

T_H17 cells in the big picture of immunology

Carsten B. Schmidt-Weber, PhD, Mübeccel Akdis, MD, PhD, and Cezmi A. Akdis, MD

Davos, Switzerland

The pathogenesis of chronic inflammatory diseases is assumed to depend on activated T cells interacting with resident tissue cells or migratory inflammatory cells. The discovery of new T-cell subsets such as the IL-17-producing T_H17 and T-regulatory cells innovated our understanding of T-cell biology. Studies on new subsets confirm the important role of T cells in the instruction of tissue cells and also demonstrate the important role of feedback regulation for the polarization toward distinct T-cell subsets. The understanding of IL-17 and T_H17 differentiation pathways has also changed the perspective of immunologists regarding the basis of chronic tissue inflammation, particularly where T_H1 cells were considered as driving force of the pathology. This review summarizes the recent developments on T_H cell subsets and integrates these findings into existing concepts of immunopathologic mechanisms. (*J Allergy Clin Immunol* 2007;120:247-54.)

Key words: Tolerance, differentiation, T_H17, T_H2, transcription factor, allergy

The discovery of new T-cell subsets changed our concepts of immune regulation and immunopathology. Antigen-specific immune responses are dependent on B and T cells, characterized by their antigen-specific receptors. In contrast with B cells, T cells do not have direct antigen/allergen contact and play a discriminative role regarding the type and the place of immune responses to be initiated. Initially only 2 subsets were described: IFN- γ -secreting T_H1 cells, assumed to play a role in inflammatory delayed type hypersensitivity, and a T_H2 subset characterized for IL-3, IL-4, IL-5, IL-9, and IL-13 secretion mediating humoral responses. IL-2 expression was observed for both subsets. Murine T_H2 cells do also express IL-10,¹ whereas IL-10 in human beings could not be attributed to either subset² and is discussed as a separate subset (T-regulatory 1 [Tr1] cells). Both T_H1 and T_H2 cells originate from naive T cells (Fig 1), which

Abbreviation used

Treg: T regulatory

polarize on initial antigen contact either to T_H1 or T_H2 cells, when IL-12 or IFN- γ or IL-4 respectively induce a cascade of events resulting in genetic imprinting. This process is assumed to modulate chromatin structures as has been shown for IL-4-induced GATA-3 in the *IL4* locus. The polarization of T-cell phenotypes involves a cross-regulation, where IL-4 inhibits the expression of the IFN- γ and vice versa.³ T_H1 commitment requires IFN- γ exposure to maintain the IL-12 receptor, and IL-4 inhibits the IL-12 receptor (R) β 2.⁴ This exclusive mechanism is also reflected by mechanisms of transcriptional regulation, where the T_H1-lineage-decisive factor T-bet physically interacts and inhibits the T_H2 factor GATA-3.⁵ Because of the genetic imprinting, dividing cells will principally maintain the polarized phenotype throughout the process of clonal expansion. The T_H2 cells are critically important for IgE induction, providing IL-4 and CD40-mediated interaction, which is necessary for the IgM to IgE switch reaction. In contrast, T_H1 cells are important in macrophage activation and induction of MHC-II. Because of the mutual exclusiveness of T_H1 and T_H2, it was hypothesized that T_H1 and T_H2 cells are in a balance with each other and that allergies are characterized and caused by a dominance on the T_H2 side of the equilibrium. This T_H1/T_H2 paradigm dominated allergy research and gave rise to the hygiene hypothesis, suggesting that increased hygiene conditions limit T_H1 reactions, which in turn allows more T_H2 reactions. The hygiene hypothesis was suggested to underlie increased allergy prevalence, although the increased prevalence of autoimmune disease was difficult to explain.⁶ With the discovery of the T-regulatory (Treg) and the T_H17 cells, this bivalent concept needs to be modified to integrate recent major progress in T-cell immunology and provide new access to epidemiologic dimensions of major immune system-related disease.

T-CELL FUNCTIONS IN ALLERGY

The understanding of T-cell responses in allergy during the last decade not only highlighted the critical importance of T_H2 cells in helping B cells toward IgE expression but also revealed that T_H2 cells interact with other cells such

From the Swiss Institute of Allergy and Asthma Research.

Supported by Swiss National Science Foundation grants 310000-112329, 3200B0-105865, 32600-113165, and 32000-112306; the Bonizzi-Theler Foundation Zurich; the Swiss Life Foundation Zurich; and the Global Allergy and Asthma European Network.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Received for publication May 18, 2007; revised June 25, 2007; accepted for publication June 29, 2007.

Reprint requests: Carsten B. Schmidt-Weber, PhD, SIAF, Obere Str 22, CH-7270 Davos, Switzerland. E-mail: csweber@siaf.uzh.ch. 0091-6749/\$32.00

© 2007 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2007.06.039

T cell phenotypes in allergy

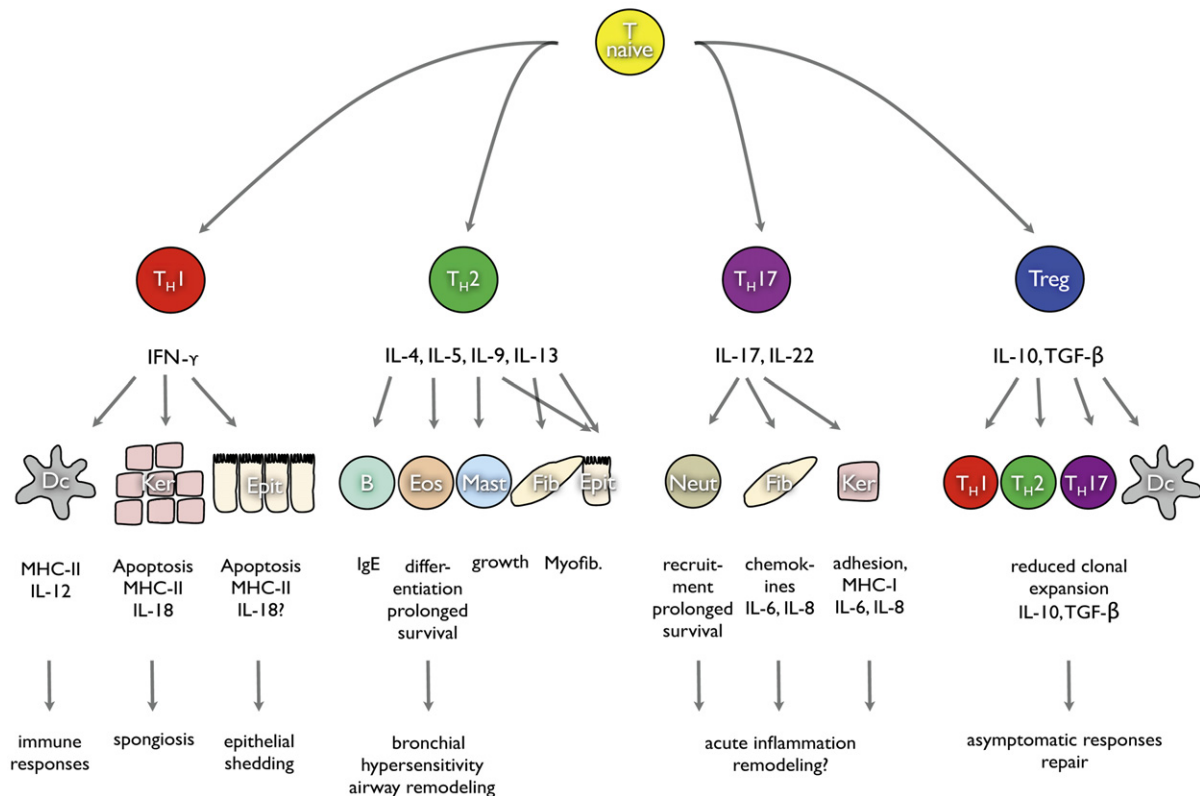


FIG 1. Schematic overview of T-cell phenotypes in allergic disease. T_H1 , T_H2 , T_H17 , and Treg cells are characterized by cytokines, which mediate specific functions in different tissue cells such as dendritic cells (Dc), keratinocytes (Ker), epithelial cells (Epi), eosinophils (Eos), mast cells (Mas), fibroblasts (Fib), and neutrophils (Neut). Myofib., Myofibroblast.

as eosinophils via IL-5; smooth muscle cells via IL-9; epithelial cells and keratinocytes via IL-13; and epithelial cells via IL-31,⁷ which modulate tissue processes in allergic diseases.^{8,9} Particular interest has been raised regarding the transition between allergen-driven IgE switch, which is mediated by IL-4 and IL-13 early in the disease process, and the airway remodeling observed on chronic allergen exposure, which has been attributed to the T_H2 cytokine IL-13 and TGF- β expressed by Treg cells as well as many other tissue cells. Thus, TGF- β is playing an important role in the induction of extracellular matrix proteins in tissue repair, but it is only marginally induced in T cells on T-cell receptor (TCR) stimulation. In contrast, the allergen-inducible TGF- β family member activin, which stimulates TGF- β expression in structural cells, could be a mediator between acute exacerbations and chronic allergic inflammation.¹⁰ It also became clear that not only T_H2 but also T_H1 cells can play a role in allergic disease,¹¹ such as in acute lesional skin, where IFN- γ is known to induce cell death in keratinocytes, causing the spongiform pathology observed in atopic dermatitis.¹² In addition, IL-21 was reported to be coexpressed with T_H2 cytokines¹³ but to suppress IgE expression.¹⁴ The IL-21R receptor was found on keratinocytes, suggesting

that IL-21 could also contribute to tissue modulation. IL-31, not yet assigned to T-cell subsets, is also likely to play a role in allergy and is acting on epithelial cells and keratinocytes,^{7,15} but appears to regulate T_H2 responses negatively.¹⁶

The interaction of Treg cells with nonlymphoid T cells is less well defined, partially because they are defined by their function rather than a cytokine product. Interestingly, TGF- β has been shown to be essential for Treg induction, which in turn is abundantly expressed in tissues, suggesting a role for Treg cells in repair responses.¹⁷ In fact, the expansion of Treg cells is most efficiently accomplished in Treg-fibroblast cultures.¹⁸ Besides antigen-specific control of effector T cells (T_H1 , T_H2 ,¹⁷ and most likely also T_H17), involving MHC class I/II-dependent mechanisms¹⁹⁻²¹ and dendritic cells, Treg cells do also act by T-cell-T-cell interactions. The triangle interaction of Treg, $T_{effector}$, and dendritic cells is important, but $T_{effector}$ and Treg cells were also shown to interact with neutrophils,²² B cells, and natural killer or natural killer T cells.²³⁻²⁵ The lymphoid target cells are contacted by the Treg cell by surface interactions including surface receptors such as lymphocyte activation gene (LAG)-3^{26,27} and cytotoxic T lymphocyte-associated antigen 4. The latter enhances the

TABLE I. IL-17-regulated genes and their cellular sources*

	Genes induced (green) or inhibited (red) by IL-17																					
	Proinflammatory cytokines			Chemokines						Matrix-modifying cytokines					Others							
	TNF- α	IL-1 β	IL-6	CXCL-1,2	CXCL 8 (IL8)	CCL-20	CINC	MCP-1	TARC	MMP-1	MMP-3	MMP-9	MMP-13	Proteoglycan	TSG-6	G-CSF	BMP-6	MUC5AC	MUC5B	COX2	ICAM-1	C3
<i>In vivo/ex vivo</i>									72 [†]	72 [†]	44 [‡]	72 [†]										
Fibroblasts		73	74, 75	75	74, 75					56					75 [§]	76	75			77	74	78
Myofibroblasts											57											
Smooth muscle cells					79																	
Epithelial cells			50	80	80, 50	81	82	83								80		28	28			
Chondrocytes														52								
Macrophages	84	84										85										
Dendritic cells								41														

CINC, Cytokine-induced neutrophil chemoattractant; TARC, thymus and activation-regulated chemokine; TSG, TNF-stimulated gene; G-CSF, granulocyte colony-stimulating factor; BMP, bone morphogenetic protein; ICAM, intercellular adhesion molecule.

*The target cells on which IL-17 acts to increase (green fields) or decrease (red fields) target genes are listed horizontally. The first row shows the effect of IL-17 on explants or of *in vivo* exposed material.

[†]IL-17-treated nasal cartilage explant cultures.

[‡]Intranasal IL-17.

[§]Synoviocytes.

expression and activity of membrane-bound TGF- β .²⁸⁻³⁰ The TGF- β is therefore presented in the contact zone, most likely as part of the immunologic synapse. In fact, TGF- β receptors are raft-resident³¹ and are found in activation contact zones.³⁰

T_H17 CELLS: A SEPARATE SUBSET

The discovery of the T_H17 cells is filling an essential gap in our understanding of inflammatory processes, because it was unclear how T_H1 cells actually mediate inflammation in the tissues by the expression of IFN- γ . T_H17 cells are characterized by IL-17 (or IL-17A), IL-17F, IL-6, TNF- α , and IL-22 expression.³²⁻³⁶ Neutralization of IL-17, but not genetic deletion of T_H1 cells, resolves tissue pathology in autoimmune models.³⁷ Furthermore, anti-IL-17 reduces joint destruction in experimental arthritis³⁸ and reduces neutrophil infiltration in an experimental asthma model while increasing eosinophil infiltration.^{39,40} Exogenously administered IL-17 reduces pulmonary eosinophil recruitment and bronchial hyperreactivity, suggesting a regulatory role of IL-17.⁴¹ Thus, it appears that the T_H17-directed neutrophil infiltration is inversely linked to the T_H2-mediated (or IL-5-mediated) eosinophil direction, similar to inverse relationships of T_H1 and T_H2 cells. In fact, it could be shown that T_H17 cells retain their IL-17-dominated phenotype after restimulation,⁴² that the IL-17 promoter undergoes chromatin remodeling,⁴³ and that T_H17 cells compete

with both T_H1 and T_H2 cells and thus represent a separate T-cell subset.³²

T_H17 CELLS: GOOD OR BAD IN ALLERGY?

Although published data have predominantly been raised in murine systems, functions of IL-17 clearly indicate a proinflammatory role and thus identify T_H17 cells as possible participants in autoimmunity. The key cytokine of T_H17 cells, IL-17, is known to induce proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6 as well as chemokines CXCL1, 2, and 8, which together are hallmarks of acute inflammatory processes (Table I).⁷²⁻⁸⁵ The chemokines mobilize neutrophil recruitment, which is discussed as a characteristic feature of T_H17-mediated inflammation, responsible for the histologically visible appearance of neutrophilic inflammation. The role of T_H17 cells in allergy is still largely unclear, but experimental models suggest that T_H17 cells may be important for neutrophilic inflammation in acute airway inflammation.^{39,44-47} Neutrophil infiltration is also observed in acute asthma attacks, including neutrophilia in bronchoalveolar lavage fluids. Interestingly, sputum IL-17 mRNA was shown to correlate with CXCL8 and neutrophil counts.⁴⁸ Furthermore, it is known that IL-17 induces chemoattractants in human airway smooth muscle⁴⁹ and airway epithelial cells.⁵⁰

IL-17 acts in synergy with other T_H17 cytokines, such as IL-6 to induce mucus proteins mucin (MUC)5B and MUC5AC,²⁸ or together with IL-1 and TNF- α to enhance

vascular endothelial growth factor expression.⁵¹ Thus, T_H17 cells integrate factors of the specific and innate immune system to reach activation thresholds for fundamental processes such as mucus secretion or angiogenesis. This activity is fundamentally different from that of T_H1 cells, where IFN- γ secretion mobilizes MHC-II expression in nonprofessional antigen-presenting cells or induces apoptosis in epithelial cells or keratinocytes. However, T_H17 cells could theoretically be of benefit to reduce matrix deposition, because T_H17 cells, in contrast with T_H2 cells, are capable of inducing metalloproteinases (Table I), which is an essential mechanism of T_H17-mediated cartilage breakdown in arthritis and could be beneficial for remodelling in allergy.^{47,52} In contrast with T_H1 and T_H2 cells, T_H17 cells thus mediate tissue inflammation by supporting neutrophil recruitment and survival, matrix degradation, and induction of proinflammatory cytokines in structural cells. Although these lead to pathological trends in several inflammatory disease, we have to keep in mind that they also serve to protect the organism from bacteria and fungi in healthy individuals.

T-CELL FUNCTION AND DEVELOPMENT REVISITED IN THE CONTEXT OF EMERGING NOVEL SUBSETS

A fundamental understanding of new T-cell phenotypes is that they not only interact with other lymphoid cells according to their helper function but also play an essential role in the instruction of tissue cells, which activates either nonspecific immune functions (apoptosis, mucus secretion, remodeling) or a immune-regulatory function such as the amplification of inflammation by secretion of chemokines and the induction of MHC molecules or proinflammatory cytokines. The aim of this education is not only effective protection against pathogens but also regulation of the immune response to the requirements of specific organs so that organ function is maintained.⁵³ T-cell-instructed tissue immune responses anchor inflammation to restricted locations, explaining why the same allergens mediate different disease manifestations in different organs such as rhinitis, asthma, gastrointestinal symptoms of food allergy, or atopic dermatitis. The T-cell-mediated adjustments also involve mechanisms of the unspecific immune system such as mucus secretion (T_H2,⁵⁴ T_H17 cells²⁸) and extracellular matrix build-up (T_H2⁵⁵) or breakdown (T_H17^{44,56,57}). Thus, individual T-cell subsets may be pathogenic or beneficial for specific disease conditions such allergic airway disease, where matrix deposition reduces lung function. In fact, it was shown that anti-IL-17 treatment is effective in silencing synovial inflammation and joint erosion.³⁸ However, it increases IL-5 expression in bronchoalveolar lavage fluids and bronchial eosinophilia.³⁹ These findings show that the coordinated and tissue-adjusted induction of T-cell phenotypes dictates the size, efficacy, type, and suitability of immune reactions.

The continuous balance of T-cell subsets at the onset and during the course of disease determines the pathogenic features. The discovery of the new T-cell subsets highlights their interdependence (Fig 2). T_H1 cells inhibit T_H2³ and T_H17 development.³⁷ T_H2 cells inhibit T_H1 development as already known. Thus, any interference with one differentiation pathway will most likely also change the balance of the other pathways. The molecular mechanisms of this pathway cross-talk have previously been shown to take place on the level of pathway-specific transcription factors, such as T-Bet, GATA-3, FOXP3, and probably retinoid orphan receptor (ROR) γ t (RORC2 in human beings) for T_H1, T_H2, Treg, and T_H17 cells, respectively.⁵⁸⁻⁶¹ Runt-related transcription factor 1 promotes Treg cells⁶² and inhibits differentiation of T_H2 cells.⁶³ T-bet interferes with T_H17 cells and directly blocks GATA-3 to bind its targets.⁵ It has been shown that these competitive interactions result in genetic imprinting or chromatin remodeling,^{43,59,64,65} which dictates the chromatin accessibility of the subset-specific genes in the progenitor cells. This accessibility for the *IL4* gene is then secondarily IL-4-independent for the evolving memory populations, which is not true for the *IL13* gene.⁵⁹

Besides this negative, competitive regulation process, the discovery of T_H17 and Treg cells underlines another key feature of T-cell biology: all differentiation pathways use a positive feedback loop, which may serve as an auto-crine and paracrine mechanism of T-cell subset polarization (Figure 2). T_H1 cells produce IFN- γ , which directly induces T-Bet in naive T cells and indirectly triggers IL-12 via antigen-presenting cells. IL-12 is, in turn, also a T-Bet inducer and an essential cytokine for T_H1 commitment. T_H2 cells produce IL-4, which is known to be essential for autocrine GATA-3-dependent differentiation. Mast cells or other sources in the microenvironment produce additional IL-4 to augment T_H2 polarization. These tissue environmental factors are increasingly recognized to be essential for T-cell differentiation, integrating signals from the target tissue. Treg cells require TGF- β for differentiation toward FOXP3-expressing cells and are also a potential source for TGF- β expression, whereas TGF- β inhibits T-Bet and GATA3 expression^{66,67} and thus excludes T_H1 and T_H2 differentiation pathways. Although both Treg differentiation and T_H17 differentiation depend on TGF- β , it could be shown that the source for TGF- β plays an important role. Interestingly, animals engineered to lack TGF- β expression in T cells lack, as predicted, the T_H17 cells, but surprisingly the Treg cell frequency is unchanged, suggesting that Tregs receive TGF- β from non-T-cell sources.⁶⁸ In contrast with Treg cells, T_H17 cells require additional IL-6 to polarize away from the Treg cell pathway toward the T_H17 phenotype.⁴² IL-17 is known to induce IL-6 in structural cells, which in turn can feed-back on the induction of T_H17 cells. IL-23 has also been shown to induce T_H17 cells and appears to be especially important for the IL-22 component of the T_H17 cells,³⁶ because IL-6 knockout cells lack IL-17 but can still produce the T_H17 cytokine IL-22 on IL-23-driven T-cell differentiation, whereas these cells

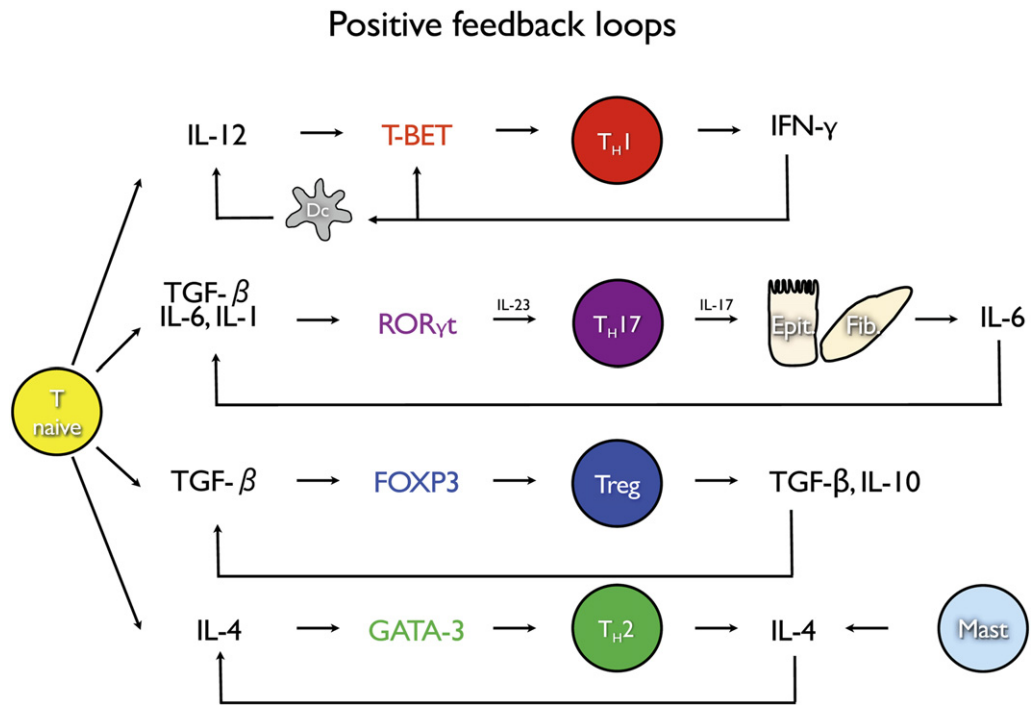


FIG 2. Positive feedback loops in transcription factors during T-cell differentiation. During naive T-cell differentiation to T_H1 , T_H17 , Treg, and T_H2 cells, IFN- γ , IL-6, TGF- β , and IL-4 produced by these cells further induce the synthesis of transcription factors T-bet, ROR γ t, FOXP3, and GATA-3, respectively. *Epit*, Epithelial cells; *Fib*, fibroblasts.

TABLE II. T_H2 -related disease*

Disease	Dominating cytokine	Absent cytokine	Reference no.
Severe respiratory syncytial virus bronchiolitis	IL-9		86
Chronic bronchitis with obstruction	IL-9		87
Pneumothorax-associated pleural eosinophilia	IL-5		88
Asthma	IL-13		89
Lung emphysema	IL-13		90
Human T-lymphotropic virus-1 infection	IL-13		91
Sarcoidosis	IL-13	IL-4	92
Atopic eczema/dermatitis syndrome	IL-13	IL-4	93
	IL-5		
<i>Schistosoma haematobium</i> infection	IL-4	IL-5	94
	IL-5	IL-4	
<i>Leishmania infantum</i> infection	IL-5	IL-4	95
	IFN- γ		
Atopic asthma	IL-4	IL-5	96
Hypereosinophilic syndrome	IL-5	IL-4, IL-2, IFN- γ	70
Hyper-IgE syndrome	IL-13	IL-4	97
Churg-Strauss syndrome	IL-4		98
	IL-13		
Allergen provocation of Asthma	IL-13	IL-6, IL-8, IFN- γ , and TNF- α	99
Atopic asthma	IL-13	IL-13 > IL-4	100
	IL-4		
Lesional skin of atopic dermatitis	IL-4	IFN- γ	101
Sezary syndrome	IL-4	(IFN- γ)	102
Benign reactive erythroderma	IFN- γ	IL-4	102
Eosinophilic esophagitis	IL-5		103

*Disease condition described to be related to T_H2 cytokines. The table shows that T_H2 cytokines are selectively expressed in specific disease, indicating that T_H2 cells mediate different disease because of distinct T_H2 cytokine expression profiles.

lack IL-17. Similar to IL-6, IL-23 is induced by IL-17 in dendritic cells⁶⁹ but not in epithelial cells. Thus, it can be hypothesized that T_H17 cells form an IL-6–driven positive feedback loop with epithelial cells and an IL-23–driven loop with dendritic cells. Taken together, these studies show that all T-cell phenotypes are interdependent, favor polarization toward a specific T-cell subset, and are enhanced by positive feedback regulation relayed by lymphoid or peripheral tissue cells. The proximity of the Treg and T_H17 differentiation pathway is of particular interest for future research, because it could be hypothesized that the T_H17-type immune response can be more efficiently turned into Treg or tolerogenic reactions than T_H2 or T_H1 pathways.

CONCLUSION

The individual T-cell subsets orchestrate immune responses in a timely, coordinated, and tissue-adjusted manner. Accordingly, T-cell phenotypes have alternating relevance in allergic and autoimmune disease, depending on the disease progression and organ involvement. The assignment of differentiation pathways to functionally different T-cell subsets may dramatically improve treatment, because it allows therapeutic intervention before T-cell differentiation. According to human genome data, not many more ILs are to be expected, but specifically for T_H2-dominated disease we have to consider that T_H5, T_H9, T_H13, and T_H31 subsets may exist that generate specific pathologies (Table II).⁸⁶⁻¹⁰³

For example, atopic asthma is characterized by a T-cell response with high IL-4 and no IL-5, whereas the hyper-eosinophilic syndrome lacks IL-4 and is dominated by IL-5.⁷⁰ In fact, gene regulation of IL-5, IL-9, and IL-13 was predominantly analyzed with the underlying T_H2 concept. Although IL-5–producing cells can be generated on T_H2 differentiation, it is possible that conditions exist that generate an IL-4–independent, predominantly IL-5–secreting T-cell phenotype. It was previously shown that *IL5* gene transcription involves the reversible histone modification catalyzed by histone deacetylase 4 and p300,⁷¹ leaving room for *IL4*–independent gene regulation. Future research must clarify whether differentiation pathways exist that can permanently imprint these phenotypes. Because T_H17 cells promote neutrophilic inflammation and IL-5–secreting T cells promote chronic eosinophilic inflammation, it remains to be elucidated whether there exist pure macrophage, mast cell, or basophil stimulatory T-cell subsets. In parallel, increasing evidence shows that specific subsets of antigen-presenting cells can be attributed to subsets of regulatory or effector T cells, thus forming lineage families, which will dramatically facilitate our understanding of the complexity in immunologic mechanisms.

The T_H17 hypothesis adds complexity to immune regulation, but at the same time helps explain reoccurring themes in T-cell differentiation. These themes now allow dissection of transcription factors, cytokines, and cell

subsets into categories and families, which is likely to facilitate our understanding of inflammatory processes in different diseases or different stages of chronic disease.

REFERENCES

- Schmidt-Weber CB, Alexander SI, Henault LE, James L, Lichtman AH. IL-4 enhances IL-10 gene expression in murine Th2 cells in the absence of TCR engagement. *J Immunol* 1999;162:238-44.
- Sornasse T, Larenas PV, Davis KA, de Vries JE, Yssel H. Differentiation and stability of T helper 1 and 2 cells derived from naive human neonatal CD4+ T cells, analyzed at the single-cell level. *J Exp Med* 1996;184:473-83.
- Nakamura T, Kamogawa Y, Bottomly K, Flavell RA. Polarization of IL-4- and IFN-gamma-producing CD4+ T cells following activation of naive CD4+ T cells. *J Immunol* 1997;158:1085-94.
- Szabo SJ, Dighe AS, Gubler U, Murphy KM. Regulation of the interleukin (IL)-12R beta 2 subunit expression in developing T helper 1 (Th1) and Th2 cells. *J Exp Med* 1997;185:817-24.
- Hwang ES, Szabo SJ, Schwartzberg PL, Glimcher LH. T helper cell fate specified by kinase-mediated interaction of T-bet with GATA-3. *Science* 2005;307:430-3.
- Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002;347:911-20.
- Dillon SR, Sprecher C, Hammond A, Bilsborough J, Rosenfeld-Franklin M, Presnell SR, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol* 2004;5:752-60.
- Bilsborough J, Leung DY, Maurer M, Howell M, Boguniewicz M, Yao L, et al. IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2006;117:418-25.
- Sonkoly E, Muller A, Lauerma AI, Pivarsci A, Soto H, Kemeny L, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006;117:411-7.
- Karagiannidis C, Hense G, Martin C, Epstein M, Ruckert B, Mantel PY, et al. Activin A is an acute allergen-responsive cytokine and provides a link to TGF-beta-mediated airway remodeling in asthma. *J Allergy Clin Immunol* 2006;117:111-8.
- Grewe M, Bruijnzeel-Koomen CA, Schopf E, Thepen T, Langeveld-Wildschut AG, Ruzicka T, et al. A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. *Immunol Today* 1998;19:359-61.
- Akdis CA, Blaser K, Akdis M. Apoptosis in tissue inflammation and allergic disease. *Curr Opin Immunol* 2004;16:717-23.
- Mehta DS, Wurster AL, Whitters MJ, Young DA, Collins M, Grusby MJ. IL-21 induces the apoptosis of resting and activated primary B cells. *J Immunol* 2003;170:4111-8.
- Harada M, Magara-Koyanagi K, Watarai H, Nagata Y, Ishii Y, Kojo S, et al. IL-21-induced Bepsilon cell apoptosis mediated by natural killer T cells suppresses IgE responses. *J Exp Med* 2006;203:2929-37.
- Chattopadhyay S, Tracy E, Liang P, Robledo O, Rose-John S, Baumann H. Interleukin-31 and oncostatin-M mediate distinct signaling reactions and response patterns in lung epithelial cells. *J Biol Chem* 2007;282:3014-26.
- Perrigoue JG, Li J, Zaph C, Goldschmidt M, Scott P, de Sauvage FJ, et al. IL-31-IL-31R interactions negatively regulate type 2 inflammation in the lung. *J Exp Med* 2007;204:481-7.
- Schmidt-Weber CB, Blaser K. Regulation and role of transforming growth factor-beta in immune tolerance induction and inflammation. *Curr Opin Immunol* 2004;16:709-16.
- Clark RA, Kupper TS. IL-15 and dermal fibroblasts induce proliferation of natural regulatory T cells isolated from human skin. *Blood* 2007;109:194-202.
- Cederbom L, Hall H, Ivars F. CD4+CD25+ regulatory T cells down-regulate co-stimulatory molecules on antigen-presenting cells. *Eur J Immunol* 2000;30:1538-43.
- Fallarino F, Grohmann U, Hwang KW, Orabona C, Vacca C, Bianchi R, et al. Modulation of tryptophan catabolism by regulatory T cells. *Nat Immunol* 2003;4:1206-12.
- Misra N, Bayry J, Lacroix-Desmazes S, Kazatchkine MD, Kaveri SV. Cutting edge: human CD4+CD25+ T cells restrain the maturation and antigen-presenting function of dendritic cells. *J Immunol* 2004;172:4676-80.

22. Lewkowicz P, Lewkowicz N, Sasiak A, Tchorzewski H. Lipopolysaccharide-activated CD4+CD25+ T regulatory cells inhibit neutrophil function and promote their apoptosis and death. *J Immunol* 2006;177:7155-63.
23. Barao I, Hanash AM, Hallett W, Welniak LA, Sun K, Redelman D, et al. Suppression of natural killer cell-mediated bone marrow cell rejection by CD4+CD25+ regulatory T cells. *Proc Natl Acad Sci U S A* 2006;103:5460-5.
24. Fields ML, Hondowicz BD, Metzgar MH, Nish SA, Wharton GN, Picca CC, et al. CD4+ CD25+ regulatory T cells inhibit the maturation but not the initiation of an autoantibody response. *J Immunol* 2005;175:4255-64.
25. Liu R, La Cava A, Bai XF, Jee Y, Price M, Campagnolo DI, et al. Cooperation of invariant NKT cells and CD4+CD25+ T regulatory cells in the prevention of autoimmune myasthenia. *J Immunol* 2005;175:7898-904.
26. Huang CT, Workman CJ, Flies D, Pan X, Marson AL, Zhou G, et al. Role of LAG-3 in regulatory T cells. *Immunity* 2004;21:503-13.
27. Macon-Lemaitre L, Triebel F. The negative regulatory function of the lymphocyte-activation gene-3 co-receptor (CD223) on human T cells. *Immunology* 2005;115:170-8.
28. Chen Y, Thai P, Zhao YH, Ho YS, DeSouza MM, Wu R. Stimulation of airway mucin gene expression by interleukin (IL)-17 through IL-6 paracrine/autocrine loop. *J Biol Chem* 2003;278:17036-43.
29. Tang Q, Boden EK, Henriksen KJ, Bour-Jordan H, Bi M, Bluestone JA. Distinct roles of CTLA-4 and TGF-beta in CD4+CD25+ regulatory T cell function. *Eur J Immunol* 2004;34:2996-3005.
30. Oida T, Xu L, Weiner HL, Kitani A, Strober W. TGF-beta-mediated suppression by CD4+CD25+ T cells is facilitated by CTLA-4 signaling. *J Immunol* 2006;177:2331-9.
31. Zhang XL, Topley N, Ito T, Phillips A. Interleukin-6 regulation of transforming growth factor (TGF)-beta receptor compartmentalization and turnover enhances TGF-beta1 signaling. *J Biol Chem* 2005;280:12239-45.
32. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol* 2005;6:1123-32.
33. Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat Immunol* 2005;6:1133-41.
34. Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, et al. Transforming growth factor-beta induces development of the T(H)17 lineage. *Nature* 2006;441:231-4.
35. Chung Y, Yang X, Chang SH, Ma L, Tian Q, Dong C. Expression and regulation of IL-22 in the IL-17-producing CD4+ T lymphocytes. *Cell Res* 2006;16:902-7.
36. Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, et al. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007;445:648-51.
37. Rangachari M, Mauermann N, Marty RR, Dirnhofer S, Kurrer MO, Komnenovic V, et al. T-bet negatively regulates autoimmune myocarditis by suppressing local production of interleukin 17. *J Exp Med* 2006;203:2009-19.
38. Bush KA, Farmer KM, Walker JS, Kirkham BW. Reduction of joint inflammation and bone erosion in rat adjuvant arthritis by treatment with interleukin-17 receptor IgG1 Fc fusion protein. *Arthritis Rheum* 2002;46:802-5.
39. Hellings PW, Kasran A, Liu Z, Vandekerckhove P, Wuyts A, Overbergh L, et al. Interleukin-17 orchestrates the granulocyte influx into airways after allergen inhalation in a mouse model of allergic asthma. *Am J Respir Cell Mol Biol* 2003;28:42-50.
40. Sergejeva S, Ivanov S, Lotvall J, Linden A. Interleukin-17 as a recruitment and survival factor for airway macrophages in allergic airway inflammation. *Am J Respir Cell Mol Biol* 2005;33:248-53.
41. Schnyder-Candrian S, Togbe D, Couillin I, Mercier I, Brouncker F, Quesniaux V, et al. Interleukin-17 is a negative regulator of established allergic asthma. *J Exp Med* 2006;203:2715-25.
42. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* 2006;441:235-8.
43. Akimzhanov AM, Yang XO, Dong C. Chromatin remodeling of interleukin-17 (IL-17)-IL-17F cytokine gene locus during inflammatory helper T cell differentiation. *J Biol Chem* 2007;282:5969-72.
44. Prause O, Bozinovski S, Anderson GP, Linden A. Increased matrix metalloproteinase-9 concentration and activity after stimulation with interleukin-17 in mouse airways. *Thorax* 2004;59:313-7.
45. Hashimoto T, Akiyama K, Kobayashi N, Mori A. Comparison of IL-17 production by helper T cells among atopic and nonatopic asthmatics and control subjects. *Int Arch Allergy Immunol* 2005;137(suppl 1):51-4.
46. Hoshino H, Laan M, Sjostrand M, Lotvall J, Skoogh BE, Linden A. Increased elastase and myeloperoxidase activity associated with neutrophil recruitment by IL-17 in airways in vivo. *J Allergy Clin Immunol* 2000;105:143-9.
47. Nakae S, Saijo S, Horai R, Sudo K, Mori S, Iwakura Y. IL-17 production from activated T cells is required for the spontaneous development of destructive arthritis in mice deficient in IL-1 receptor antagonist. *Proc Natl Acad Sci U S A* 2003;100:5986-90.
48. Bullens DM, Truyen E, Coteur L, Dilissen E, Hellings PW, Dupont LJ, et al. IL-17 mRNA in sputum of asthmatic patients: linking T cell driven inflammation and granulocytic influx? *Respir Res* 2006;7:135.
49. Dragon S, Rahman MS, Yang J, Unruh H, Halayko AJ, Gounni AS. IL-17 enhances IL-1beta-mediated CXCL-8 release from human airway smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* 2007;292:L1023-9.
50. van den Berg A, Kuiper M, Snoek M, Timens W, Postma DS, Jansen HM, et al. Interleukin-17 induces hyperresponsive interleukin-8 and interleukin-6 production to tumor necrosis factor-alpha in structural lung cells. *Am J Respir Cell Mol Biol* 2005;33:97-104.
51. Honorati MC, Cattini L, Facchini A. IL-17, IL-1beta and TNF-alpha stimulate VEGF production by differentiated chondrocytes. *Osteoarthritis Cartilage* 2004;12:683-91.
52. Lubberts E, Joosten LA, van de Loo FA, van den Gersselaar LA, van den Berg WB. Reduction of interleukin-17-induced inhibition of chondrocyte proteoglycan synthesis in intact murine articular cartilage by interleukin-4. *Arthritis Rheum* 2000;43:1300-6.
53. Akdis CA. Allergy and hypersensitivity: mechanisms of allergic disease. *Curr Opin Immunol* 2006;18:718-26.
54. Kuperman DA, Huang X, Koth LL, Chang GH, Dolganov GM, Zhu Z, et al. Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. *Nat Med* 2002;8:885-9.
55. Lee CG, Homer RJ, Zhu Z, Lanone S, Wang X, Koteliansky V, et al. Interleukin-13 induces tissue fibrosis by selectively stimulating and activating transforming growth factor beta(1). *J Exp Med* 2001;194:809-21.
56. Chabaud M, Garnero P, Dayer JM, Guerne PA, Fossiez F, Miossec P. Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis. *Cytokine* 2000;12:1092-9.
57. Inatomi O, Andoh A, Yagi Y, Ogawa A, Hata K, Shiomi H, et al. Matrix metalloproteinase-3 secretion from human pancreatic periacinar myofibroblasts in response to inflammatory mediators. *Pancreas* 2007;34:126-32.
58. Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. *Cell* 2000;100:655-69.
59. Yamashita M, Ukai-Tadenuma M, Miyamoto T, Sugaya K, Hosokawa H, Hasegawa A, et al. Essential role of GATA3 for the maintenance of type 2 helper T (Th2) cytokine production and chromatin remodeling at the Th2 cytokine gene loci. *J Biol Chem* 2004;279:26983-90.
60. Khattri R, Cox T, Yasayko SA, Ramsdell F. An essential role for Scurfin in CD4+CD25+ T regulatory cells. *Nat Immunol* 2003;4:337-42.
61. Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelletier A, Lafaille JJ, et al. The orphan nuclear receptor RORgamma directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell* 2006;126:1121-33.
62. Ono M, Yaguchi H, Ohkura N, Kitabayashi I, Nagamura Y, Nomura T, et al. Foxp3 controls regulatory T-cell function by interacting with AML1/Runx1. *Nature* 2007;446:685-9.
63. Komine O, Hayashi K, Natsume W, Watanabe T, Seki Y, Seki N, et al. The Runx1 transcription factor inhibits the differentiation of naive CD4+ T cells into the Th2 lineage by repressing GATA3 expression. *J Exp Med* 2003;198:51-61.
64. Letimier FA, Passini N, Gasparian S, Bianchi E, Rogge L. Chromatin remodeling by the SWI/SNF-like BAF complex and STAT4 activation synergistically induce IL-12Rbeta2 expression during human Th1 cell differentiation. *EMBO J* 2007;26:1292-302.

65. Ansel KM, Djuretic I, Tanasa B, Rao A. Regulation of Th2 differentiation and Il4 locus accessibility. *Annu Rev Immunol* 2006;24:607-56.
66. Gorelik L, Fields PE, Flavell RA. Cutting edge: TGF-beta inhibits Th type 2 development through inhibition of GATA-3 expression. *J Immunol* 2000;165:4773-7.
67. Heath VL, Murphy EE, Crain C, Tomlinson MG, O'Garra A. TGF-beta1 down-regulates Th2 development and results in decreased IL-4-induced STAT6 activation and GATA-3 expression. *Eur J Immunol* 2000;30:2639-49.
68. Li MO, Wan YY, Flavell RA. T cell-produced transforming growth factor-beta1 controls T cell tolerance and regulates Th1- and Th17-cell differentiation. *Immunity* 2007;26:579-91.
69. Kim HR, Cho ML, Kim KW, Juhn JY, Hwang SY, Yoon CH, et al. Up-regulation of IL-23p19 expression in rheumatoid arthritis synovial fibroblasts by IL-17 through PI3-kinase-, NF-kappaB- and p38 MAPK-dependent signalling pathways. *Rheumatology (Oxford)* 2007;46:57-64.
70. Brugnoli D, Airo P, Rossi G, Bettinardi A, Simon HU, Garza L, et al. A case of hypereosinophilic syndrome is associated with the expansion of a CD3-CD4+ T-cell population able to secrete large amounts of interleukin-5. *Blood* 1996;87:1416-22.
71. Han S, Lu J, Zhang Y, Cheng C, Han L, Wang X, et al. Recruitment of histone deacetylase 4 by transcription factors represses interleukin-5 transcription. *Biochem J* 2006;400:439-48.
72. Koshy PJ, Henderson N, Logan C, Life PF, Cawston TE, Rowan AD. Interleukin 17 induces cartilage collagen breakdown: novel synergistic effects in combination with proinflammatory cytokines. *Ann Rheum Dis* 2002;61:704-13.
73. Koenders MI, Kolls JK, Oppers-Walgreen B, van den Bersselaar L, Joosten LA, Schurr JR, et al. Interleukin-17 receptor deficiency results in impaired synovial expression of interleukin-1 and matrix metalloproteinases 3, 9, and 13 and prevents cartilage destruction during chronic reactivated streptococcal cell wall-induced arthritis. *Arthritis Rheum* 2005;52:3239-47.
74. Yao Z, Painter SL, Fanslow WC, Ulrich D, Macduff BM, Spriggs MK, et al. Human IL-17: a novel cytokine derived from T cells. *J Immunol* 1995;155:5483-6.
75. Kehlen A, Pachnio A, Thiele K, Langner J. Gene expression induced by interleukin-17 in fibroblast-like synoviocytes of patients with rheumatoid arthritis: upregulation of hyaluronan-binding protein TSG-6. *Arthritis Res Ther* 2003;5:R186-92.
76. Cai XY, Gommoll CPJ, Justice L, Narula SK, Fine JS. Regulation of granulocyte colony-stimulating factor gene expression by interleukin-17. *Immunol Lett* 1998;62:51-8.
77. Faour WH, Mancini A, He QW, Di Battista JA. T-cell-derived interleukin-17 regulates the level and stability of cyclooxygenase-2 (COX-2) mRNA through restricted activation of the p38 mitogen-activated protein kinase cascade: role of distal sequences in the 3'-untranslated region of COX-2 mRNA. *J Biol Chem* 2003;278:26897-907.
78. Katz Y, Nadv O, Rapoport MJ, Loos M. IL-17 regulates gene expression and protein synthesis of the complement system, C3 and factor B, in skin fibroblasts. *Clin Exp Immunol* 2000;120:22-9.
79. Rahman MS, Yang J, Shan LY, Unruh H, Yang X, Halayko AJ, et al. IL-17R activation of human airway smooth muscle cells induces CXCL-8 production via a transcriptional-dependent mechanism. *Clin Immunol* 2005;115:268-76.
80. Jones CE, Chan K. Interleukin-17 stimulates the expression of interleukin-8, growth-related oncogene-alpha, and granulocyte-colony-stimulating factor by human airway epithelial cells. *Am J Respir Cell Mol Biol* 2002;26:748-53.
81. Kao CY, Huang F, Chen Y, Thai P, Wachi S, Kim C, et al. Up-regulation of CC chemokine ligand 20 expression in human airway epithelium by IL-17 through a JAK-independent but MEK/NF-kappaB-dependent signaling pathway. *J Immunol* 2005;175:6676-85.
82. Awane M, Andres PG, Li DJ, Reinecker HC. NF-kappa B-inducing kinase is a common mediator of IL-17-, TNF-alpha-, and IL-1 beta-induced chemokine promoter activation in intestinal epithelial cells. *J Immunol* 1999;162:5337-44.
83. Andoh A, Takaya H, Makino J, Sato H, Bamba S, Araki Y, et al. Cooperation of interleukin-17 and interferon-gamma on chemokine secretion in human fetal intestinal epithelial cells. *Clin Exp Immunol* 2001;125:56-63.
84. Jovanovic DV, Di Battista JA, Martel-Pelletier J, Jolicoeur FC, He Y, Zhang M, et al. IL-17 stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages. *J Immunol* 1998;160:3513-21.
85. Jovanovic DV, Martel-Pelletier J, Di Battista JA, Mineau F, Jolicoeur FC, Benderdour M, et al. Stimulation of 92-kd gelatinase (matrix metalloproteinase 9) production by interleukin-17 in human monocyte/macrophages: a possible role in rheumatoid arthritis. *Arthritis Rheum* 2000;43:1134-44.
86. McNamara PS, Flanagan BF, Baldwin LM, Newland P, Hart CA, Smyth RL. Interleukin 9 production in the lungs of infants with severe respiratory syncytial virus bronchiolitis. *Lancet* 2004;363:1031-7.
87. Panzner P, Lafitte JJ, Tsicopoulos A, Hamid Q, Tulic MK. Marked up-regulation of T lymphocytes and expression of interleukin-9 in bronchial biopsies from patients with chronic bronchitis with obstruction. *Chest* 2003;124:1909-15.
88. Kalomenidis I, Guo Y, Peebles RS, Lane KB, Papiris S, Elias J, et al. Pneumothorax-associated pleural eosinophilia in mice is interleukin-5 but not interleukin-13 dependent. *Chest* 2005;128:2978-83.
89. Park SW, Jangm HK, An MH, Min JW, Jang AS, Lee JH, et al. Interleukin-13 and interleukin-5 in induced sputum of eosinophilic bronchitis: comparison with asthma. *Chest* 2005;128:1921-7.
90. Boutten A, Bonay M, Laribe S, Leseche G, Castier Y, Lecon-Malas V, et al. Decreased expression of interleukin 13 in human lung emphysema. *Thorax* 2004;59:850-4.
91. Chung HK, Young HA, Goon PK, Heidecker G, Princler GL, Shimoza O, et al. Activation of interleukin-13 expression in T cells from HTLV-1-infected individuals and in chronically infected cell lines. *Blood* 2003;102:4130-6.
92. Hauber HP, Gholami D, Meyer A, Pforte A. Increased interleukin-13 expression in patients with sarcoidosis. *Thorax* 2003;58:519-24.
93. Simon D, Borelli S, Braathen LR, Simon HU. Peripheral blood mononuclear cells from IgE- and non-IgE-associated allergic atopic eczema/dermatitis syndrome (AEDS) demonstrate increased capacity of generating interleukin-13 but differ in their potential of synthesizing interferon-gamma. *Allergy* 2002;57:431-5.
94. Scott JT, Turner C, Mutapi F, Woolhouse ME, Chandiwana SK, Mdu-luza T, et al. Dissociation of interleukin-4 and interleukin-5 production following treatment for *Schistosoma haematobium* infection in humans. *Parasite Immunol* 2000;22:341-8.
95. Mary C, Auriault V, Faugere B, Dessein AJ. Control of Leishmania infantum infection is associated with CD8(+) and gamma interferon- and interleukin-5-producing CD4(+) antigen-specific T cells. *Infect Immun* 1999;67:5559-66.
96. Krug N, Jung T, Napp U, Wagner K, Schultze-Werninghaus G, Heusser C, et al. Frequencies of T cells expressing interleukin-4 and interleukin-5 in atopic asthmatic children: comparison with atopic asthmatic adults. *Am J Respir Crit Care Med* 1998;158:754-9.
97. Gudmundsson KO, Sigurjonsson OE, Gudmundsson S, Goldblatt D, Weemaes CM, Haraldsson A. Increased expression of interleukin-13 but not interleukin-4 in CD4+ cells from patients with the hyper-IgE syndrome. *Clin Exp Immunol* 2002;128:532-7.
98. Kiene M, Csernok E, Muller A, Metzler C, Trabandt A, Gross WL. Elevated interleukin-4 and interleukin-13 production by T cell lines from patients with Churg-Strauss syndrome. *Arthritis Rheum* 2001;44:469-73.
99. Prieto J, Lensmar C, Roquet A, van der Ploeg I, Gigliotti D, Eklund A, et al. Increased interleukin-13 mRNA expression in bronchoalveolar lavage cells of atopic patients with mild asthma after repeated low-dose allergen provocations. *Respir Med* 2000;94:806-14.
100. Kotsimbos TC, Ernst P, Hamid QA. Interleukin-13 and interleukin-4 are coexpressed in atopic asthma. *Proc Assoc Am Physicians* 1996;108:368-73.
101. Ramb-Lindhauer C, Feldmann A, Rotte M, Neumann C. Characterization of grass pollen reactive T-cell lines derived from lesional atopic skin. *Arch Dermatol Res* 1991;283:71-6.
102. Sigurdsson V, Toonstra J, Bihari IC, Bruijnzeel-Koomen CA, van Vloten WA, Thepen T. Interleukin 4 and interferon-gamma expression of the dermal infiltrate in patients with erythroderma and mycosis fungoides: an immuno-histochemical study. *J Cutan Pathol* 2000;27:429-35.
103. Stein ML, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006;118:1312-9.