T Cell Regulation in Allergy, Asthma and Atopic Skin Diseases
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Preface
Role of T-Cell Subtypes in Allergic Inflammations

Allergic diseases are immune reactions which represent the currently best knowledge of cellular and molecular mechanisms, generating and regulating different clinical manifestations at different organs. The knowledge on the immunological background of allergy meets the current state of the art in immunology and immune-related inflammatory guises. One reason for this is the knowledge and accessibility of the ultimate trigger of the disease, the allergen, which can relatively easily be determined and produced in pure form. This and other typical properties of allergy provide a most suitable disease model for the study of specific immune responses. It has definitely overcome the state where allergy was defined as equal to serum-IgE antibody content and the knowledge on the disease has escaped the state of simple IgE antibody measure. Allergic diseases have their origin in a deregulated immunity to exogenous molecules, being harmless as such, facilitated mostly by a preferential genetical constitution. Thus, in normal immunity to allergen mostly IgG4 antibodies are elicited, which can block the allergen and do not display Fc-related antibody functions, such as binding complement or Fc receptors on effector cells. The regulation of both normal and allergic immunity is fully T-cell-dependent and relies exclusively on the activation and action of different subtypes of T cells and their products, which in consequence activate and direct the entire network of immune and involved tissue cells.

Allergic inflammations are induced by increasingly generated Th2 cells, which dominantly secrete IL-4, IL-13 and IL-5 cytokines, triggering IgE antibodies and prolonging eosinophilic granulocyte survival. Interestingly it appeared that inhibited apoptosis by IL-5/GM-CSF and not extensive production of eosinophils is the cause of eosinophilia. While allergy initially depends on Th2 cells, Th1 cells producing TNF and IFN-γ, and which are induced at a later stage by bacterial or viral superinfections and superantigenic activation, are involved in the chronic progression of the disease. Both TNF and IFN-γ are able to induce death receptors on tissue cells and thus, together with other ligands, induce tissue cell death, such as bronchial epithelial and smooth muscle cells and keratinocytes in skin diseases. Activated effector T cells are directed by tissue-selective homing receptors and attracted by the aid of different chemokines. This basic knowledge could be generated only after recombinant cytokines became available after 1980.

It is established today that a set of T-regulatory cells (Tregs) as well as other T-cell subtypes are
involved in the mechanisms and regulation of allergic inflamations and that the interaction with tissue cells and effector cells plays an important role in the chronicity of the disease; Treg cells regulate the immune response to foreign triggers and participate in the maintenance of peripheral and central tolerance. Of decisive importance in immune response regulation to allergens and other specific triggers are functional Tregs (fig. 1). However, different functional Treg populations, such as CD4+CD25<sup>high</sup> Tregs, Tr1, Th3 lymphocytes and NK cells exist, which can be distinguished by different cytokine profiles and marker expression. Tregs in allergy are highly activated, CD25<sup>high</sup> peripheral T cells, which require continuous activation. TGF-β promotes the development of CD4+CD25<sup>high</sup> FOXP3+ Tregs from naive CD4+ T cells. They are allergen-specific T cells, displaying immune suppressive functions, which are mediated by their IL-10 and/or TGF-β secretion. Thus, Tregs secreting these suppressive cytokines are true regulatory cells in that they suppress effector cells of allergy and IgE production by B cells, while they activate blocking antibodies of IgG4 and IgA type and promote development of Tregs from naive T-cell populations (fig. 2). At initiation they express the transcription factor FOXP3 (forkhead box protein 3), while Th2 cells express GATA3 and Th1 cells, T-BET (fig. 3). Peripheral Tregs, like Th1 and Th2, represent an independent T-cell lineage, developing from naive T cells after activation by allergen and DC contact, with the aid of TGF-β. They cannot develop from Th2 cells, e.g. in specific immunotherapy. Moreover, FOXP3 and Treg development is suppressed by GATA3 and IL-4, and therefore after activation of Th2 cells. Accordingly, it is difficult to skew an established allergic or atopic state into a Treg-equilibrated normal immune state. This is probably the reason for the long immunization procedure required for successful allergen-specific immunotherapy, although Tregs are induced by
high allergen doses within a short time after the first immunization (2–3 days). Tregs are required in sufficient numbers proportional to the specific Th effector cells and their suppressive function depends exclusively on their numbers in relation to the effector T cells.

An important T-cell subtype in chronic allergic responses are the Th17 cells, being defined by their IL-17 production. The Th17 subset is distinct from the Th1, Th2 and Tregs. They are important players in chronic inflammatory responses such as allergy and autoimmunity, organ transplantation and tumor development. Differentiation of Th17 is initiated by TGF-β in combination with IL-6. Also IL-21, highly expressed by mouse Th17 cells, potently induces Th17 differentiation and suppresses FOXP3, the nuclear factor for Treg differentiation. The Th17 differentiation is initiated by the orphan nuclear receptor RORyt, for humans termed RORC2. Th17 cells induce and amplify the inflammatory IL-1β and TNF-α response. Without the influence of these proinflammatory cytokines, IL-23 mainly from activated dendritic cells expands and stabilizes the Th17 population. In humans, Th17 cells are suppressed by IL-12, in the mouse, Th17 differentiation is inhibited by IFN-γ. GM-CSF is a crucial factor for granulocyte development and survival and development of organ-related autoimmune diseases. Innate GM-CSF induces IL-6 responses and generation of pathological Th17. TGF-β promotes the development of CD4+CD25^{high}+FOXP3+ Tregs from naive CD4+ T cells. The balance between Th17 and Tregs is regulated by IL-2, which displays differential effects on the two T-cell lineages. Treg cells increase under the influence of IL-2, whereas
Th17 cell numbers are reduced and IL-2 neutralization boosts the Th17 differentiation. Both Th1 and Th2 differentiation depends on the strength of T-cell receptor activation and co-stimulatory interaction. Th17 cells require higher antigen doses for differentiation by enhancing IL-6 production and CD40L expression on dendritic cells. A lack of CD40-CD40L interaction leads to impaired Th17 production and autoimmunity. Thus, GM-CSF, antigen dose, and CD40-CD40L interaction regulate the IL-6 production, a key cytokine for Th17 development. A better understanding of transcriptional regulation of the different cell types and its relation to the inflammatory disease will provide further insight into the regulatory events involved in immune regulation of these chronic inflammatory diseases.

The present edition of 'Molecular Immunology' on 'T-Cell Regulation in Allergy, Asthma and Atopic Skin Diseases' provides the latest overview on the regulatory mechanisms by T lymphocytes and their subtypes in the organ-related allergic manifestations and specific treatments of the diseases. The issue is divided into three parts, the first part providing a modern view of the immunoregulatory processes in allergic inflammations. In particular, the development and the role of Treg cells in the induction of peripheral tolerance to allergens and the function of the Th17 cells in chronic inflammatory processes are described. In addition, the regulatory role of NK cells and the feedback interactions by activated mast cells, a major effector cell of the allergic reaction, are considered.

The second part describes the regulation and immunological events in different allergic diseases, such as asthma and atopic skin diseases, in parasite infection and delayed-type hypersensitivity. Special attention is paid to mucosal tolerance, which is important in many respects including...
also oral immunotherapy and tolerance induction. Finally, a most important part is devoted to the clinical consequences of the current immunological knowledge on T-cell regulation in novel therapeutic interventions. For almost 100 years it could not be demonstrated whether the effects of specific allergen immunizations rely on true immunological mechanisms or not. Thus, the demonstration of the immunological mechanism in allergen-specific immunotherapy, including the role of peripheral Tregs and their secreted suppressive cytokines, was a decisive step in both the understanding of the immunological background of this allergen-specific treatment and in allergic diseases in general. For a long time, and against clear facts, it was originally believed that specific allergen treatment should skew a Th2 into a Th1 response, which is clearly not the case since both extremes reflect pathogenic situations. From the understanding of mechanisms in allergen-specific immunotherapy, the knowledge of peripheral tolerance induction and the importance of the allergen-specific Treg cells have mostly appeared.

While on the one hand the aspects of Tregs and tolerance induction in allergen-specific immunotherapy and different procedures of vaccination are described, one chapter is added which describes future possibilities of stem cell transplantation in genetically linked disorders.

Thus, based on the role of different subpopulations of T cells activated by allergen and their cytokine production and interaction with effector and tissue cells, leading to different allergic manifestations, this book provides a modern overview on the T-cell-dependent immunoregulatory events in allergic inflammations and their clinical and therapeutic applications.

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