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The role of T helper subsets in autoimmunity and allergy

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The classification of T helper (T_H) cells in subsets has progressively expanded and more effector subsets, besides T_H1 and T_H2 , have been documented. These include follicular helper T cells (T_{FH}), and the more recent T_H17 , ' T_H9 ', and ' T_H22 '. In addition, T_H are no longer thought of as terminally committed effector cells, with plasticity now recognized. Identification of the molecular mechanisms that drive differentiation of T_H cells has established a link between environmental factors and T_H subsets, with regard to both the initiation and severity of immune disorders. The role of T_H in autoimmune-disorders and allergic-disorders is now re-evaluated, with current data suggesting a central role for T_H17 in orchestrating adaptive-immune responses, while T_{FH} are instrumental in coordinating B cell immunity.

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Introduction

The encounter of the innate-immune system with antigen will set the stage for the initiation of an adaptive-immune response. Tight management of this response is essential for host function and survival, maintaining a balance between antigen clearance and immune pathology, while tolerance to all components of self as well as many harmless antigens needs to be preserved. The dichotomous classification of T_H in those orchestrating cell-mediated or humoral-mediated responses was based on the selective production of interferon (IFN)- γ and interleukin (IL)-4. As a result it was postulated that many autoimmune-disorders, including multiple sclerosis (MS) and Rheumatoid arthritis (RA) resulted from aberrant T_H1 responses, while allergies were thought of as T_H2 mediated. Why anyone develops an autoimmunity or allergy is one of the central questions in immunology, but it is widely believed that the interactions between

environmental exposures and genetic predisposition contribute to the onset of disease.

Following the original classification in T_H1 and T_H2 , more T_H subsets have been documented, each with their own repertoire of cytokines and transcription factors. These include regulatory T cells (T_{reg}), follicular helper T cells (T_{FH}), T_H17 , and most recently those that produce IL-9 (T_H9) and IL-22 only (T_H22). Furthermore, plasticity in the adaptation of effector profiles has now been recognized, forcing immunologists to revisit and reinterpret existing models of autoimmunity and allergy. In addition, insights into the initiation of novel and existing subsets have provided exciting links with environmental triggers.

Plasticity of T helper subsets

T cell receptor (TCR) recognition of peptide–MHCII on antigen presenting cells (APC) constitutes the first main event in the development of T_H responses; however, continued or multiple contacts are required for maximum responses [1,2]. The requirement for sequential cognate interactions offers the opportunity for fine-tuning T_H responses as well as the delivery of new programming signals. T_H1 and T_H2 cells, after prolonged polarization, were thought of as terminally differentiated cell types, antagonizing each other's development. The first cultures leading to IL-17-producing cells, based on the successful blockage of T_H1 and T_H2 development, suggested that this would apply for T_H17 as well [3,4]. T_H1 and T_H2 lineage transcription factors control T_H17 development, as shown for Tbet and growth factor independent (Gfi)-1 [3,5]. Furthermore, the repressive state of the *Il17* and *Rorc* locus [6•], confirms that conversion of T_H1 or T_H2 into T_H17 seems unlikely. However, IL-17-producing cells have the capacity to produce IFN γ . These readily found 'double'-producing cells would not fit in a paradigm of T_H classification consisting of three independent pillars. Indeed, exploiting IL-17F reporter mice and an IL-17A capture assay it was shown that some highly purified T_H17 cells are able to give rise to T_H1 cells after encountering IL-12 for which they express the receptor, and similarly the encounter with IL-4 has been reported to result in T_H2 conversion [7,8•,9]. Together with the bivalent or heterogeneous state of *Tbet* and *Gata3*, in contrast to *Ifng* and *Il4* which contain repressive marks [6•], this suggests that T_H17 are responsive to new programming signals.

Plasticity does not seem to be a unique feature of T_H17 . Although *Foxp3* contains repressive marks in all effector subsets except T_H17 , *Tbet*, *Gata3*, and *Rorc* seem bivalent

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in T_{reg} [6^{••}]. Although this is in line with multiple reports on the instability of T_{reg} , which might only reflect a minor uncommitted population [10], it has become clear that T_{reg} utilize characteristic factors from effector T_H to regulate their responses [11^{••},12^{••}]. The bivalency of these factors may thus reflect the potential of T_{reg} to call upon those genes to regulate the T_H counter part, rather than their conversion potential. Another example of plasticity was recently reported, whereby committed T_H2 are not just inhibited by TGF β but undergo a complete reprogramming, switching off Gata3 and the production of IL-4, IL-5, and IL-13, while initiating the transcription of IL-9 *in vitro* [13^{••}]. It remains to be determined if ' T_H9 ' development requires prior T_H2 development, or if a common progenitor stage exists.

A similar scenario could exist for other T_H cells, whereby only partially committed cells are able to respond to new signals, while fully established T_H cells, possibly by repeatedly encountering cues that reinforce their identity, could lose this ability. Indeed, only a fraction of *in vivo* generated T_H17 has been reported to convert under

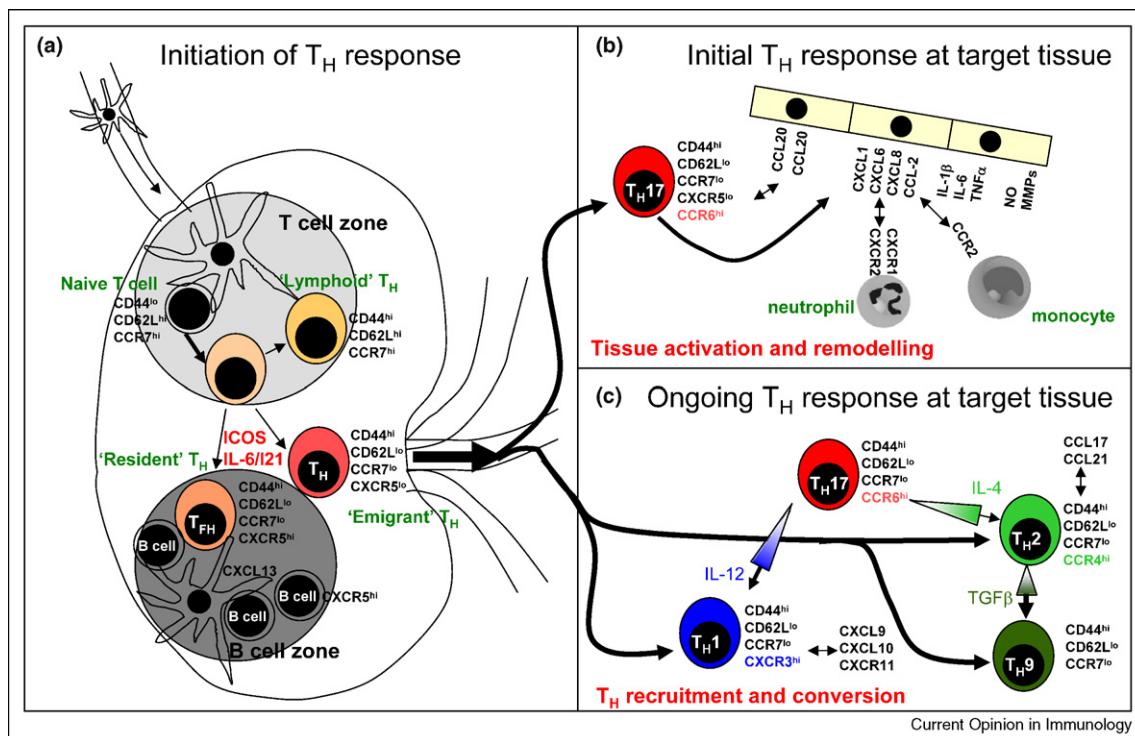
T_H1 or T_H2 culture conditions, whereby the majority maintained their T_H17 profile [9].

T_{FH} , retained in the B cell areas of lymph nodes, arise from T cells with the strongest peptide–MHCII binding and more restricted junctional diversity [14^{••}], and display a heterogeneous pattern of cytokine production and transcription factor usage [14^{••},15[•],16,17[•],18,19]. However, this does not result in differential expression of effector molecules between cells poised to migrate to sites of infection, or those retained in the T or B cell areas of lymph nodes (Figure 1A). The study of T_{FH} –B cell conjugates indicates that T_{FH} cytokines have local rather than systemic effects, while pairing of antibody isotypes with peripheral cell function still occurs [17[•]]. This would be most consistent with the activation of shared cytokine loci before the migration of T_H into follicles or to sites of inflammation, and subsequent maturation.

Organ-specific autoimmunity and allergy

Autoimmune diseases form a spectrum ranging from organ-specific conditions to systemic diseases in which

Figure 1



Initiation of T helper cell responses and tissue specificity. **(A)** Following the encounter with antigen, naive T cells can differentiate toward multiple T helper lineages. Upon activation, CD44 is upregulated, and those with high affinity TCRs downregulate CD62L and CCR7 and express CXCR5 to migrate into the B cell zones to become T_{FH} , while those that retain CD62L and CCR7 expression reside in the T cell zone. CD62L^{lo}CCR7^{lo} cells that do not express CXCR5, but may express CCR6, migrate to target organs. **(B)** At the tissue epithelial barriers expression of CCL20, indicating inflammation, preferentially attracts CCR6 positive putative T_H17 cells, which can activate tissue cells to produce a range of chemokines and cytokines, resulting in additional recruitment of myeloid cells, including neutrophils and monocytes, while the induction of nitric oxide and matrix metalloproteinases allows for further tissue remodeling. **(C)** Subsequent recruitment of myeloid cells and T_H subsets depends on the local microenvironment and chemokine expression, for example CXCL9–11 will contribute to T_H1 recruitment, while T_H17 conversion under the influence of local cytokine concentrations can also play a role.

the pathology is diffused throughout the body. Past studies linked T_H1 responses with autoimmune-disorders, while T_H2 cells were associated with allergic reactions. How do new T_H fit with this paradigm?

Besides autoimmune-disorders, IL-17 is also found during allergic reactions and asthma. Its effects are characterized by a strong reliance on innate-immune cells, inducing a variety of cytokines and chemokines, thereby coordinating additional immune-cell recruitment [20,21]. T_H17 are typified by CCR6 expression [22,23], directing them to sites that express its ligand CCL20 (Figure 1B). CCL20 is implicated in the formation and function of mucosal tissues because of its ability to attract myeloid cells toward epithelial barriers that surround tissues, including liver, lung, intestine, and skin. Indeed, expression of CCL20 has been implicated in the initial entry of T_H17 into to central nervous system (CNS) and the joints [23,24]. Additional recruitment of immune cells, often dominated by T_H1 , appears independent of CCR6 expression [24]. The encounter with many microbial factors can result in the expression of CCL20, and is not only found in autoimmunity, but also allergic reactions are characterized by its induction [25–28]. This places T_H17 as orchestrators of adaptive-immune responses, linking innate and adaptive immunity and providing tissue access.

The role of IL-9-producing cells in aberrant immunity will have to be determined in the coming years. Although, ' T_H9 ' have already been linked with autoimmunity [29], IL-9 has mainly been associated with allergy. Allelic associations between polymorphic markers of IL-9 and IL-9R have been reported in allergic pulmonary disease. Lymphocytic and eosinophilic infiltration, epithelial cell hypertrophy, mucus production, and smooth muscle cell contraction, as well as mast cell and goblet cell hyperplasia have all been linked with IL-9, although its role may not be obligatory [30]. Recent data place basophils at the center of initiating T_H2 responses, independent of mast cells and eosinophils [31,32,33,34], which express the IL-9R and have been implicated in T_H2 -mediated immunity. This suggests that IL-9 may not play a role in the initiation of allergic reactions, but might be important in sustaining and modulating subsequent responses. Indeed, mast cells, important in IgE-mediated allergic inflammation, are recruited from the bone marrow as immature cells and differentiate *in situ*, in which IL-9 makes an important contribution [35]. In addition, it influences the survival and maturation of eosinophils and increases their susceptibility to IL-5, thereby enhancing type 2 immune responses. This could link the expression of TGF β in inflamed tissue with the possible reprogramming of T_H2 into ' T_H9 ' [13].

Systemic autoimmunity

While most autoimmune conditions are characterized by the presence of autoantibodies, disorders like Graves'

disease and systemic lupus erythematosus (SLE) depend on their production. The role of T_{FH} in SLE was highlighted by the observation that patients have increased numbers of these cells in their blood. The prevailing model is that autoantibodies result from defective negative selection of self-reactive B cells, as reported for some SLE patients, whereby B cells otherwise programmed to undergo apoptosis are rescued by signals from aberrant T_{FH} , resulting in memory B cells and high antibody secreting plasma cells (for review see [36]). However, recent studies found increased serum levels of IL-17 and IL-23 in SLE patients [37,38], and T_H17 were suggested to be responsible for the selection and prolonged retention of autoreactive B cells in antigen independent germinal center formation [39]. Indeed, IL-17, especially in synergy with the B cell-activating factor (BAFF), was shown to protect B cells from apoptosis, thereby promoting their proliferation, survival, and differentiation into plasma cells [40]. Inhibition of BAFF in a CIA model has recently been reported to be able to decrease numbers of both T_H17 as well as plasma cells, suggesting BAFF may amplify IL-17 production [41]. Together with the reported close relationship between T_H17 and T_{FH} , both utilizing ICOS, IL-21, and the transcription factor c-maf [15], this indicates that T_H17 controls important aspects of B cell biology and systemic autoimmunity. It is tempting to speculate that IL-17-producing T cells are, together with T_{FH} , a first effector T cell to arise, utilizing CCR6 to direct adaptive-immune responses in target tissues (Figure 1A).

Environmental factors

Environmental factors might be the trigger for the development of autoimmune or allergic responses in genetically predisposed individuals. These factors could be pathogen related, or derive from drugs or environmental pollutants. This would be an explanation why the chance that identical twins both develop a disease is 20–40% for common autoimmune-disorders and allergies. Pathogen-derived products have long been suspected to be involved in the initiation of aberrant immune responses, initially proposed to be the result of molecular mimicry, but proof for this has been difficult to establish.

Recent identification of microbial factors able to initiate or strengthen allergic inflammation has been intriguing. Pathogen-derived products, via extracellular and intracellular microbial sensors and the inflammasome, induce the expression of IL-1, IL-18, and possibly IL-33 (for review see [42]). These IL-1-family members are known to enhance and alter T_H17 , T_H1 , and T_H2 responses, respectively. T_H17 especially are under constant control of activated APC, requiring both IL-1 and IL-23 for maintenance and function [43,44], linking genetic predispositions resulting in inappropriate functioning of pathogen recognition receptors and chronic inflammation with autoimmune-disorders [45].

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Previously, chitin, found in fungi, crustaceans, helminthes, and insects, had been shown to induce alternative macrophages, recruiting eosinophils and basophils, but not mast cells [46^{••}]. Chitin could therefore constitute an example of a pathogen-derived molecule that supports the accumulation of immune cells implicated in allergic reactions, linking those individuals that come into contact with high levels of it with high incidence of asthma [47].

The failure of APC to make sufficient IL-4, and their inability to phagocyte large parasites, prompted the hypothesis that secreted products such as proteases, could be the drivers behind some T_H2 immune reactions [48^{••}]. Indeed, the protease, papain, was identified to cleave an as-yet unidentified host-derived sensor of proteolytic activity, subsequently activating the innate-immune system, including basophils to secrete IL-2, IL-4, IL-13, creating the microenvironment for Th2 differentiation [48^{••}]. In addition, Derp2, the main house-dust-mite allergen and major contributor to allergic asthma, shows remarkable homology with MD-2-related lipid-recognition domain proteins [49^{••}]. It facilitates direct signaling through the Toll like receptor (TLR)4, effectively stimulating innate-immune and subsequent adaptive-immune responses. This would link house-dust-mites via Derp2 with reported low dose LPS induced T_H2 responses, ultimately resulting in asthma via the activation of TLR4 on lung-epithelial cells, APC activation and priming of T_H cells [50[•]].

A more direct effect of an environmental factor on T_H-mediated autoimmunity was recently reported with the discovery of the expression of the aryl hydrocarbon receptor (AhR) in T_H17 [51^{••},52^{••}]. AhR is a transcription factor involved in direct recognition of aromatic hydrocarbons found in cigarette smoke, grilled food, and industrial contaminants. Encountering an AhR ligand during the initiation of a T_H17-mediate response directly influences the strength of the response, characterized by increased polarization and cytokine production resulting in more rapid onset as well as increased severity of autoimmunity. Although the molecular mechanism is currently not known, AhR seems to act by inhibiting the activity of signal transducer and activator of transcription (Stat)1 and Stat5 [53]. Natural occurring AhR ligands have been described and the tryptophan metabolite 6-formylindolo[3,2-*b*] carbazole (FICZ) was shown to have very high affinity for AhR comparable to that of dioxin. Indirect evidence shows that photoproducts of tryptophan such as FICZ, could be synthesized *in vivo* in skin, or in culture medium [54]. In addition to an overall enhanced Th17 response, AhR ligands induce IL-22 expression [52^{••}]. Although not essential in mediating EAE [55], IL-22 has been implicated in disrupting blood-brain barrier tight junctions [56]. AhR, *albeit* at 50–100-fold lower levels than T_H17, was also found in T_{reg}, in accordance with the low level expression of other T_H

transcription factors in this subset [51^{••},52^{••}]. It is currently unclear whether the low levels of AhR expression in T_{reg} cells have physiological consequences for the functional activity of these cells; the more since AhR is reported to inhibit Stat5, a crucial T_{reg} transcription factor. Although it was suggested that it might be involved in the induction of iT_{reg} [51^{••}], the dioxin ligand used cannot be metabolized and causes prolonged stimulation resulting in toxic effects, potentially causing a proportional shift in the more resistant T_{reg} population rather than an expansion of this subset. The contribution of AhR ligands to autoimmune-disorders is currently unknown, and it remains to be determined whether human AhR polymorphisms exist that would link environmental pollutants with a genetic predisposition to the development of autoimmunity.

Conclusions

In recent years new insights into immune responses have been substantial, and a strong link between the initiation as well as the severity of autoimmunity and allergy with pathogen-related factors has been established. Autoadjuvant properties provide a context in which unwanted responses against harmless antigens can be initiated, while man-made pollutants, epidemiologically linked with both autoimmune-disorders as well as asthma, like aromatic hydrocarbons found in cigarette smoke, can now directly be linked via the expression of AhR in T_H17.

Instead of constituting a third independent pillar of the original dichotomous paradigm, T_H17 seem to play a more regulatory role in local and systemic immune responses, linking innate and adaptive immunity, with involvement in both cell-mediated and humoral-mediated reactions. The established plasticity of T_H, substantiated by epigenetic data, predicts, at least at the initiation, a higher degree of flexibility of the adaptive-immune response than previously thought. Conversion of certain T_H subsets into others, of which the limits have not been explored in detail, has the potential to upturn the established classification of T_H subsets, and will have important implications regarding future therapeutic strategies for autoimmune-disorders and allergic disorders.

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