

T cells in health and disease

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Various populations of effector and regulatory T (Treg) cells have been shown to play a central role in chronic inflammation in various diseases, the maintenance of peripheral homeostasis, and the establishment of controlled immune responses. Depending on the substances coexposed with the antigen and the status of the cells and cytokines in the microenvironment, CD4⁺ naive T cells can differentiate into T_H1, T_H2, T_H9, or T_H17 effector cells.¹ Based on their respective cytokine profiles, responses to chemokines, and interactions with other cells, these T-cell subsets can promote different types of inflammatory responses. The last 2 issues of the *Journal of Allergy Clinical Immunology* have complemented each other with extensive "Review articles" and "Current perspectives" articles on effector and Treg cell subsets. The current issue has a special focus on T_H17 cells. Since its identification, IL-17 has been described as a T cell–derived cytokine that is highly expressed during autoimmune disorders and is able to activate epithelial cells during inflammatory responses. Retinoic acid–related orphan receptor γ t in mice and retinoic acid–related orphan receptor C2 in human subjects were identified as lineage-specific transcription factors, and T cells that predominantly produce IL-17A were classified as T_H17 cells in 2006. More data have been accumulated, and it was shown that they produce IL-22, IL-17F, CCL20, and IL-26. In addition, it was understood that T_H17 cells play important roles in other T cell–mediated inflammatory diseases, such as in autoimmunity, asthma, and organ transplantation. As a default mechanism, T_H17 cells contribute to host defense with roles in protection against extracellular bacteria through activities on immune and nonimmune cells.

In this issue of the *Journal*, Louten et al² review conditions for differentiation of T_H17 cells in both mouse and human systems, T_H17-specific cytokines, and transcription factors in their "Current perspectives" article. Their roles in asthma and autoimmunity are emphasized, and T-cell receptor $\gamma\delta$ T cells, inducible natural killer T cells, NK-22 cells, and lymphoid tissue inducer–like cells are discussed as additional subsets of IL-17–producing cells, IL-22–producing cells, or both.² In the same issue Kopf et al³ review IL-17–producing T cells in lung immunity and

inflammation in a more clinically relevant focus on lung immunity. IL-17 is upregulated in lung diseases, such as severe asthma, chronic obstructive pulmonary disease, and cystic fibrosis. The authors discuss the recent literature regarding the function of T_H17 cells and their associated cytokines in pulmonary immune responses and allergic airway inflammation.

Peripherally induced Treg cells and T_H17 effector cells arise in a mutually exclusive fashion, depending on whether they are activated in the presence of TGF- β or TGF- β plus inflammatory cytokines, such as IL-6. The mucosal surface of the intestine alone forms the largest surface that is exposed to exogenous antigens and microbes, as well as the largest collection of lymphoid tissue in the body. A protective immune activity must coexist with efficient regulatory mechanisms to maintain the health status of these organisms. In their "Current perspectives" article, Mucida and Salek-Ardakani⁴ address the protective and pathogenic roles of T_H17 cells in the mucosal surfaces and immune regulatory mechanisms that control their development. Under the influence of microbial-derived stimuli and adenosine 5'-triphosphate, lamina propria CD70^{high} dendritic cells, CD103⁺ dendritic cells, or both induce T_H17 differentiation through the production of TGF- β , IL-6, and IL-23. Production of TGF- β by lamina propria cells also promotes the anti-inflammatory forkhead box protein 3–positive induced Treg cells. The balance between T_H17 and Treg cell development is favored toward Treg cells on the influence of retinoic acid produced by lamina propria and Peyer patch CD103⁺ dendritic cells, lamina propria macrophages, and intestinal epithelial cells. A part of their Fig 1, which suggests a mechanism for T_H17 and Treg cell induction in the gut is displayed as the cover figure of the present issue.

The most significant data for the *in vivo* relevance of lymphocytes in human subjects has been demonstrated in primary immune deficiency diseases with deficient expression of essential factors for their induction and effector functions. In the present issue Ochs et al⁵ reviewed features and primary immune deficiency associations of CD4⁺ T-cell subsets in their "Clinical reviews" article. Heterozygous signal transducer and activator of transcription 3 defects are shown to be the molecular cause of autosomal dominant hyper-IgE syndrome with the demonstration that patients with this disorder might have defective T_H17 cell development, function, or both. In addition, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome is reviewed, and other single genes that, if mutated in human subjects, result in reduced Treg function, such as CD25, signal transducer and activator of transcription 5b, autoimmune regulator, and Wiskott-Aldrich syndrome protein, are mentioned.

The April 2009 issue of the *Journal* had a special focus on Treg cells. The identification of Treg cells as key regulators of immunologic processes in peripheral tolerance to allergens, organ transplantation, autoimmunity, tumor tolerance, and tolerance to microorganisms during chronic infections has opened an important era in prevention and treatment. Current strategies for drug development exploit these observations with the potential

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for preventive therapies and cures for T cell–mediated diseases. In their review article in the April issue of the *Journal*, Miyara et al⁶ discussed how Treg cell–related immunomodulation can be used as a treatment strategy. Activation and expansion of antigen-specific Treg cells *in vivo* and cell therapy with *in vitro* activated and expanded Treg cells are the 2 strategies being pursued. These Treg cell–based therapeutic methods are discussed in the context of the molecular and cellular basis of Treg cell development and function.

IL-2 plays a pivotal role in regulating the adaptive immune system by controlling the survival and proliferation of Treg cells, which are required for the maintenance of immune tolerance, as well as homeostasis of effector T-cell subsets, including T_H1, T_H2, T_H17, and memory CD8⁺ T cells. In his “Current perspectives” article, Létourneau et al⁷ reviewed these findings and integrated them into the current understanding of T-cell homeostasis. IL-2 exerts apparently contradictory functions, promoting proliferation, differentiation, and function of activated CD4⁺ and CD8⁺ T cells while inducing the activation-induced cell death of CD4⁺ T cells and mediating the survival of Treg cells. Increasing evidence now suggests a key role for IL-2 in maintaining the balance between protection from pathogens and suppression of self-reactive T cells by providing a powerful negative feedback loop to immune responses. In the same issue Akdis and Akdis¹ reviewed the essential role of forkhead box protein 3–positive Treg and Treg type 1 cells and molecular and cellular mechanisms in allergic disease. The cover of the April issue suggests that more functional T-cell subsets are emerging, as shortly introduced in the article. In addition, suppressive functions of IL-10 and TGF- β , as well as Treg cells and specific IgE and IgG4 antibodies, and their relationship to Treg cells in healthy immune responses to allergens and allergen-specific immunotherapy are discussed.

The same issue highlights 2 key findings for Treg cells. Nguyen et al⁸ demonstrated that Treg cells, but not CD4⁺CD25[–] T cells, from allergic asthmatic subjects showed decreased chemotactic response, specifically to CCL1, in comparison with those from their healthy control and nonallergic asthmatic counterparts.

The decreased chemotactic response to CCL1 in Treg cells from allergic asthmatic subjects significantly correlated with asthma severity and decreased pulmonary function in these subjects. An interesting extension of the hygiene hypothesis is reported by Schaub et al.⁹ Their study demonstrates that farm exposure during pregnancy increases the number and function of cord blood Treg cells associated with lower T_H2 cytokine secretion and lymphocyte proliferation on innate exposure. Their findings suggest a “natural model of intrauterine immunomodulation” and role for Treg cells in the hygiene hypothesis.

Given the speed of recent growth in the area along with the recent advances in the knowledge of effector and Treg cells and related mechanisms that lead to inflammation, tissue injury, or peripheral tolerance, developments regarding safer approaches and better treatments for many immune-mediated diseases are imminent.

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