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 TH17 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 TH17 differentiation pathways has also changed the perspective of immunologists regarding the basis of chronic tissue inflammation, particularly where TH1 cells were considered as driving force of the pathology. This review summarizes the recent developments on TH1 cells subsets and integrates these findings into existing concepts of immunopathologic mechanisms. (J Allergy Clin Immunol 2007;120:247-54.)

Key words: Tolerance, differentiation, TH17, TH2, 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 TH1 cells, assumed to play a role in inflammatory delayed type hypersensitivity, and a TH2 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 TH2 cells do also express IL-10, whereas IL-10 in human beings could not be attributed to either subset and is discussed as a separate subset (T-regulatory 1 [Tr1] cells). Both TH1 and TH2 cells originate from naive T cells (Fig 1), which polarize on initial antigen contact either to TH1 or TH2 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. TH1 commitment requires IFN-γ exposure to maintain the IL-12 receptor, and IL-4 inhibits the IL-12 receptor (R) β2. This exclusive mechanism is also reflected by mechanisms of transcriptional regulation, where the TH1-lineage-decisive factor T-bet physically interacts and inhibits the TH2 factor GATA-3. Because of the genetic imprinting, dividing cells will principally maintain the polarized phenotype throughout the process of clonal expansion. The TH2 cells are critically important for IgE induction, provided IL-4 and CD40-mediated interaction, which is necessary for the IgM to IgE switch reaction. In contrast, TH1 cells are important in macrophage activation and induction of MHC-II. Because of the mutual exclusiveness of TH1 and TH2, it was hypothesized that TH1 and TH2 cells are in a balance with each other and that allergies are characterized and caused by a dominance on the TH2 side of the equilibrium. This TH1/TH2 paradigm dominated allergy research and gave rise to the hygiene hypothesis, suggesting that increased hygiene conditions limit TH1 reactions, which in turn allows more TH2 reactions. The hygiene hypothesis was suggested to underlie increased allergy prevalence, although the increased prevalence of autoimmune disease was difficult to explain. With the discovery of the T-regulatory (Treg) and the TH17 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 TH2 cells in helping B cells toward IgE expression but also revealed that TH2 cells interact with other cells such as...
as eosinophils via IL-5; smooth muscle cells via IL-9; epithelial cells and keratinocytes via IL-13; and epithelial cells via IL-31, which modulate tissue processes in allergic diseases. 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 TH2 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. It also became clear that not only T_{H2} but also T_{H1} cells can play a role in allergic disease, 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. In addition, IL-21 was reported to be coexpressed with T_{H2} cytokines but to suppress IgE expression. 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, but appears to regulate T_{H2} responses negatively.

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. In fact, the expansion of Treg cells is most efficiently accomplished in Treg-fibroblast cultures. Besides antigen-specific control of effector T cells (T_{effector}, 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, B cells, and natural killer or natural killer T cells. The lymphoid target cells are contacted by the Treg cell by surface interactions including surface receptors such as lymphocyte activation gene (LAG)-3, and cytotoxic T lymphocyte–associated antigen 4. The latter enhances the
expression and activity of membrane-bound TGF-β.\textsuperscript{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-resident\textsuperscript{31} and are found in activation contact zones.\textsuperscript{30}

### TH17 CELLS: A SEPARATE SUBSET

The discovery of the TH17 cells is filling an essential gap in our understanding of inflammatory processes, because it was unclear how TH1 cells actually mediate inflammation in the tissues by the expression of IFN-γ. TH17 cells are characterized by IL-17 (or IL-17A), IL-17F, IL-6, TNF-α, and IL-22 expression.\textsuperscript{32-36} Neutralization of IL-17, but not genetic deletion of TH1 cells, resolves tissue pathology in autoimmune models.\textsuperscript{37} Furthermore, anti–IL-17 reduces joint destruction in experimental arthritis,\textsuperscript{38} and reduces neutrophil infiltration in an experimental asthma model while increasing eosinophil infiltration.\textsuperscript{39,40} Exogenously administered IL-17 reduces pulmonary eosinophil recruitment and bronchial hyperreactivity, suggesting a regulatory role of IL-17.\textsuperscript{41} Thus, it appears that the TH17-directed neutrophil infiltration is inversely linked to the TH12-mediated (or IL-5-mediated) eosinophil direction, similar to inverse relationships of TH1 and TH2 cells. In fact, it could be shown that TH17 cells retain their IL-17-dominated phenotype after restimulation,\textsuperscript{42} that the IL-17 promoter undergoes chromatin remodeling,\textsuperscript{43} and that TH17 cells compete with both TH1 and TH2 cells and thus represent a separate T-cell subset.\textsuperscript{32}

### TH17 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 TH17 cells as possible participants in autoimmunity. The key cytokine of TH17 cells, IL-17, is known to induce proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 as well as chemokines CXCL1, 2, and 8, which together are hallmarks of acute inflammatory processes (Table I).\textsuperscript{72-85} The chemokines mobilize neutrophil recruitment, which is discussed as a characteristic feature of TH17-mediated inflammation, responsible for the histologically visible appearance of neutrophilic inflammation. The role of TH17 cells in allergy is still largely unclear, but experimental models suggest that TH17 cells may be important for neutrophilic inflammation in acute airway inflammation.\textsuperscript{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.\textsuperscript{48} Furthermore, it is known that IL-17 induces chemoattractants in human airway smooth muscle\textsuperscript{49} and airway epithelial cells.\textsuperscript{50} IL-17 acts in synergy with other TH17 cytokines, such as IL-6 to induce mucus proteins mucin (MUC)5B and MUCSAC,\textsuperscript{28} or together with IL-1 and TNF-α to enhance...
vascular endothelial growth factor expression.51 Thus, TH17 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 TH1 cells, where IFN-γ secretion mobilizes MHC-II expression in nonprofessional antigen-presenting cells or induces apoptosis in epithelial cells or keratinocytes. However, TH17 cells could theoretically be of benefit to reduce matrix deposition, because TH17 cells, in contrast with TH2 cells, are capable of inducing metalloproteinases (Table I), which is an essential mechanism of TH17-mediated cartilage breakdown in arthritis and could be beneficial for remodelling in allergy.47,52 In contrast with TH1 and TH2 cells, TH17 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 an 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 (TH2,54 TH17 cells28) and extracellular matrix build-up (TH255) or breakdown (TH17)34,56,57. 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). TH1 cells inhibit TH1723 and TH17 development.37 TH2 cells inhibit TH1 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)γt (RORC2 in human beings) for TH11, TH2, Treg, and TH17 cells, respectively.58-61 Runt-related transcription factor 1 promotes Treg cells62 and inhibits differentiation of TH12 cells.63 T-bet interferes with TH17 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.33,59,64,65 which dictates the chromatin accessibility of the subset-specific genes in the progenitor cells. This accessibility for the IL4 gene is then secondarily IL4–independent for the evolving memory populations, which is not true for the IL13 gene.59

Besides this negative, competitive regulation process, the discovery of TH17 and Treg cells underlines another key feature of T-cell biology: all differentiation pathways use a positive feedback loop, which may serve as an autocrine and paracrine mechanism of T-cell subset polarization (Figure 2). TH1 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 TH11 commitment. TH12 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 TH12 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 expression66,67 and thus excludes TH11 and TH12 differentiation pathways. Although both Treg differentiation and TH17 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 TH17 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, TH17 cells require additional IL-6 to polarize away from the Treg cell pathway toward the TH17 phenotype.45 IL-17 is known to induce IL-6 in structural cells, which in turn can feed-back on the induction of TH17 cells. IL-23 has also been shown to induce TH17 cells and appears to be especially important for the IL-22 component of the TH17 cells.66 because IL-6 knockout cells lack IL-17 but can still produce the TH17 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<sub>H1</sub>, T<sub>H17</sub>, T<sub>reg</sub>, and T<sub>H2</sub> cells, IFN-γ, IL-6, TGF-β, and IL-4 produced by these cells further induce the synthesis of transcription factors T-bet, RORγt, FOXP3, and GATA-3, respectively. Epit, Epithelial cells; Fib, fibroblasts.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dominating cytokine</th>
<th>Absent cytokine</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe respiratory syncytial virus bronchiolitis</td>
<td>IL-9</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>Chronic bronchitis with obstruction</td>
<td>IL-9</td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>Pneumothorax-associated pleural eosinophilia</td>
<td>IL-5</td>
<td></td>
<td>88</td>
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<tr>
<td>Asthma</td>
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<td></td>
<td>89</td>
</tr>
<tr>
<td>Lung emphysema</td>
<td>IL-13</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>Human T-lymphotrophic virus-1 infection</td>
<td>IL-13</td>
<td>IL-4</td>
<td>91</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>IL-13</td>
<td>IL-4</td>
<td>92</td>
</tr>
<tr>
<td>Atopic eczema/dermatitis syndrome</td>
<td>IL-13</td>
<td>IL-4</td>
<td>93</td>
</tr>
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<td>Schistosoma haematobium infection</td>
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<td></td>
<td>94</td>
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<td>Allergen provocation of Asthma</td>
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<td>IL-6, IL-8, IFN-γ, and TNF-α</td>
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<td>IL-13 &gt; IL-4</td>
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<td>IFN-γ</td>
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<td>Sezary syndrome</td>
<td>IL-4, (IFN-γ)</td>
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<tr>
<td>Benign reactive erythroderma</td>
<td>IFN-γ</td>
<td>IL-4</td>
<td>102</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>IL-5</td>
<td></td>
<td>103</td>
</tr>
</tbody>
</table>

*Disease condition described to be related to T<sub>H2</sub> cytokines. The table shows that T<sub>H2</sub> cytokines are selectively expressed in specific disease, indicating that T<sub>H2</sub> cells mediate different disease because of distinct T<sub>H2</sub> cytokine expression profiles.
lack IL-17. Similar to IL-6, IL-23 is induced by IL-17 in dendritic cells but not in epithelial cells. Thus, it can be hypothesized that T(H)17 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(H)17 differentiation pathway is of particular interest for future research, because it could be hypothesized that the T(H)17-type immune response can be more efficiently turned into Treg or tolerogenic reactions than T(H)2 or T(H)1 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(H)2-dominated disease we have to consider that T(H)5, T(H)9, T(H)13, and T(H)31 subsets may exist that generate specific pathologies (Table I). 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(H)2 concept. Although IL-5–producing cells can be generated on T(H)2 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 IL-5 gene transcription involves the reversible histone modification catalyzed by histone deacetylase 4 and p300, 71 leaving room for IL-4–independent gene regulation. Future research must clarify whether differentiation pathways exist that can permanently imprint these phenotypes. Because T(H)17 cells promote neutrophil 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(H)17 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.

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