Clinical reviews in allergy and immunology

Series editors: Donald Y. M. Leung, MD, PhD, and Dennis K. Ledford, MD

T_H17 cells and regulatory T cells in primary immunodeficiency diseases

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Activity Objectives

1. To understand the biology, development, and function of T_H17 and regulatory T cells.

2. To understand the differences in T_H17 and regulatory T-cell development between murine and human naive $CD4^+$ T cells.

3. To identify the role of T_H17 and regulatory T cells in primary immunodeficiency diseases.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: H. D. Ochs has served on intravenous immunoglobulin advisory boards for Baxter and CSL-Behring and has received research support from the Jeffrey Modell Foundation and CSL-Behring. T. R. Torgerson has served on an advisory board for Baxter Healthcare and has received research support from CSL-Behring.

After activation by unique cytokines, $CD4^+$ naive T cells differentiate into lineages of helper/effector (T_H) and regulatory T (Treg) cells that are characterized by distinct developmental pathways and unique biologic functions. The trusted binary system of T_H1 and T_H2 has been expanded to include the IL-17–producing T_H17 cell lineage, which plays a role in immune responses to infectious agents and maintenance of autoimmune diseases. Acting as counterbalance, Treg cells maintain peripheral tolerance and protect the host from autoaggressive lymphocytes. T_H1 cells produce IFN-γ and are involved in cell-mediated immunity, T_H2 cells produce IL-4 and contribute to humoral immunity, T_H17 cells generate IL-17 and play an important role in immune responses to fungi and extracellular pathogens, and forkhead box protein 3–positive ($FOXP3^+$) Treg cells secrete TGF-β and IL-10 and downregulate effector T cells. Autosomal dominant hyper-IgE syndrome, a rare primary immunodeficiency disorder, is caused by hypomorphic heterozygous mutations of signal transducer and activator of transcription 3 (STAT3), preventing T_H17 lineage differentiation and increasing susceptibility to *Staphylococcus* and *Candida* species infections. Mutations in the *FOXP3* gene interfere with Treg cell development and cause immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. Other single-gene defects resulting in reduced Treg cell function include CD25, signal transducer and activator of transcription 5b, autoimmune regulator, and Wiskott-Aldrich syndrome protein. These observations emphasize the importance of functionally distinct T-cell lineages in maintaining a balanced innate and cognate immune system. (J Allergy Clin Immunol 2009;123:977-83.)

Key words: *Regulation of T effector cell lineage differentiation, T_H17 cells, regulatory T cells, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, forkhead box protein 3, autosomal dominant hyper-IgE syndrome, signal transducer and activator of transcription 3, IL-17, TGF-β, IL-10*

Based on their pioneering work, Mosmann and Coffman[1] proposed some 20 years ago that T_H cells could be divided into 2 distinct subsets, T_H1 and T_H2, characterized by distinct cytokine profiles and effector functions. T_H1 cells produce large quantities of IFN-γ, elicit delayed-type hypersensitivity responses, activate macrophages, and are highly effective in clearing intracellular

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Received for publication March 2, 2009; revised March 23, 2009; accepted for publication March 26, 2009.

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0091-6749/$36.00

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doi:10.1016/j.jaci.2009.03.030

Abbreviations used
AD-HIES: Autosomal dominant hyper-IgE syndrome
AIRE: Autoimmune regulator gene
APECED: Autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy
FOXP3: Forkhead box protein 3
FuT7: α-1, 3-Fucosyltransferase VII
IPEX: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked
RORγt: Retinoic acid–related orphan receptor γ T
STAT: Signal transducer and activator of transcription
T-bet: T-box transcription factor
Treg: Regulatory T
WAS: Wiskott-Aldrich syndrome
WASP: WAS protein

pathogens. T_H2 cells, on the other hand, produce IL-4, IL-5, IL-13, and IL-25 and are important for IgE production, eosinophilic inflammation, and the clearance of helminthic parasite infections.[2] In light of recent data, the T_H1/T_H2 dichotomy is now being revisited. The discovery of the IL-17 family of cytokines and the analysis of IL-23–mediated effector functions on T cells have suggested the existence of an additional subset of $CD4^+$ T cells that produce IL-17 and for this reason were designated T_H17 cells.[3-6] The independence of the T_H17 subset with regard to T_H1 and T_H2 cells was firmly established with the identification of specific cytokines and transcription factors required for lineage differentiation ie the combination of IL-6 and TGF-β[7-9] and the transcription factors retinoic acid–related orphan receptor γ (RORγt)[10] and signal transducer and activator of transcription (STAT) 3.[11,12] T_H17 effector functions are distinct from T_H1- and T_H2-mediated immunity. T_H17 cells appear to be critical for enhancement of host protection against extracellular bacteria and fungi, which are not efficiently cleared by T_H1 and T_H2 responses. In addition, T_H17 cells have emerged as potent mediators of autoimmune disease.

Including the regulatory T (Treg) cell subset,[13] there are now 4 functionally unique populations of $CD4^+$ T cells that are directly involved in the regulation of immune responses to pathogens, allergens, and self-antigens. Any molecular defect involving either the entire $CD4^+$ T-cell population, such as severe combined Immunodeficiency, or individual subsets, such as lack of Treg cells[14] or IL-17 cells,[15] might result in human disease (Table I). In this review we explore the biology of T_H17 and Treg cells and their roles in human primary immune deficiency diseases.

DIFFERENTIATION AND FUNCTION OF T_H17 CELLS

Since their discovery, T_H17 cells have been recognized as a unique effector T-cell subset capable of producing IL-17, a cytokine originally cloned in 1995.[16] IL-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines[17] and initiates the recruitment of neutrophils, linking adaptive and innate immunity.[18]

Initial studies of T_H17 cell biology performed in mice focused on identifying key factors required for the differentiation and function of T_H17 cells. Early investigations of T_H17 cell development in human subjects suggested that it might differ from that observed in the mouse[19-21]; more recent reports, however, suggest that major events controlling T_H17 cell development are similar in both species.[22-24]

To become T_H17 cells, naive murine $CD4^+$ T cells have to be activated through the T-cell receptor in the presence of TGF-β and IL-6, which leads to the expression of the transcription factor RORγt.[10] Just as IFN-γ, IL-12, and T-box transcription factor (T-bet) control T_H1 development and IL-4 and GATA3 control T_H2 development, TGF-β, IL-6, and RORγt drive naive $CD4^+$ T cells toward the T_H17 lineage, at least in part, by directly inducing the expression of IL-17.[25] The effects of IL-6 on T_H17 cell differentiation are mediated by the transcription factor STAT3, which is required for RORγt expression (Table I).[11,12,26] In patients with autosomal dominant hyper-IgE syndrome (AD-HIES) caused by heterozygous *STAT3* mutations that cause the generation of nonfunctional STAT3, RORγt expression and T_H17 cell development is severely impaired.[15,27]

In human effector T-cell differentiation, TGF-β and IL-6 are important in the generation of T_H17 cells, but IL-1β also appears to play a prominent role in the induction of RORγt. This is further enhanced by IL-23.[19,20] In mice IL-23 seems to play a role only in activated T cells that express the IL-23 receptor and therefore might induce T_H17 differentiation in memory, but not in naive, T cells,[28] suggesting that IL-23 upregulates IL-17 production and promotes survival and expansion of activated memory T_H17 cells. If this assumption is correct, IL-23 must be crucial for the maintenance of autoimmune inflammation.[4,29] A recent in-depth analysis has concluded that TGF-β, IL-23, and the proinflammatory cytokines IL-1β and IL-6 are, in fact, essential mediators of human T_H17 cell differentiation and are required for the expression of IL-17, IL-23 receptor, and RORγt.[23] These observations were confirmed by the Littman laboratory, which reported that human cord blood $CD4^+$ T cells, naive by definition, differentiate into T_H17 cells only if TGF-β, IL-1β, IL-6, and IL-23 or IL-21 are present and that this process requires the expression of RORγt but not T-bet or GATA3.[22] These studies demonstrate that TGF-β and IL-6 are important for T_H17 development in both human subjects and mice, whereas IL-1β and IL-23 play a more important role in human subjects than mice.

CYTOKINE PRODUCTION BY T_H17 CELLS

The T_H17 signature cytokines IL-17 (IL-17A) and IL-17F are closely related and form biologic active homodimers or heterodimers. By interacting with its receptor, IL-17 initiates nuclear factor κB activation, which leads to the transcription of multiple target genes involved in innate immunity. These include chemokines, such as CXCL8 (IL-8) and CCL20; the cytokines IL-6, TNF-α, granulocyte colony-stimulating factor (G-CSF), and GM-CSF; acute-phase proteins, such as C-reactive protein; and antimicrobial peptides and mucins.[30] Thus IL-17 plays an important role in antimicrobial defenses by recruiting and expanding the neutrophil lineage and producing antimicrobial factors. In addition, antibody responses to T-dependent antigens are defective in IL-17–deficient mice[31] and in patients with AD-HIES who lack T_H17 cells.[32]

In addition to IL-17, activated murine T_H17 cells produce IL-21, which appears to play an important autocrine role in maintaining T_H17 cell differentiation, similar to the autocrine function of IFN-γ in the generation of T_H1 cells and IL-4 in promoting T_H2 cells (Table I and Fig 1). In mice IL-21 expression is under the control of STAT3, which binds to the IL-21 promoter in T_H17

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