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REVIEW

A brief history of T_H17, the first major revision in the T_H1/T_H2 hypothesis of T cell–mediated tissue damage

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For over 35 years, immunologists have divided T-helper (T_H) cells into functional subsets. T-helper type 1 (T_H1) cells—long thought to mediate tissue damage—might be involved in the initiation of damage, but they do not sustain or play a decisive role in many commonly studied models of autoimmunity, allergy and microbial immunity. A major role for the cytokine interleukin-17 (IL-17) has now been described in various models of immune-mediated tissue injury, including organ-specific autoimmunity in the brain, heart, synovium and intestines, allergic disorders of the lung and skin, and microbial infections of the intestines and the nervous system. A pathway named T_H17 is now credited for causing and sustaining tissue damage in these diverse situations. The T_H1 pathway antagonizes the T_H17 pathway in an intricate fashion. The evolution of our understanding of the T_H17 pathway illuminates a shift in immunologists' perspectives regarding the basis of tissue damage, where for over 20 years the role of T_H1 cells was considered paramount.

The T_H1/T_H2 hypothesis was developed out of an attempt to answer two major questions that immunologists confronted in the mid 1980s: (i) was there a distinct T_H subset that mediated delayed-type hypersensitivity, whereby T_H cells damage tissues, and (ii) was there another T_H subset that provided help for B cells, leading to antibody production[1–3]? The answers to these questions, posed by Robert Coffman and Tim Mosmann 20 years ago, made a startling impact on how immunologists viewed the world of inflammation. They showed that so-called type 1 CD4 T-helper cells (T_H1) drive cell-mediated immune responses leading to tissue damage, and they learned that these T_H1 cells also drive antibody-mediated responses in certain subclasses of the G isotype of immunoglobulin (Ig) antibody, specifically termed IgG_{2a}. In contrast, type 2 CD4 T-helper cells (T_H2) drive certain antibody-mediated responses, particularly those that are involved in allergy dominated by the IgE isotype[3]. Like all hypotheses, there were certain phenomena, particularly in the area of T cell–mediated tissue damage, that could not be explained by T_H1 and T_H2 and where the predictions of the hypothesis stood in stark contrast to the experimental data. Nevertheless, given our primitive state of knowledge about cytokines at that time, compared to our current level of understanding, the T_H1/T_H2 hypothesis had remarkable durability, despite its flaws and blemishes. Most importantly, it gave to us immunologists the notion that whole sets of T cells could reciprocally inhibit the functions of other sets of T cells: cytokines produced by T_H1 cells could negatively regulate the function of T_H2 cells and vice versa[1–3].

This idea was a natural progression from prevailing views of T-'helper' and T-'suppressor' subsets that were all in vogue in the 1970s, only to be driven hard and fast into oblivion with the advent of molecular immunology in the early 1980s. In 1982 the mouse major histocompatibility region (MHC) was cloned[4]. A proposed determinant of 'suppressor' T-cell function—named I-J—had previously been laboriously mapped within the MHC, but, to the chagrin of immunologists working on subsets of T cells, no gene could be found within the MHC that encoded this function. Major holes were present in the T-suppressor story, including the fact that the I-J molecules had never been isolated biochemically, despite a large number of studies reporting their functional activities. In a caustic News and Views in *Nature* entitled "Trouble in the J-land," it was suggested that I-J genes "do not exist[5]." From that point on, the concept of T suppressors exited the stage, never to return, at least not under that name[4]. Its re-emergence in the last few years, under the guise of T 'regulator' (T_{reg}) modulated by T_H17, is an ironic twist. T suppressor is still a phrase that has a certain taboo in the psychology and lexicon of immunologists, since the times of "Trouble in the J-land[5]."

The T_H1/T_H2 hypothesis was remarkable for how soon it was formulated after the disappointment of the T-suppressor saga. Perhaps Coffman and Mosmann were emboldened by the dawn of molecular immunology, with its signature initial achievement of the discovery of the T-cell receptor[6,7]. Although the shift toward molecular biology in immunology had shattered the idea of T suppressors, it gave rise to a new and much stronger hypothesis for T-cell subsets. The lingering theme of T-suppressor cells inhibiting T-'effector' cells must have been ingrained deeply in how immunologists perceived the behavior of whole populations of T cells. This idea of opposing populations of T cells provided

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the intellectual framework for not only the T_H1/ T_H2 hypothesis, but also for the newest theory, termed the T_H17 hypothesis, to explain cell-mediated tissue damage in both autoimmunity and immunity triggered by microbial infection.

The T_H17 hypothesis has its own shortcomings and will ultimately be refined and probably replaced. It is likely to become established that no single cytokine can regulate a vital process like tissue damage and that it is a constellation of cytokines, tuned in concert, that ultimately produces a complex phenotype like 'tissue damage' or 'recovery from tissue damage'.

T-cell subsets in the age of molecular immunology

A historical perspective on the T_H1/T_H2 hypothesis is illuminating, both for its insights into important immunological phenomena and for its revelations about how groups of highly trained intellectuals, in this case immunologists, can adhere to an idea for so many years, even in the face of its obvious flaws. In two papers published in 1986 in the *Journal of Immunology*, Coffman and Mosmann outlined a bold new concept for T-helper cell function[1,2]. They proposed a clever and affirmative answer to the following older question: "Are B cell help and delayed-type hypersensitivity mediated by different types of $CD4^+$ T_H cells[3]?"

Inherent in the hypothesis is that T_H1 cells mediate delayed-type hypersensitivity (DTH). DTH reactions were originally defined as cell-mediated immune reactions manifest by swelling, induration and redness appearing 24 to 72 hours after intradermal injection of a challenge antigen. The tuberculin skin test is a classic example of a delayed-type hypersensitivity reaction in an individual sensitive to the purified protein derivative of *Mycobacterium tuberculosis*. The tuberculin skin test is still in common use in clinical medicine, to assess one's immune status to *M. tuberculosis*. DTH reactions are characterized by a cellular infiltrate comprised primarily of lymphocytes and macrophages. Examples of DTH reactions in microbial diseases include pulmonary tuberculosis, tuberculoid leprosy and contact sensitivity to allergens in the skin. In autoimmune diseases, perivascular infiltrates present in the brains of individuals with multiple sclerosis bear the hallmarks of DTH, as do the lymphocytic infiltrates found in the joints of rheumatoid arthritis patients. Mosmann and his research group claimed that they had "confirmed experimentally that T_H1 cells but not T_H2 cells mediated classical delayed-type hypersensitivity reactions[8]."

Mosmann actually measured the capacity of T_H1 or T_H2 antigen–specific T-cell clones to cause footpad swelling in naive mice. In experimental pathology in the 1980s, the experimental assay measuring footpad swelling in response to antigenic challenge, usually in a sensitized host, was often taken as a surrogate for DTH. Mosmann further modified the footpad swelling assay to test swelling induced by T-cell clones: T-cell clones were injected, with or without antigen, into the footpads of naive mice that had not previously been sensitized to the antigen. In these experiments, injection of cloned T_H1 cells caused footpad swelling at 24 hours, whereas injection of T_H2 clones did not cause swelling[8]. Injection of soluble antigen caused no swelling at all, because the mice were not immunized to the soluble antigen under study. This measurement of footpad swelling was the sole platform for assessment of DTH in the pivotal paper in which Mossman made his claim[8].

Despite the fact that, at the time, footpad swelling was a widely used measure of DTH in the mouse, the assay may have accounted only for the edema seen in cell-mediated inflammation. Footpad swelling may not have been an adequate marker for the tissue damage seen in many of the classic models of autoimmune and infectious disease that were being intensively studied at the same time. The use of a single assay, conventional as it was at the time, may have led to an erroneous conclusion, namely that DTH, and by inference cell-mediated tissue damage, was due to T_H1 cells. Nevertheless, the immunology community greeted this experiment with great enthusiasm. In retrospect, the measurements were correct, but the extrapolations from a single overly simplified assay to a pathological process as complex as cell-mediated tissue damage were overstated.

Nonetheless, the T_H1/T_H2 paradigm gave us the important concept that there could be reciprocal interactions between whole sets of T cells. The demonstration in 1989 that IL-10, a T_H2 cytokine[9], could inhibit the function of T_H1 cells established a new model, best described by Coffman: "The key idea is that each T_H subset has the ability to stimulate one set of coordinated anti-pathogen effector functions and to promote the development of more cells of the same T_H subset while inhibiting both the development of the opposite subset and many of its most important effector functions[3]."

The discoveries and concepts developed by Coffman and Mosmann in the period between 1983 and 1990 were remarkable, given the paucity of tools at their disposal. At the onset of their research, they had only one monoclonal antibody to one cytokine, γ-interferon[3]. It should be no surprise that a concept derived at a time when our understanding was much more primitive than it is today would not be able to dominate our thinking indefinitely. The implications of the T_H1/T_H2 hypothesis, particularly its emphasis on the notion of reciprocal interactions among T-cell subsets, continue to guide our perspective about the physiological and pathological significance of functionally related groups of T cells. But like all brilliant and cutting-edge hypotheses, the T_H1/T_H2 model has shortcomings, and there were key pieces of data that could not be explained at all by T_H1/T_H2.

Over the past five years, there has been a remarkable evolution in thinking, leading us to revise our opinions about T_H1 and to develop a new model to explain the regulation of tissue damage defined by DTH, which underlies pathology in many autoimmune conditions and in many microbial infections. This new model is called the T_H17 hypothesis and it is the first significant (and certainly overdue) revision of the T_H1/T_H2 hypothesis since it was enunciated in 1986.

Historically, we see major ideas in other areas of science undergoing revision. Most famously, the 'laws' of physics underwent dramatic conceptual changes about a century ago, as experimental phenomena could no longer be explained by older ways of thinking. The laws of what is now termed classical mechanics, first described by Newton and that had governed physics for centuries, finally were supplanted with the quantum mechanics of Einstein, Planck and Heisenberg. Explanations of experimental data on relativity, and atomic and subatomic interactions could not be handled via the classical mechanics of Newton and instead required a whole new framework. Immunology is undergoing a similar conceptual change in the way we analyze how immune T cells damage tissue. Fortunately we immunologists never called our prevailing concepts 'laws'. Immunologists, rather modestly and probably appropriately, referred to our theoretical frameworks as 'hypotheses'. Whether this difference in terminology actually eased the revisions in our thinking about T_H1 and T_H2 can be debated, for the hypothesis was slow to change in the face of considerable contradictory data.

Flaws in the T_H1/T_H2 hypothesis

One of the enduring models of tissue damage mediated by cells, rather than antibody, has been the animal model experimental allergic encephalomyelitis (EAE)[10]. EAE is more commonly referred to these days as experimental autoimmune encephalomyelitis. The abbreviation EAE in this review refers to both of these terminologies: experimental allergic and experimental autoimmune encephalomyelitis. The term delayed-type hypersensitivity was used to describe tissue damage in EAE and other cell-mediated autoimmune conditions, such as experimental

Table 1 Flaws in predictions from the T_H1/T_H2 hypothesis and outcomes in experimental autoimmune encephalomyelitis

Prediction	Outcome
Administration of γ-IFN would worsen EAE	Administration of γ-IFN protected from EAE
γ-IFN knockouts would be resistant to EAE	EAE worse in γ-IFN knockouts
Antibody to γ-IFN would protect in EAE	Antibody to γ-IFN worsened EAE
TNF knockouts would be resistant to EAE	TNF knockouts had worsened EAE
Administration of TNF would worsen EAE	Administration of TNF protected from EAE

allergic thyroiditis and contact sensitivity, which could be transmitted to animals by adoptive transfer of lymphoid cells but not by transfer of immune serum[11–13]. So if T_H1 cells could mediate DTH, as proclaimed by Coffman and Mosmann[3,8], then it would be predicted that administration of γ-interferon (γ-IFN)—the archetypal T_H1 cytokine—would worsen EAE and that an antibody to γ-IFN would ameliorate EAE. Further, with modern gene deletion techniques, one would have also predicted that EAE would be attenuated or absent in a mouse deficient in γ-IFN (refs. 14,15).

In fact these predictions were all completely wrong, and the results were just the opposite (**Table 1**). At about the same time that Coffman and Mosmann were publishing the details of the T_H1/T_H2 hypothesis, a number of laboratories were showing that the administration of γ-IFN itself ameliorated paralysis in EAE and improved joint function in another well-studied animal model of autoimmune arthritis, termed adjuvant arthritis[14–19]. In the studies on adjuvant arthritis[19], the timing of the administration of γ-IFN was critical. When given 24 hours before administration of the adjuvant, arthritis was worsened, whereas when given 24 to 48 hours after immunization with adjuvant, arthritis was ameliorated[19]. In adjuvant arthritis, when γ-IFN was given daily over a period of 20 days following immunization, bone lesions regressed with γ-IFN treatment and both the erythrocyte sedimentation rate, a good surrogate for inflammation, and levels of fibrinogen decreased with γ-IFN administration[20]. Moreover, antibodies to γ-IFN exacerbated both EAE (ref. 14) and adjuvant arthritis, when given at certain time points during the course of the disease[19]. T-cell clones producing high amounts of γ-IFN actually ameliorated adjuvant arthritis (ref. 19 and **Table 1**).

In the mid 1980s, immunologists became proficient at cloning T cells that caused autoimmune diseases like EAE and arthritis. Studies on the pathogenicity of T-cell clones that could induce EAE with paralysis, clinical relapses and demyelination were shown to produce mainly T_H1 cytokines. However, the degree of pathogenicity of these clones—their virulence, so to speak—did not correlate with the amounts of γ-IFN that such clones produced[21–23]. Thus, there were often glaring inverse relationships between levels of the T_H1 cytokine γ-IFN and autoimmune tissue destruction in EAE and adjuvant arthritis.

Studies in gene-deleted mice were also difficult to reconcile with the T_H1/T_H2 paradigm[15]. Paralysis in the EAE model was worsened in mice in which the gene for γ-IFN was deleted. The same was true in mice genetically deficient in another T_H1 cytokine, tumor necrosis factor (TNF)[24]. Furthermore, the disease was reversed when recombinant TNF was administered[24]. Taken together, these results with modulation of γ-IFN and TNF in models of EAE and arthritis might have argued that T_H1 cytokines antagonized tissue damage at least in animal models.

It should be noted that in certain human diseases, the T_H1 hypothesis looked magnificent: administration of γ-IFN worsened MS (ref. 25), whereas therapy with antibodies to TNF (anti-TNF) was a triumph in the treatment of rheumatoid arthritis and Crohn disease[26]. These observations would support a role for T_H1 in MS and in rheumatoid arthritis and Crohn disease. However, in other examples, clinical experience did not fit the T_H1/T_H2 paradigm so well: anti-TNF worsened MS, and the class of TNF inhibitors that is approved for use in rheumatoid arthritis carries a label from the US Food and Drug Administration warning about the treatment's potential for worsening MS and other demyelinating disorders[26,27]. So results in animal models certainly could not support T_H1 as the mediator of tissue damage in autoimmune disease, while from studies on human disease, despite the notable example of worsened MS with γ-IFN and the triumphs of anti-TNF therapy in rheumatoid arthritis and Crohn disease, one could certainly not conclude that the T_H1 cytokines γ-IFN and TNF mediated tissue damage in all autoimmune diseases.

It remains a puzzle that scientists confronted with these obvious challenges to a dominant hypothesis like T_H1/T_H2 held on to their cherished ideas, even in the face of considerable contradictory data. Perhaps the answer to why this occurred in immunology is a question for some future historian of science to ponder. A successor to Thomas Kuhn, the eminent historian of science who coined the term "paradigm shift[28]," might find this evolution of ideas a rich story with important lessons. Certainly one of those lessons might be to 'question the aberrant data', because it could be teaching us something important. When modulation of γ-IFN, referred to as the "signature cytokine[29]" of the T_H1/T_H2 hypothesis, repeatedly and persistently produced results directly contrary to what was expected, we immunologists should have been aggressively challenging and revising the prevailing concept of T_H1/T_H2. The revision of this hypothesis could have been hastened.

The emergence of a new hypothesis to explain tissue damage

The T_H1/T_H2 hypothesis arose after the older concept of T suppressors had fallen with the molecular cloning of the major histocompatibility complex. However, many molecular biology experiments modulating the archetypal T_H1 cytokines with advanced technologies involving gene knockouts[15], transgenes[24], recombinant proteins[16–18,20,24] and monoclonal antibodies[14,19], which should have cast doubt on the T_H1/T_H2 hypothesis, failed to dislodge it from its dominant position in describing cell-mediated tissue damage. Apparently, it is not easy to revise an entrenched scientific theory, even with a wealth of contradictory data. Finally, however, the T_H1/T_H2 hypothesis could not withstand the assault of the ever-expanding knowledge of cytokine molecules. Experiments delineating the role of the cytokine IL-23 in EAE finally broke the hold of T_H1/T_H2. Ironically, much of the decisive work on IL-23 was performed at the same location where Coffman and Mosmann had performed their classic studies two decades earlier[30]. Perhaps the imprimatur of work coming from the same renowned institution—the DNAX Research Institute—permitted the evolution of a concept that supplanted the T_H1/T_H2 hypothesis.

The cytokine IL-23 is a heterodimeric molecule, sharing the p40 subunit with the T_H1 cytokine IL-12 but differing from IL-12 because of its unique p19 subunit. IL-23, unlike IL-12, does not induce T_H1 cells, which produce γ-IFN. In 2003, researchers at the DNAX Institute, showed that mice with the gene for IL-23 deleted were resistant to the induction of various animal models of autoimmunity, including EAE, collagen arthritis and inflammatory bowel disease[30,31].

IL-23 drives a population of T cells that produce IL-17, IL-6 and TNF (ref. 32). In adoptive transfer experiments, T cells producing IL-17 induced EAE, but T cells producing γ-IFN could not (ref. 32), although both types of T cells could cross the blood-brain barrier. Moreover, EAE severity was greatly reduced, though the disease was not abrogated, upon treatment with a monoclonal antibody to IL-17 in mice that were actively immunized with myelin antigen and adjuvant[32]. Likewise, mice

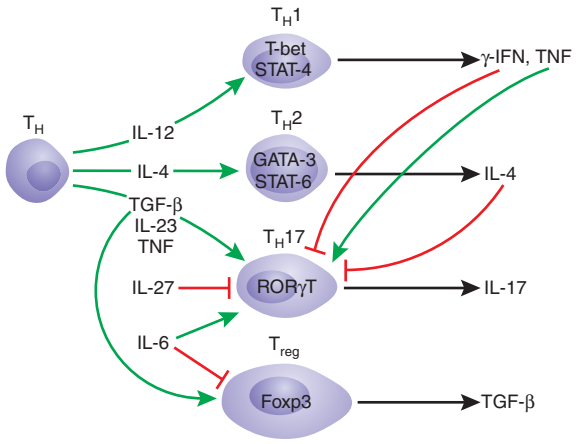

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Figure 1 T-helper cell differentiation and regulation. Green arrows indicate upregulation, while red lines indicate inhibition. Transcription factors for particular lineages are placed in the nucleus. This figure is updated from ref. 37, with new data on regulation of T_H17 by TNF and IL-27 (refs. 43,67,68) and with the identification of the transcription factor for T_H17 as RORγt (ref. 52).

treated with antibodies to IL-23 failed to develop EAE (ref. 33). Park and colleagues showed that treatment with antibodies to IL-17 initiated nine days after inducing EAE delayed the onset of paralysis. When treatment was started at the peak of paralysis, disease progression was attenuated[34].

A number of investigators showed that there were reciprocal interactions between γ-interferon and IL-17. Park and colleagues, for example, showed that a combination of exogenous γ-IFN and IL-4, when added to antibodies to CD3 and CD28, stimulated effector memory T cells that were $CD4^+CD62L^{lo}$ and reduced IL-17 production, although administration of either the signature T_H1 cytokine γ-IFN or the signature T_H2 cytokine IL-4, by themselves, failed to attenuate IL-17 (ref. 34). However, treatment with antibodies to either IL-4, γ-IFN or both greatly increased IL-17 production. Thus, both the signature T_H1 and T_H2 cytokines were required to reciprocally reduce IL-17, while administration of antibody to either T_H1 or T_H2 cytokines increased IL-17 (ref. 34). Cua and colleagues showed that EAE, driven by IL-23 and IL-17, was worsened with administration of neutralizing antibody to γ-IFN (ref. 32), adding further evidence to the notion that perhaps T_H1 and T_H17 were reciprocal in terms of their function. Just as Coffman and Mossman had articulated the reciprocity of T_H1 and T_H2, the reciprocity between T_H1 and T_H17 became clear with T_H1 acting as an anti-inflammatory brake, protecting tissues from damage induced by T_H17. That would of course represent a total reversal of the role for T_H1 from what was proposed in the T_H1/T_H2 hypothesis.

Further reciprocal interactions involving T_H17 and a class of regulatory T cells termed T_{reg} were described in a definitive set of experiments from two groups[35–37]. These interactions revealed the dual characteristics of two other cytokines: IL-6 and transforming growth factor-β (TGF-β). IL-6, a cytokine with a mixed history of both promoting and inhibiting inflammation[38–41] but also known as an acute phase reactant that produces fever[42], along with TGF-β, a cytokine thought to have anti-inflammatory properties, actually collaborated to induce T_H17 T cells (refs. 35–37 and **Fig. 1**). Moreover, $CD4^+CD25^+Foxp3^+$ T_{regs}, whose activity inhibits autoimmunity and protects against tissue injury, were induced by TGF-β in the absence of IL-6 (refs. 35–37). Thus, TGF-β functioned as a critical regulator of both tissue-damaging T_H17 T cells when collaborating with IL-6, and as an activator of anti-inflammatory T_{regs} when acting without IL-6 (**Fig. 1**).

To make the situation even more complicated, while anti-IL-6 has been shown to be anti-inflammatory and to improve EAE (ref. 38), and while IL-6 knockout mice are resistant to EAE (ref. 39) and mount stronger T_H2 responses[40], recombinant IL-6 itself has also been shown to ameliorate EAE (ref. 41). The concept of cytokines with Janus-like activities (after the Roman god with two bearded heads looking in opposite directions) is exemplified in these mechanistic studies. Of interest, IL-6 has long defied characterization as a T_H1 or a T_H2 cytokine, though on occasion it has been considered in one camp or the other. It would be very important not to consider IL-6 as simply 'pro-inflammatory', even if it has a strategic role in the primary febrile response[42,43], in mediating the transmigration of lymphocytes by increasing expression of adhesion molecules on inflamed endothelium (**Fig. 2** and ref. 42) and in inducing T_H17 T cells[35,36].

Support for the pathogenic role of T_H17 cells in autoimmunity and infectious disease

Komiyama and colleagues showed that EAE could still occur in IL-17 knockout mice but that disease progression was severely attenuated[44]. Adoptive transfer of EAE from myelin-reactive T cells in $IL\text{-}17^{-/-}$ mice was severely attenuated. One can interpret these experiments to mean that IL-17 may not be critical for initiation of disease and that there might still be a critical role for T_H1 T cells in disease initiation. T_H1 cells, by secreting γ-IFN, may make the vascular endothelium at the site of inflammation more adherent to intravascular lymphocytes (**Fig. 2**). γ-IFN and TNF secreted by T_H1 cells play a key role in the induction of vascular cellular adhesion molecule-1 (VCAM-1). VCAM-1 binds lymphocytes with α4 integrin, and this step is a critical tipping point in the pathophysiology of several experimental autoimmune diseases, including EAE, type 1 diabetes mellitus in the NOD mouse, and collagen arthritis[45–47]. Blockade of α4 integrin has led to the most effective therapy to date for MS (refs. 45,46) and has been shown to be effective in the treatment of rheumatoid arthritis and Crohn disease. One might argue that initiation of VCAM-1 is a direct consequence of T_H1 interaction with the vascular endothelium. Following the state of increased vascular adherence, induced via T_H1 T cells, T_H17 T cells can gain access to tissues and produce autoimmune damage. IL-6 increases expression of intercellular adhesion molecule-1 (ICAM-1), the receptor for leukocyte function associated antigen-1 (LFA-1) on activated T cells[43]. The increased footpad swelling induced by T_H1 cells may be due to the heightened transmigration of lymphocytes triggered by these actions of T_H1 cells on the inflamed endothelium. This may help explain the result seen by Mosmann using the footpad swelling assay that led to the conclusion that T_H1 cells mediated delayed-type hypersensitivity[8].

A critical role for IL-17 in other autoimmune and allergic conditions has been demonstrated: both collagen-induced arthritis and allergic airway hypersensitivity were suppressed in IL-17–deficient mice[48–50]. Studies in models of experimental myocarditis revealed that in mice lacking the T box transcription factor T-bet, required for T_H1 differentiation, inflammation of the heart was worsened compared to wild-type mice. The critical cells involved in pathogenesis in myocarditis were producers of IL-17, and depletion of IL-17 reduced the severity of disease. Worsening of disease was associated with the loss of γ-IFN secretion by CD8 T cells in the heart, implying that γ-IFN and T_H1 cells suppress myocarditis[51].

The key transcription factor for IL-17 was shown to be the orphan nuclear receptor RORγt (ref. 52 and (**Fig. 1**) . Mice with RORγt-deficient T cells have attenuated EAE, though mild and delayed disease is seen. However, emphasizing the fact that T_H1 does play a role in the pathogenesis of autoimmune tissue damage, the deletion of T-bet, essential for driving T_H1 development, also prevents EAE (ref. 53).

The roles of T_H1 and T_H17 are apparently critical in bone destruction and remodeling as well. T_H17 is responsible for proliferation of osteoclasts causing bone resorption, while γ-IFN opposes this effect. T_H1 plays a protective role in bone metabolism, while T_H17 is destructive[54].

Effects of IL-17 in causing tissue damage in yet another tissue were shown by Park and colleagues, who placed IL-17 under the Cc10 promoter, overexpression of T_H17 in lung endothelial cells. Airway inflammation was seen with CD4 infiltration of bronchi and increased production of mucus by lung endothelium[34]. Thus, IL-17 is associated with tissue damage in the brain, joints, heart, lungs and intestines in experimental models.

IL-23 and the T_H17 pathway also play a key role in sustaining tissue damage in models of microbial infection. Development of colitis from *Citrobacter rodentium* infection is dependent on IL-17 (ref. 55). However, a protective response against *Citrobacter rodentium* is dependent on IL-23 (ref. 55). Mice treated with antibody to TGF-β developed severe ulcerative and hemorrhagic intestinal lesions. In these mice there were diminished or absent IL-17 cells in mesenteric lymph nodes and in the lamina propria of the intestines. These findings reinforced the importance of TGF-β in development of the T_H17 lineage[55]. IL-17 was also shown to be protective in host defense against *Klebesiella pneumoniae*[56,57]. IL-17 may actually be protective in models of asthma, where its administration in the chronic phase reduced eosinophilia and bronchial hyper-reactivity[58].

There is a growing body of information about the role of IL-17 in human diseases. In 2002 Lock and colleagues noted increased levels of transcripts for IL-17 and IL-6 in MS lesions . IL-17 was particularly prominent in more chronic lesions[59]. IL-17–secreting lymphocytes were detected in the cerebrospinal fluid of MS patients[60]. IL-17–producing T-cell clones have been established from patients with contact dermatitis[61,62], from synovial tissues from rheumatoid arthritis patients[63], and from synovial fluid of patients with Lyme arthritis[64]. The IL-23 and T_H17 pathways have now been shown to be associated with susceptibility to Crohn disease and ulcerative colitis[65].

Synergies, antagonists and fine tuning of T_H17

The T_H17 pathway has many of the features of T_H1/T_H2, where we see both synergies as well as antagonistic interactions among cytokines. For example, Park and colleagues showed that in CD4 memory T cells, IL-4 and γ-IFN together reduced IL-17 production, though neither cytokine alone could accomplish this by itself[3]. The studies of Bettelli[35], Mangan[55] and Veldhoen[36] demonstrated that synergy between IL-6 and TGF-β together are necessary for optimal production of IL-17, while TGF-β alone stimulated T_{reg} differentiation. Sutton and colleagues showed that TNF synergized with IL-23 to enhance IL-17 and that this was IL-1 dependent[66]. In RORγt T_H17 cells, a large fraction express both γ-IFN and IL-17 (ref. 52). The dual appearance of these antagonistic cytokines in the same cell is interesting and has not been explained[52].

In addition to the apparent antagonism between the T_H1 cytokines like γ-IFN and TNF, additional antagonistic cytokines for T_H17 have been discovered. One of the more remarkable stories is that of IL-27, a member of the IL-12 family; IL-27 and its receptor (IL-27R) share similarities with IL-6 and IL-6R, respectively. IL-27–induced signaling suppressed development of IL-17. This was demonstrated in two studies where defective IL-27 signaling led to a predicted increase in inflammation in the brain resulting from either EAE (refs. 67,68) or microbial infection with *Toxplasma gondii*[68]. *T. gondii* is known to produce a delayed-type hypersensitivity reaction in the brain[69]. All these findings taken together suggest that often it requires more than the action of a single cytokine to influence cell-mediated tissue damage. An idea that may gain traction is that fine-tuning of multiple cytokines may ultimately account for tissue damage and that there is not likely to be a single dominant cytokine in a pathway that would serve as a 'signature cytokine', in the way that γ-IFN fulfilled the role for T_H1. The interactions between various cytokines and T-helper cells are described in **Figure 1** and ref. 37.

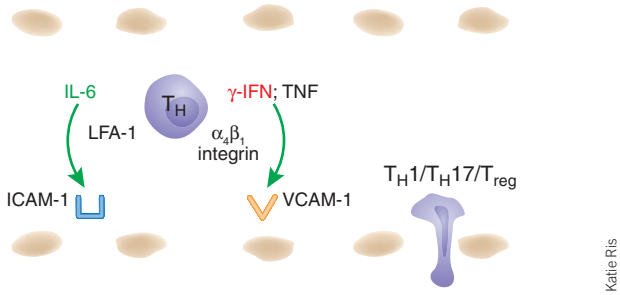

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Figure 2 IL-6, TNF and γ-interferon upregulate adhesion molecules, allowing T-helper cells to gain access to critical organs in autoimmune disease.

Some speculation on the future of T_H17

Immunologists, maybe unbeknownst to them, have displayed a long affection for sociobiology and population biology. Not only do we define various populations of subsets of T cells, we assign personalities to these subsets as we name them. We ascribe qualities to T cells—like altruism in the naming of the T-'helper' subset. The quality of antagonism was represented with the term T-'suppressor' cell, a term that fell from common usage in the early 1980s. We have renamed T-suppressor cells as regulatory T cells, ascribing them with the quality of 'authority'. Even homicidal intent is assigned to certain cells—the T-'killer' (cytotoxic) cells.

These categorizations of T_H subsets have been reorganized periodically into ever more intricate groupings. Cantor and the Herzenbergs first used antibodies and either flow cytometry or complement-dependent cytotoxicity to define these categories of T cells[70,71]. Next Coffman and Mossman defined the universe of T_H1 and T_H2. And now numerous immunologists have defined and developed the concept of T_H17. These ideas have common features, including the influence of a whole population of T cells on the behavior of another whole population of T cells. The net result of the activity of a whole subset of cells, such as T_H17 cells, is tissue damage, produced by a complex set of interactions of many cytokines. The actual effector mechanisms producing the tissue damage have not yet been elaborated. Certainly concepts like DTH and even 'tissue damage' represent a spectrum of pathologies involving more than T_H1 or T_H17 cells and involve granulocytes, macrophages and dendritic cells, as well as local specialized cells at the disease site in question—whether the skin, brain, joint or intestine, for example. T_H1 cells account for only part of the damage in delayed-type hypersensitivity as Mosmann's subsequent work astutely revealed[72].

Simple categorization of tissue damage is really an intellectual edifice and may no more represent what is happening biologically than our concept of cell death can be divided into 'necrosis' or 'apoptosis': in reality, both concepts are likely to involve many nuances. Complex phenotypes are just that—complicated—and attempts at reductionism are useful only if they raise new questions and lead to new insights. We should not become fixated on the hypothesis, as if it were a 'Law', which in any case may fall in the face of new data that such a Law cannot explain. Most importantly, we should not ignore aberrant data that cannot be explained by a concept, whether it is deemed a Law or, more modestly, a Hypothesis. We should always be careful to explain those quirky aberrant points in the data and those annoying blemishes and flaws in the scientific theory. They may be hiding a tremendous new insight.

It would be dangerous to assign too much importance to any single cytokine, especially at this relatively early stage of understanding. Other cytokines and cytokine-like molecules are likely to have a big impact on the story, including high mobility group box-1 (HMGB-1) and osteopontin[73–75]. HMGB-1 can activate IL-6, γ-interferon and TNF via its activation of nuclear factor-κB (NF-κB)[73]. Osteopontin, though regulated by T-bet, can trigger relapses of autoimmune disease by influencing both T_H1 and T_H17, as well as physiological processes like apoptosis[74,75]. The boundaries and components of T_H17 will be revised as we integrate information about molecules like HMGB-1 and osteopontin into the scheme.

The scope of T_H17 may extend beyond T cells expressing the α- and β-chains of the T-cell receptor. While T_H17 cells are now very popular, not much is known about the potential role of IL-17–producing NKT cells in immune responses, despite the fact that the mouse IL-17 was initially cloned from these cells by Zlotnik and colleagues at DNAX in 1996 (ref. 76). IL-17 is also produced in prodigious amounts in nonimmune cells, including those in gynecological tissues such as uterine fibroids and leiomyomas (A. Zlotnik, personal communication).

Thus the T_H17 hypothesis will undergo modification and will almost certainly evolve into an even more intricate story, as immunologists dissect the exquisitely orchestrated mechanisms inherent in tissue damage in response to microbial infection, in the perpetuation of an autoimmune response and in the surveillance and response to cancer[77]. T_H17 is the latest and most exciting theory to explain these phenomena underlying T cell–mediated damage to tissue.

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COMPETING INTERESTS STATEMENT

The author declares that he has no competing financial interests.

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Erratum: A brief history of T_H17, the first major revision in the T_H1/T_H2 hypothesis of T cell–mediated tissue damage

Lawrence Steinman

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In the version of this article initially published, the labeling in Figure 1 is incorrect. Tregs should be shown as producing TGF-β, not IL-17. The error has been corrected in the HTML and PDF versions of the article.

Corrigendum: Functional engraftment of human ES cell–derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes

Neeta S Roy, Carine Cleren, Shashi K Singh, Lichuan Yang, M Flint Beal & Steven A Goldman

Nature Medicine **12, 1259–1268 (2006); published online 22 October 2006.**

In page 1264 of this article, it is stated that "The donor cells were dispersed over an average radius of 1.6 ± 0.6 mm, and the mean number of HNA^+ nuclei/mm^3 within each was 136,726 ± 23,515". The authors wish to clarify that they used the word "radius" in the non-geometric sense, as in this definition of the American Heritage Dictionary: "A bounded range of effective activity or influence". At the same time, they want to remark that the numbers, figures and scale bars shown in the paper are correct.