaches to fulfill these unmet needs on finding predictive biomarkers of AIT and better understanding the adjuvants, respectively.

Gueguen et al studied mRNA expression of 17 genes in the whole blood of patients in a double-blind placebo-controlled clinical trial with sublingual house dust mite tablets, in order to uncover the potential predictive biomarkers to AIT.¹ They found that higher initial IL10 mRNA expression levels predicted better clinical response to sublingual HDM AIT over one-year treatment period. Therefore, the authors suggest that IL10, so far recognized as a parameter in monitoring efficacy of AIT in different cellular settings (Figure 1), could now be considered a predictive biomarker of potential benefit from allergen immunotherapy.¹

Immunological and clinical effects of AIT, either in subcutaneous or sublingual settings, are the results of precise combination of allergen component and the adjuvant in the vaccine (Figure 2). The study performed by Johnson-Weaver et al in this issue of the journal

Early desensitization of mast cells and basophils

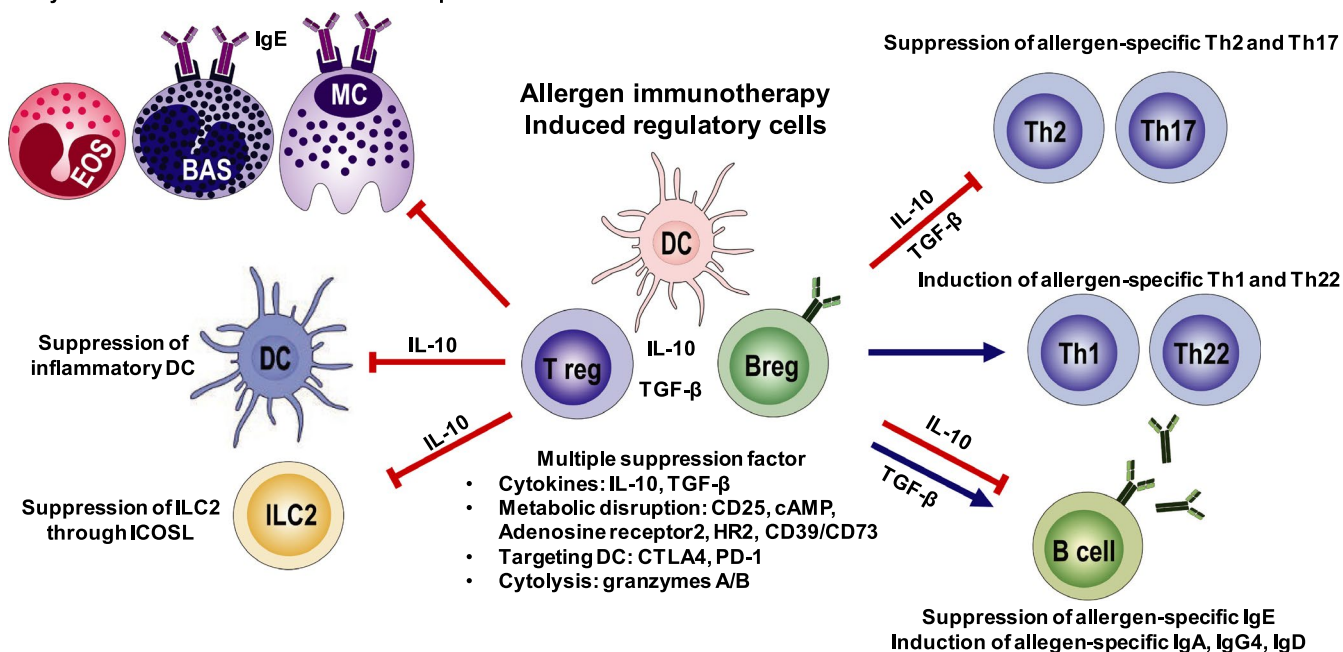


FIGURE 1 Mechanisms of immune tolerance to allergen induced by allergen-specific immunotherapy (AIT). AIT induces regulatory cells including allergen-specific Treg, Breg and DCreg. Treg cells apply several mechanisms for precise suppression of type-2 immunity, including inhibitory cytokines, cytolysis, metabolic disruption, and targeting APCs, using soluble and surface-bound molecules. IL-10-secreting Treg and Breg cells suppress innate and adaptive immune mechanisms involved in allergic inflammation, such as mast cells, basophils, and eosinophils, as well as Th2, IgE-producing B cells, and ILC2. AIT induces allergen-specific immunoglobulin class switching, promoting the production of IgG4, IgA, and IgD. Accordingly, Gueguen et al¹ in this issue of the journal proposed that higher initial IL10 mRNA expression levels in the whole blood cells predict better clinical response to AIT. Consequently, the study by Johnson-Weaver et al in this issue of the journal, comparing the effect of an adjuvanted and nonadjuvanted vaccine in a mouse model of nasal allergen-specific immunotherapy, noted that several of these mechanisms are being induced by AIT²

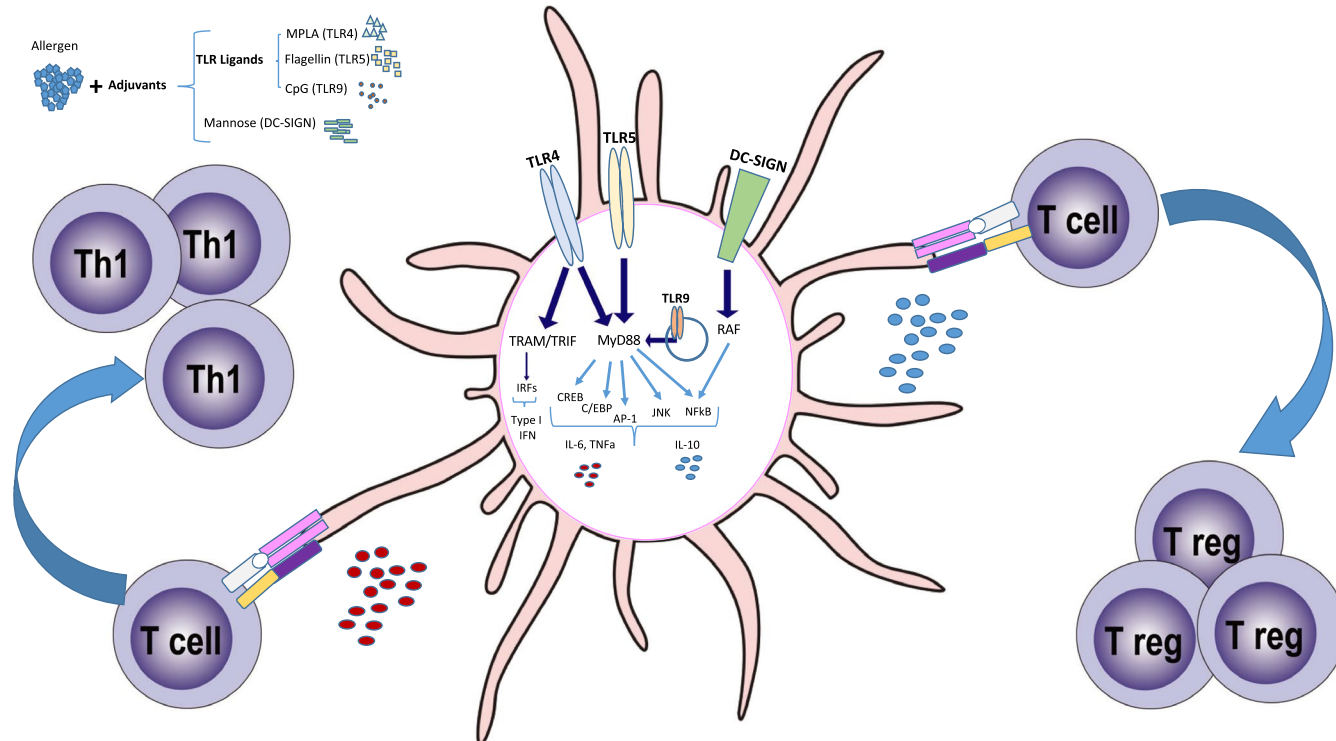


FIGURE 2 Signaling pathways induced by adjuvants in allergen-specific Immunotherapy (AIT). The activation of TLRs by adjuvants-allergen complex on antigen-presenting cells (APCs), mainly dendritic cells, promotes both innate inflammatory responses and the induction of adaptive immunity. This scheme represents the pathways induced by PPRs ligands such as MPLA (the first approved TLR agonist used as adjuvant in licensed vaccines), flagellin, CpG, or mannose. Using different molecular pathways (MyD88-dependent and MyD88-independent), they are able to induce inflammatory cytokines (TNF α , IL-6) and IL10. Both involved in the further acquisition of a Th1 and Treg immune response. Consequently, the study by Johnson-Weaver et al in this issue of the journal confirmed that adding CpG to a peanut extract in mouse model of nasal allergen-specific immunotherapy had superior effect on several AIT-induced mechanisms in comparison with the extract alone²

investigated the effect of CpG adjuvant introduction onto a peanut extract.² The effect of an adjuvanted and nonadjuvanted vaccine was studied in a mouse model of nasal allergen-specific immunotherapy. The authors demonstrated clinical superiority of the adjuvanted preparation. Moreover, using IL-13-lineage-tracing mice they demonstrated transition of Th2 cells to IFN- γ -producing Th1 cells and increase in IL10-producing non-Th2 cells. These effects were accompanied by an increase in IgG2c, mucosal IgA, IL-10, and IFN- γ and a decrease in IL-13.²

Parallel to the search of biomarkers, we need to study the mechanisms of AIT-induced immune tolerance in more detail, as these two approaches are often complementary. It has been shown previously that AIT induces allergen-specific regulatory T (Treg) and B (Breg) cells which can inhibit ongoing allergic inflammation by acting at different immunomodulatory levels (Figure 1).³ There are at least four groups of suppressive mechanism used by Treg cells in AIT including (a) secretion of the suppressive cytokines, interleukin (IL)-10, and transforming growth factor- β (TGF- β), (b) influence on cellular metabolism by CD25, cAMP, adenosine receptor 2, histamine receptor 2 (HR2), CD39, and CD73, (c) suppression of antigen-presenting cells and ILC2 activation by membrane-bound molecules, programmed death 1 (PD-1), cytotoxic T lymphocyte antigen 4 (CTLA-4), or the inducible T-cell costimulatory ligand (ICOSL), and (d) cytotoxicity (granzymes A

and B). Moreover, AIT enhances IL-10-producing inducible Treg and Breg cells which increase in number and achieve the function similar to the immune status observed in healthy subjects.⁴⁻⁶ IL-10-producing Treg cells suppress Th2-type immune response and IL-17-producing Th cells. AIT also promotes allergen-specific IL-22 and interferon (IFN)- γ -producing Th cells.⁴ Moreover, AIT involves upregulation of the activated Treg and downregulation of the dysfunctional Treg cells.⁴ Recent prospective immunological kinetic study⁵ confirmed the key role of T regulatory response for a sustained clinical benefit of AIT and noted a high variability among patients in the acquisition of a regulatory phenotype during the therapy. Allergen-specific B cells in patients responding to AIT are characterized by increased numbers of IgA- and IgG4-expressing allergen-specific B cells, plasmablasts, and IL-10 and/or IL-1RA Breg cells.⁶ The improvement of allergic symptoms has a significant correlation with the increase in Treg and Breg cells number during AIT.^{4,6} IL-10 can suppress antigen-specific IgE and augment IgG4-producing class-switched B cells. IgG4 blocks IgE antibodies by mopping up free allergen, and IgE fails to trigger Fc receptors. Also, IgG4 prevents mast cell activation through Fc γ III. Also, AIT induces allergen-specific IgD and IgD constrains IgE-mediated basophil degranulation. Furthermore, other cells of innate immunity such as dendritic cells and innate lymphoid cells are also targeted by immunotherapy³ (Figure 1).

Adjuvants are administered to boost immunological response (Figure 2). Alum salts are the reference adjuvant system for human use. Introduced in the 1920s, yet only recently we have started to understand its immunological mechanisms. Alum stimulates innate immune system, among others, by activation of NLRP3 inflammasome and, at the same time, creates a persistent reservoir of antigen in the site of injection (depot effect). Furthermore, TLR ligands have been used in allergy vaccination in combination with a glutaraldehyde modified extract and tyrosine. Currently, there are other adjuvant systems that are being explored for AIT (Figure 2), such as virus-like particles, dendrimers, or TLR5-inducing approaches, by incorporating flagellin to the allergen. There are other new interesting approaches that are exploring targeting C-type lectin receptors (CLRs). Allergen conjugation to nonoxidized mannan has proven to induce a strong regulatory response. CD206, CD209, and specially DC-SIGN could be new targets for allergy vaccine design with a focus on regulation, more than immunogenicity.

The experience accumulated in the last decades of AIT and adjuvant research should pave the way to more exploratory trials, as the one performed by Johnson-Weaver et al, that would eventually end up in the design of improved allergen-specific intervention strategies. Moreover, there is an urgent need to establish a biomarker or, more probably, a set of biomarkers which can predict efficacy of AIT even before the initiation of the therapy or relatively early in its course. To achieve this, a forefront approach in big clinical trials is needed, like the one initiated by Gueguen et al, where the measurements of vaccine efficacy are linked with the discovery of novel biomarkers by the precision medicine and omics technology approaches.⁷⁻⁹

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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