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T cell Plasticity and Cytokine Networks in Allergic Disorders

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Introduction

Allergic disorders such as asthma, atopic dermatitis, allergic rhinitis, and food allergies are characterized by dysregulated immune responses to harmless environmental antigens. Central to their pathogenesis is the imbalance of T cell-mediated immunity, wherein effector T helper cell subsets and their associated cytokines orchestrate inflammatory cascades. Traditionally, allergic diseases were considered primarily Th2-driven disorders, with cytokines such as IL-4, IL-5, and IL-13 promoting immunoglobulin E (IgE) production, eosinophil recruitment, and airway hyperresponsiveness. However, advances in immunology have revealed that the T cell compartment is highly plastic, and immune responses in allergy cannot be explained by a simple Th1/Th2 dichotomy. Instead, a dynamic interplay of T helper subsets—including Th17, Th9, Th22, T follicular helper (Tfh), and regulatory T cells (Tregs)—shapes allergic inflammation through complex cytokine networks. This paradigm shift underscores that allergic disorders result from a continuum of T cell phenotypes, capable of interconverting depending on environmental cues, cytokine milieu, and epigenetic regulation. Understanding T cell plasticity and cytokine crosstalk is crucial for unraveling allergy pathogenesis and identifying novel therapeutic strategies [1].

Description

The concept of T cell plasticity arises from the observation that T helper cells, once thought to be terminally differentiated, can adapt their phenotype and function in response to extracellular signals. For example, Th17 cells may adopt Th1-like characteristics under the influence of IL-12, producing IFN-γ in addition to IL-17. Similarly, Th2 cells may co-express IL-9 or IL-22 depending on the cytokine microenvironment. This flexibility allows T cells to mount context-specific responses but also contributes to pathological inflammation when misregulated. In allergic disorders, the plasticity of Th2 cells is particularly relevant, as they may amplify inflammation through cross-talk with other subsets. For instance, Th2/Th17 hybrid cells have been identified in severe asthma, correlating with corticosteroid resistance and neutrophilic inflammation. These hybrid phenotypes blur the boundaries between classical T helper lineages and demonstrate how plasticity contributes to heterogeneity of allergic disease phenotypes [2].

The cytokine milieu plays a central role in shaping T cell differentiation and plasticity. Naïve CD4+ T cells differentiate into specific lineages depending on antigen stimulation and cytokine signals. IL-4 promotes Th2 differentiation, IL-6 and TGF-β favor Th17 differentiation, IL-2 and TGF-β support Treg generation, and IL-12 drives Th1 differentiation. However, these signals are not fixed; they interact dynamically and can redirect lineage commitment. In allergic diseases, epithelial-derived cytokines such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 act as upstream alarmins, priming dendritic cells and T cells toward type 2 inflammation. These alarmins activate innate lymphoid cells (ILC2s), which in turn secrete IL-5 and IL-13, further promoting Th2 responses. Importantly, the cytokine network is bidirectional: T cell-derived cytokines also influence epithelial and innate immune cells, creating a feed-forward loop that sustains allergic inflammation. Thus, the cytokine environment is not only a driver of T cell differentiation but also a product of T cell activity, forming a self-reinforcing circuit [3,4].

Regulatory T cells (Tregs) represent a counterbalance to effector T cell-mediated inflammation by maintaining tolerance to allergens. Tregs, particularly those expressing the transcription factor FOXP3, suppress Th2 responses through the production of IL-10 and TGF-β, as well as through cell–cell contact-dependent mechanisms. In allergic individuals, Treg frequency and function are often impaired, leading to inadequate suppression of type 2 inflammation. Moreover, Treg plasticity adds another layer of complexity: under pro-inflammatory conditions, Tregs can lose FOXP3 expression and convert into effector-like cells, producing IL-4 or IL-17 and contributing to disease pathology. This instability of Treg lineage fidelity underscores the delicate balance between tolerance and inflammation in allergic disorders. Restoring Treg stability and function is therefore a major therapeutic goal in allergy management. Epigenetic regulation also underlies T cell plasticity and cytokine network dynamics in allergic diseases. DNA methylation, histone modifications, and non-coding RNAs shape the transcriptional programs of T cells and determine their lineage commitment. For instance, the GATA3 locus, essential for Th2 differentiation, is epigenetically regulated, and its demethylation facilitates persistent Th2 responses [5].

Conclusion

Allergic disorders exemplify the complexity of T cell plasticity and cytokine networks in shaping immune responses. The traditional Th1/Th2 paradigm has evolved into a multidimensional framework where diverse T helper subsets, hybrid phenotypes, and regulatory cells interact in dynamic and context-dependent ways. Cytokine networks form self-reinforcing circuits that sustain inflammation, while epigenetic and environmental factors continuously remodel T cell programs. The heterogeneity of allergic diseases reflects this interplay, explaining variations in clinical presentation, severity, and treatment response. A deeper understanding of T cell plasticity and cytokine cross-talk not only advances our knowledge of allergy pathogenesis but also guides the development of precision therapies that move beyond one-dimensional cytokine blockade. By targeting the cellular and molecular plasticity that underlies allergic inflammation, future strategies may achieve not just symptom control but also immune tolerance and long-term disease modification.

Acknowledgement

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Conflict of Interest

None.

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