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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.

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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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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

TABLE I. Characteristic features and disease association of $CD4^+$ T-cell subsets

Characteristic properties	$CD4^+$ T-cell subsets			
	T_H1	T_H2	T_H17	Induced Treg cells
Signature cytokines	IFN-γ	IL-4	IL-17, IL-17F	TGF-β
Additional cytokines produced	Lymphotoxin α, IL-2	IL-5, IL-13, IL-25	IL-21, IL-22	IL-10, IL-35
Autocrine cytokines	IFN-γ	IL-4	IL-21	TGF-β
STAT regulators	STAT1, STAT4	STAT6, STAT5	STAT3	STAT5
Lineage-specific transcription factors	T-bet	GATA-3	RORγt	FOXP3
Cytokine/chemokine receptors	IL-12R, IL-18Rα, CXCR3	IL-4Rα, IL-33Rα, CCR3, CCR4, CCR8	IL-23R, CCR6, CCR4	CD25 (IL-2 receptor α)
Associated primary immunodeficiency diseases	IFN-γ receptor 1/2 deficiency	Omenn syndrome	AD-HIES (STAT3 deficiency)	IPEX (FOXP3 deficiency)
	IL-12/23 receptor β1 deficiency	Allergic diathesis	IL-12/23 receptor β1 deficiency	IPEX-like/SCID (CD25/IL-2 receptor α deficiency)
	IL-12 p40 deficiency	Overexpression of T_H2 cells	IL-12p40 deficiency	Laron dwarfism (STAT5β deficiency)
	STAT1 deficiency			WAS (WASP)
				APECED (AIRE)
	T^- SCID caused by mutations of γc, JAK3, IL-7 receptor α, CD45, CD3δ/CD3ϵ/CD3ζ, RAG1/2, Artemis, ADA			

SCID, severe combined immunodeficiency; *WASP*, WAS protein; *JAK3*, Janus kinase 3; *RAG*, recombinase-activating gene; *ADA*, adenosine deaminase.

cells. Although IL-21 production is RORγt independent, IL-21 itself helps to sustain expression of RORγt and IL-17 and induces IL-23 receptor expression.[33-35] A role for IL-21 in the differentiation of human T_H17 cells is less clear, although it is likely based on the observation that IL-21 upregulates IL-17 production and downregulates Treg cell function.[36,37]

Other proinflammatory cytokines produced by human and murine T_H17 cells include TNF-α, IL-22, and IL-26, which are involved in innate immunity, and IL-6, which directs $CD4^+$ T-cell differentiation toward the T_H17 lineage, as discussed above.[38] IL-22 has been associated with the generation of defensins, acute-phase proteins, and inflammatory cytokines.[30,39] Some subsets of T_H17 cells can coexpress IL-17 and IFN-γ[19] or IL-17 and IL-10,[40] respectively; however, the function of these double-positive T cells remains to be determined. It has been suggested, based on mouse models, that T_H17 cells are not as stable as T_H1 or T_H2 cells and that in the presence of IL-12, T_H17 cells might revert to T_H1-like cells.[41]

TRAFFICKING OF T_H17 CELLS

To be effective, the adaptive immune system has the fundamental task of facilitating the encounter of antigen-specific T and B lymphocytes with exogenous antigens and with one another. Exogenous antigens are picked up, processed, and presented by antigen-presenting cells in specialized microenvironments within secondary lymphoid organs, skin, and mucous membranes. CCR7, expressed by mature dendritic cells and T cells, including Treg cells, and its ligands CCL19 and CCL21 play a major role in the homing of dendritic cells and naive T cells to secondary lymphoid organs, where antigen presentation and effector T-cell differentiation takes place.[42]

Both human and murine T_H17 cells express CCR6,[43,44] although not all $CCR6^+$ cells are T_H17 cells. Coexpression of CCR4 with CCR6 appears to correlate with a classic T_H17 cell phenotype, including RORγt expression and IL-17 production.[43] Interestingly, CCR6 induces homing of cells to skin and mucosal sites and plays a causative role in many inflammatory diseases considered to be initiated and/or maintained by IL-17, including psoriasis, ulcerative colitis, asthma, and rheumatoid arthritis. The CCR6 ligand CCL20 is expressed by T_H17 cells and is upregulated in stromal cells by IL-17, allowing the attraction of additional T_H17 cells into inflamed tissue.[44]

FORKHEAD BOX PROTEIN 3–POSITIVE TREG CELLS

Whereas naive murine $CD4^+$ T cells differentiate into T_H17 cells if cocultured with TGF-β and IL-6, as described above, exposure to TGF-β and IL-2 causes differentiation into a Treg cell phenotype, including forkhead box protein 3 (Foxp3) expression and suppressive function.[8] Furthermore, addition of retinoic acid to the culture enforces the generation of Treg cells and inhibits the differentiation of T_H17 cells.[45]

Treg cells play a critical role in the maintenance of self-tolerance by suppressing, in a dominant manner, immune activation of self-aggressive T effector cells.[13] Upregulation of Treg cell function or increases in the numbers of cells might be beneficial for treating autoimmune diseases and allergies and for preventing allograft rejection. Conversely, inhibiting Treg cell function or decreasing Treg cell numbers might boost immunity against tumors and microorganisms.

Treg cells are characterized by the expression of the transcription factor FOXP3,[46-48] which is induced by TGF-β in the presence of IL-2 (Table I and Fig 1).[49] Absence of FOXP3 in patients with immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome[14] or scurfy mice[50] results in lack of functional Treg cells. Overexpression of FOXP3 in conventional T cells directs them to a Treg cell phenotype with suppressive activity, leading to a state of immune deficiency.[46,51] The majority of Treg cells express high levels of CD25 (IL-2 receptor α),[13] suggesting a major influence of IL-2 for the long-term maintenance and competitiveness of these cells. STAT5, which is activated by IL-2, has been shown to be required for the maintenance of FOXP3 expression through binding to its promoter.[52,53] Treg cells also express TGF-β, IL-10, cytotoxic T lymphocyte–associated antigen 4

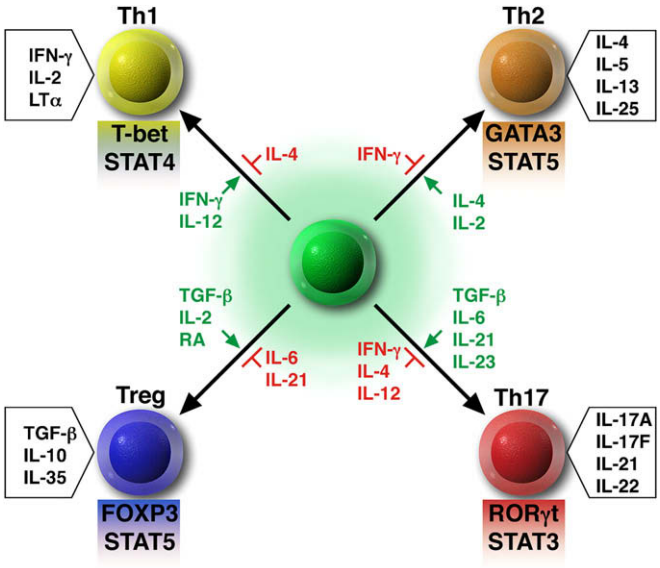

FIG 1. Model of $CD4^+$ T-cell differentiation through the use of cytokine- and transcription factor–driven pathways. Each of the 4 $CD4^+$ T-cell subsets generates a unique set of cytokines that control their biologic functions. *Shaded boxes* below each subset indicate key transcription factors involved in the development and maintenance of each subset. *Green*, Cytokines that promote development of each particular subset. *Red*, Cytokines that prevent the development of each particular subset. *LTα*, Lymphotoxin α; *RA*, retinoic acid.

(CTLA4), and glucocorticoid-induced TNF receptor (GITR), which might play a role in their function.

Treg cells can either differentiate in the thymus and emigrate into the periphery as fully functional natural suppressor cells, or they can be induced in the periphery from naive T-cell precursors. The differentiation of Treg cells from naive CD4 T cells occurs when exposed to TGF-β and IL-2.[8] It has recently been demonstrated in mice that Treg cell–derived TGF-β can generate *de novo* $CD4^+Foxp3^+$ T cells *in vitro* from naive precursor T cells.[54]

Homing of Treg cells to sites of inflammation is required for their suppressive function. Schneider et al[55] recently demonstrated that in CCR7 knockout mice, $CD4^+CD25^+Foxp3^+$ Treg cells were unable to home to lymph nodes and were unable to suppress antigen-induced T-cell responses. When compared with wild-type Treg cells, the CCR7-deficient Treg cells were less effective in preventing the development of inflammatory bowel disease when transferred into a severe combined immunodeficiency mouse model. The importance of cutaneous Treg cells for the maintenance of immune homeostasis in the skin has been elegantly demonstrated in transfer experiments using Foxp3-deficient scurfy mice. Neonatal scurfy mice were injected with functional Treg cells that were manipulated to no longer be able to migrate to the skin by inducing a targeted mutation of the gene encoding α-1, 3-fucosyltransferase VII (FuT7). This enzyme is required for the generation of the carbohydrate determinants of the E- and P-selectin ligands, which are required for optimal migration of T cells to the skin. FuT7-deficient Treg cells restored the Treg cell compartment, except for the skin. Loss of FuT7 selectively reduced Treg cell accumulation in the skin and resulted in severe cutaneous inflammation without other scurfy-associated symptoms.[56]

T_H17 CELLS IN PRIMARY IMMUNODEFICIENCY DISEASES

As described above, differentiation of murine T_H17 cells from naive $CD4^+$ T cells depends on IL-6 and TGF-β signaling and the activation of STAT3. This was confirmed by the observation that $CD4^+$ T cells conditionally deficient in STAT3 demonstrated impaired differentiation into T_H17 cells and showed reduced production of IL-17.[11,26] The recent identification of heterozygous STAT3 defects as the molecular cause of AD-HIES raised the interesting possibility that patients with this disorder might have defective T_H17 cell development, function, or both. In addition, the observations that patients with AD-HIES/Job syndrome are uniquely susceptible to *Candida* species infections,[57,58] that *Candida* species–specific human memory T cells are predominantly present in the T_H17 cell subset,[43] and that IL-17– and IL-17 receptor–deficient mice had substantially reduced survival compared with that seen in control mice when challenged with *Candida albicans*[59] led to a systematic assessment of T_H17 cells in patients with AD-HIES.[15,27,60,61] AD-HIES is an autosomal dominant primary immune deficiency disorder characterized by eczema, *Staphylococcus aureus* skin abscesses, pneumonia with pneumatocele formation, *Candida* species infections, and skeletal and connective tissue abnormalities.[58] Immunologic defects reported include markedly increased serum IgE levels, eosinophilia, a neutrophil chemotactic defect,[62] abnormal cytokine production,[63] and abnormal antibody responses to bacteriophage ΦX174.[32] As a result, patients with AD-HIES have abnormal susceptibility to a narrow spectrum of infections, including *S aureus* and *C albicans*.

Flow cytometric analysis of peripheral blood lymphocytes and $CD4^+$ T cells from patients with AD-HIES and healthy control subjects showed a comparable distribution of naive and memory T cells. However, the proportion of circulating T_H17 cells was noted to be markedly diminished.[15,27,60,61] Circulating $CD4^+$ T cells from healthy control subjects, if activated with anti-CD3/anti-CD28 mAb, secreted abundant amounts of IL-17 and IL-22; in contrast, cells from patients with AD-HIES did not secrete either of these lymphokines, demonstrating that in human subjects production of both IL-17 and IL-22 by activated T cells is dependent on functional STAT3.[27] Furthermore, purified naive T cells from patients with AD-HIES were unable to differentiate *in vitro* to T_H17 cells when submitted to T-cell receptor activation (anti-CD3/anti-CD28) in the presence of a cocktail of cytokines (IL-1β, IL-6, and IL-23).[15,27] Interestingly, the expression of RORγt mRNA was also markedly impaired in AD-HIES cells cultured under these conditions,[15,27] which is in agreement with the hypothesis that impaired STAT3 function interferes with the expression of RORγt, which is required for T_H17 cell differentiation.

To test the effect of other cytokines that govern the differentiation of T_H17 cells in humans, de Beaucoudrey et al[60] studied T_H17 cell development in patients with mutations in the IL-1 receptor–associated kinase 4 gene *(IRAK4)* or myeloid differentiation primary response gene 88 *(MYD88)*, the cells of which do not respond to IL-1β, and in patients with mutations in the IL-12 p40 subunit gene *(IL12B)* or IL-12 p40 subunit receptor 1 gene *(IL12RB1)*, the cells of which do not express or do not respond to IL-12 or IL-23. Results of these *in vitro* studies demonstrated that mutations in *IRAK4*/*MYD88* had no detectable effect on T_H17 cell generation but that mutations in IL12B and IL12RB1 led to impaired generation of IL-17–producing cells, although

less pronounced than seen in patients with heterozygous STAT3 mutations. These observations suggest that IL-12 and IL-23 are important for T_H17 cell differentiation in human subjects but that T cells that are hyporesponsive to IL-1β can still be driven into the T_H17 lineage (Table I).

FOXP3$^+$ TREG CELLS IN PRIMARY IMMUNODEFICIENCY DISEASES

Mutations in the FOXP3 transcription factor result in IPEX syndrome (Table I). The majority of affected individuals lack circulating and tissue-associated FOXP3$^+$ Treg cells and have multiple autoimmune disorders affecting the gut, skin, endocrine organs, blood cells, and joints. Death typically occurs in early childhood unless treated with aggressive immunosuppression, hematopoietic stem cell transplantation, or both.[14] The scurfy mouse, characterized by lymphocytic infiltrates in multiple organs and early death as a result of Treg cell deficiency,[50] has a naturally occurring mutation of Foxp3: a 2-bp insertion upstream of the forkhead domain, resulting in a frame shift and loss of the DNA-binding domain.[64]

A clinical syndrome resembling IPEX syndrome is associated with mutations in the α-chain of the IL-2 receptor (CD25). Patients lacking CD25 present with an IPEX-like phenotype; in addition, they have infectious complications resembling those observed in patients with T-cell deficiency, such as recurrent cytomegalovirus-induced pneumonitis, *Candida* species infections, and chronic gastrointestinal disease.[65,66] CD25-deficient mice have a phenotype similar to that of scurfy mice.[67] Although Treg cell development in the thymus and *in vitro* suppressive function of CD4$^+$Foxp3$^+$ T cells are normal, these mice have a defect in survival, maintenance, and competitive fitness of mature Treg cells.[68,69]

Mutations of STAT5b, a key mediator of IL-2–induced gene transcription, cause a rare recessive disorder characterized by dwarfism (Laron dwarfs) and low serum concentrations of insulin-like growth factor 1 (but normal serum growth hormone levels).[70-72] Other physical features include a prominent forehead, a saddle nose, and a high pitched voice. Most patients have a marked immune deficiency characterized by recurrent varicella and herpes virus infections and *Pneumocystis jiroveci*–induced pneumonia, suggesting defective T-cell and natural killer cell function.[71,72] In addition, most patients with STAT5b mutations present with diarrhea, eczema, and lymphocytic interstitial pneumonitis, suggesting immune dysregulation.[70-72] Patients studied for Treg cell pathology showed fewer CD4$^+$CD25^{high} cells with decreased FOXP3$^+$ expression,[70,72] and the 1 patient evaluated for Treg cell function demonstrated reduced suppressive activity against either autologous or allogeneic effector cells.[70] A likely explanation for this observation was the markedly decreased CD25 expression (20% of normal values) by this patient's T cells in response to activation because of STAT5b deficiency, as well as defective signaling from the IL-2 receptor complex. This reduced expression of CD25/IL-2 receptor α and defective STAT5b-mediated gene transcription interferes with IL-2 signals required for the maintenance of FOXP3 expression and Treg cell function.[70]

Autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED) syndrome is an autosomal recessive disorder characterized primarily by hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis. Type 1 diabetes, gonadal failure, and pernicious anemia also occur but are less frequent. APECED syndrome is caused by mutations in the autoimmune regulator gene *(AIRE)*, a transcription factor responsible for the ectopic expression of tissue-specific antigens on thymic medullary epithelial cells. As a consequence, AIRE is essential for the negative selection of autoreactive T-cell clones.[73,74] Lymphocytes from patients with APECED syndrome were evaluated by means of flow cytometry and quantitative real-time PCR to address the possibility of AIRE playing a role in the generation of functional Treg cells. Consistently, the percentages of CD4$^+$CD24^{high} cells were decreased, the amount of FOXP3 expressed per cell was diminished, and the ability to suppress effector T cells was reduced.[75]

The Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder caused by mutations in the gene encoding WAS protein (WASP).[76] In addition to thrombocytopenia, small platelets, eczema, recurrent infections caused by cellular immunodeficiency, and malignancies, approximately 40% to 70% of the patients with classic WAS experience autoimmune diseases.[77,78] In mice WasP does not play a role in thymic Treg cell production but is required for peripheral Treg cell expansion and survival and for effective suppressive function.[79-81] Although WASP deficiency in human subjects is not associated with a decrease in the percentage of Treg cells in the peripheral blood, Treg cell function was found to be consistently reduced, as demonstrated by the inability to suppress proliferation of effector T cells.[81]

CONCLUSION

Recent advances made in our understanding of the role of T-cell subsets in the regulation of immune responses against infectious agents and self-antigens have provided new insight into human immunopathology. The discovery that specific cytokines and unique transcriptional regulators control the differentiation of distinct T-cell subsets have expanded and refined the aging T_H1/T_H2 paradigm. New lineage-specific cytokines have been discovered, and their role in the activation of transcription factors, such as T-bet, GATA3, RORγt, and FOXP3, have been explored. Together with members of the STAT family of transcriptional regulators, these DNA-binding proteins direct the differentiation of naive CD4$^+$ T cells into T_H1, T_H2, T_H17, and Treg cells and induce the expression of signature cytokines unique for each T-cell lineage. This impressive progress was made possible by the development of novel biotechnologies that facilitate the study of gene regulation, protein expression, and cell differentiation and by the creation of unique genetically engineered mouse models. These innovative experimental strategies were complemented by careful observation of patients with unique congenital syndromes characterized by immune dysfunction, severe infections, autoimmune diseases, and allergic complications. The beneficiaries of these efforts (as of February 2009, there are 60,000 hits on PubMed when searching for T_H1, T_H2, T_H17, and Treg cells) are the clinical immunologists who have at their disposal new diagnostic techniques, more therapeutic options based on scientific medicine, and the hard facts required for authoritative genetic counseling of these complex patients. It is likely that these advances will lead to entirely new treatment strategies for severe infections, allograft rejection, cancer, and autoimmune and allergic diseases.

What do we know?

- **Naive $CD4^+$ T cells undergo differentiation into functionally unique lineages using distinct developmental pathways.**
- **The signature cytokines for T_H17 cells are IL-17A and IL-17F, and the lineage-specific STAT regulator and transcription factor for T_H17 cells are STAT3 and RORγt, respectively.**
- **The signature cytokine for Treg cells is TGF-β, and the lineage-specific STAT regulator and transcription factor for Treg cells are STAT5 and FOXP3, respectively.**
- **Heterozygous hypomorphic *STAT3* mutations result in AD-HIES/Job syndrome, lack of T_H17 cells, and susceptibility to *S aureus* and *Candida* species infections. Mutations in the X chromosome–associated *FOXP3* gene cause IPEX syndrome.**

What is still unknown?

- **It is possible that there are other $CD4^+$ cell lineages with unique functions.**
- **Can one functionally unique $CD4^+$ lineage change into another unique lineage?**
- **The mechanisms by which IL-17 interacts with the immune system to keep *S aureus* and *Candida* species infections under control are unknown.**
- **The mechanisms by which antigen-specific Treg cells achieve suppression of effector T cells are not understood.**
- **How can one manipulate the function of T_H17 and Treg cells to cure autoimmunity, immune deficiencies, overwhelming infections, graft rejection, graft-versus-host disease, and the development of malignancies?**

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