A rush to judgment on Th17

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Some immunologists have characterized T helper (Th)17 T cells as the master mediators of tissue damage in a variety of pathological conditions. New data now demonstrate that Th1 and Th17 T cells are independently capable of inducing disease in two established models of autoimmunity. Thus, the role of Th17 cytokines as the central mediators of pathological tissue damage seems to require clarification.

Immunologists have famously categorized different subsets of T cells and attributed different biological functions to these cell populations. Nearly 40 years ago, T cells were divided into helper, cytotoxic, and suppressor (now "regulatory") cell types. 20 years later, the Th cells were further divided into Th1 and Th2 subsets. Th2 T cells were associated with allergy, whereas Th1 cells were associated with various organ-specific autoimmune diseases. More recently, a new subset of Th cells was described and named Th17 based on production of the cytokine interleukin (IL)-17 (1–3).

Although such tidy categorization may be attractive in its simplicity, it has become apparent that the original Th1/Th2 paradigm is much more complicated than originally appreciated. Human diseases such as multiple sclerosis (MS) and rheumatoid arthritis (RA), for example, were commonly considered to be Th1 mediated, but we now realize that such generalizations were inaccurate and oversimplified. For over a decade, various anomalies that contradicted the Th1/Th2 paradigm went unexplained (1). One example was the well-known finding that in one version of the "Th1-driven" disease experimental autoimmune encephalitis (EAE), a mouse model of MS, treating mice with the prototype Th1 cytokine interferon (IFN)-γ actually reversed disease, and blocking IFN-γ worsened disease (4–6). These findings seem to contradict the idea that Th1 responses drive EAE and suggest that IFN-γ may play diverse roles depending on the stage of disease, or that certain EAE models may not accurately reflect the human disease. For years, the implications of these contradictory data went largely unchallenged, as the complexities of the Th1/Th2 axis in this model of T cell–mediated autoimmune disease were not fully grasped.

The identification of the Th17 subset has now broadened our understanding of inflammatory processes in human disease and has helped to explain some of the anomalies seen in the Th1/Th2 axis. However, we may now be facing similar pitfalls by invoking Th17 cells to explain disease processes—in particular, immune-mediated tissue damage—without considering many as yet unexplained inconsistencies in the experimental data. Immunologists are repeating many of the intellectual mistakes that were made for Th1/Th2 a decade earlier, as we confront the new concept of Th17. Two papers in the *Journal of Experimental Medicine*, one by Luger et al. in a recent issue (7) and another by Kroenke et al. (8) on page 1535 of this issue, as well as other recent work (9–12), help provide a more balanced view of the role of Th17 cells in autoimmune disease and immune-mediated tissue damage.

Using a model of experimental autoimmune uveitis (EAU), Luger et al. (7) showed that either Th1 or Th17 cells can drive tissue damage depending on the methods used to initiate disease. In this issue, Kroenke et al. (8) show that adoptive transfer of either Th1 or Th17 cells can induce EAE and clinical paralysis in mice, but the pathology induced by Th17 cells differs from that induced by Th1 cells. Thus Th17 cells are unlikely to be the sole players in driving tissue damage in these classical models of autoimmunity.

Non–IL-17 culprits in tissue damage

In our rush to embrace Th17 cells as the purveyors of tissue damage, we should not forget that cytokines produced by Th1 cells and other cell types are critical in promoting various forms of inflammation. Administration of IFN-γ, for example, worsened disease in patients with MS (13). And blocking tumor necrosis factor (TNF), which can be produced by various cell types, is a gold standard for treatment of diseases now thought to be driven largely by Th17 cells, including RA, Crohn's disease, and various forms of psoriasis (1). Furthermore, type I IFNs, which are therapeutic in MS (14, 15), are pathogenic in systemic lupus erythematosus (16). It is worth noting that the role of IL-17 in these major human diseases is much less well understood than TNF, IFN-γ, or type I IFNs.

Ex vivo studies have also suggested that cytokines of the Th1/Th2 axis are critical determinants in mycobacterial diseases ranging from tuberculoid leprosy, which is primarily driven by IL-12 and Th1 cells, to lepromatous leprosy, which is mediated by Th2 cells (17). And Th2 responses drive many aspects of allergic responses (3). Although Th17 is a welcome addition to our understanding of immune-mediated tissue damage, we still need the Th1/Th2 axis and other inflammatory mediators to explain many aspects of human autoimmune, allergic, and infectious diseases.

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Th17 cells as disease inducers

In a recent issue of the *JEM*, Luger et al. (7) demonstrated that IL-17 and IL-23, a cytokine that drives expansion of Th17 cells, are important in the pathogenesis of EAU, a model that reflects many aspects of both infectious and autoimmune uveitis in man. In that study, administration of antibodies against IL-17 inhibited the development of EAU after immunization with the retinal antigen intra-retinal binding protein (IRBP) in complete Freund's adjuvant (CFA), and also reversed established disease (7). Antibodies against IL-23 also aborted the development of EAU in this model, but only when given early in the disease (Fig. 1 A). Blocking IL-23 was no longer effective by day 7, a time when T cells capable of inducing uveitis were already present. The authors thus concluded that IL-23 is important for the priming of uveitis-inducing T cells, but not for their effector function. Supporting a role for IL-23 in EAU induction, mice lacking the IL-23 subunit p19 or p40, which is also shared by IL-12, were protected against disease. Mice lacking the IL-12–only subunit p35, by contrast, were more susceptible to EAU than were wild-type mice (Fig. 1 A). Finally, transfer of in vitro–polarized, IRBP-specific Th17 cells into recipient mice triggered EAU, even in the complete absence of IFN-γ (Fig. 1 B).

These findings in EAU are similar to studies in EAE, in which chronic disease is reduced in IL-17$^{-/-}$ mice, although these mice still develop acute paralysis of their hind limbs (18). Adoptive transfer of myelin-reactive T cells from IL-17$^{-/-}$ mice into wild-type mice also leads to much milder EAE, as measured by incidence and severity of paralysis, compared with transfer of myelin-reactive T cells from wild-type mice (18).

Th17 cells as innocent bystanders

Other data from Luger et al., however, suggested that EAU can also develop in the absence of Th17 cells. Transfer of a Th1 clone specific for IRBP, for example, caused severe disease in the absence of IL-17 production (Fig. 1 B). Moreover, disease severity in response to immunization with IRBP plus CFA was comparable in wild-type and IL-17–deficient mice (7). It should be noted that many investigators equate the loss of IL-17A in the IL-17$^{-/-}$ mice (7) with a complete loss of Th17 cells, but these cells also produce other cytokines, including IL-17F, IL-21, and IL-22. Although Luger et al. conclude that the development of EAU in IL-17$^{-/-}$ mice required an IFN-γ–producing effector T cell, they did not formally rule out a role for other Th17 cytokines (7).

These results are difficult to interpret given other studies showing a protective role for IFN-γ in EAU. Neutralization of IFN-γ has been shown to exacerbate EAU, just as it does EAE (4–6). Furthermore, EAU develops efficiently in mice depleted of IFN-γ, and, perplexingly, recombinant IFN-γ has been shown to protect against disease (19, 20). How, then, could an IFN-γ–producing effector cell be important for the pathogenesis of EAU, if recombinant IFN-γ is itself protective? These results must be considered paradoxical and problematic at the least. Akin to the anomalies and paradoxes seen with Th1 cells in EAE, these results are probably telling us something highly important, although we do not yet have enough knowledge to explain it. But the data certainly conflict with the notion of IL-17 as a master mediator of tissue damage, at least in EAU.

Luger et al. went on to induce EAU by immunizing mice with IRBP-pulsed dendritic cells, a model that is independent of CFA (Fig. 1 C). In this model, the disease was characterized by an influx of T cells that produce large amounts of IFN-γ but little IL-17. And IFN-γ–deficient mice immunized with IRBP-pulsed dendritic cells were protected against disease despite the robust production of IL-17 (7). It is possible that the use of adjuvants in certain animal models of autoimmune disease, such as EAE, EAU, and collagen-induced arthritis, might skew the importance of IL-17. Indeed, the presence of adjuvants that, like CFA, contain killed mycobacteria might provide a critical clue to explain the discrepancies between different models.

In this issue, Kroenke et al. show that adoptive transfer of either Th1- or Th17-polarized myelin-reactive T cells induces EAE (8). Ascending paralysis ensued in both models, but the cellular infiltrate induced by Th17 cells was rich in neutrophils, whereas macrophages predominated the Th1-induced infiltrate—a pathological picture similar to MS, in which neutrophilic infiltration is rare. The pathology seen with IL-17–induced EAE was reminiscent of that seen in acute disseminated encephalomyelitis, and other rare demyelinating conditions such as Marburg's disease, and also resembles certain aspects of neuromyelitis optica—all conditions in which neutrophils are common. Neuromyelitis optica is also similar to Th17–induced EAE in that the pathology is most intense in the spinal cord and optic nerves. Consistent with this, Stromnes et al. (9) showed that EAE is most intense in the brain when Th17/Th1 ratios are high, whereas inflammation is focused on the spinal cord when Th17/Th1 ratios are more widely varied.

The overall picture that emerges suggests that EAE has a variety of histological and anatomical manifestations depending on the cytokines produced by the disease-inducing T cells (8, 9). Thus, one cannot conclude at all that EAE is driven by Th17 cells. The data from Kroenke et al. (8) confirm that EAE can be induced by either Th1 or Th17 T cells. Finally, earlier work from Lafaille et al. (21) indicated that even Th2 cells can induce EAE in RAG-deficient mice. In that study, the cellular infiltrate was rich in eosinophils. Such pathology replete with eosinophils, typical of allergic disorders, would be worthy of the original term for EAE, "experimental allergic encephalomyelitis."

Other cytokines like osteopontin drive the production of IFN-γ (22, 23), and osteopontin has also recently been shown to drive the production of IL-17 (24). Osteopontin is critical in triggering relapses of EAE and is elevated in the plasma of patients suffering MS relapses (25). Is it thus possible that osteopontin is the main driver of tissue damage and MS relapses, and not IFN-γ or IL-17? It can hardly be concluded at this point that Th17 is the sole driver of tissue damage in MS or EAE.

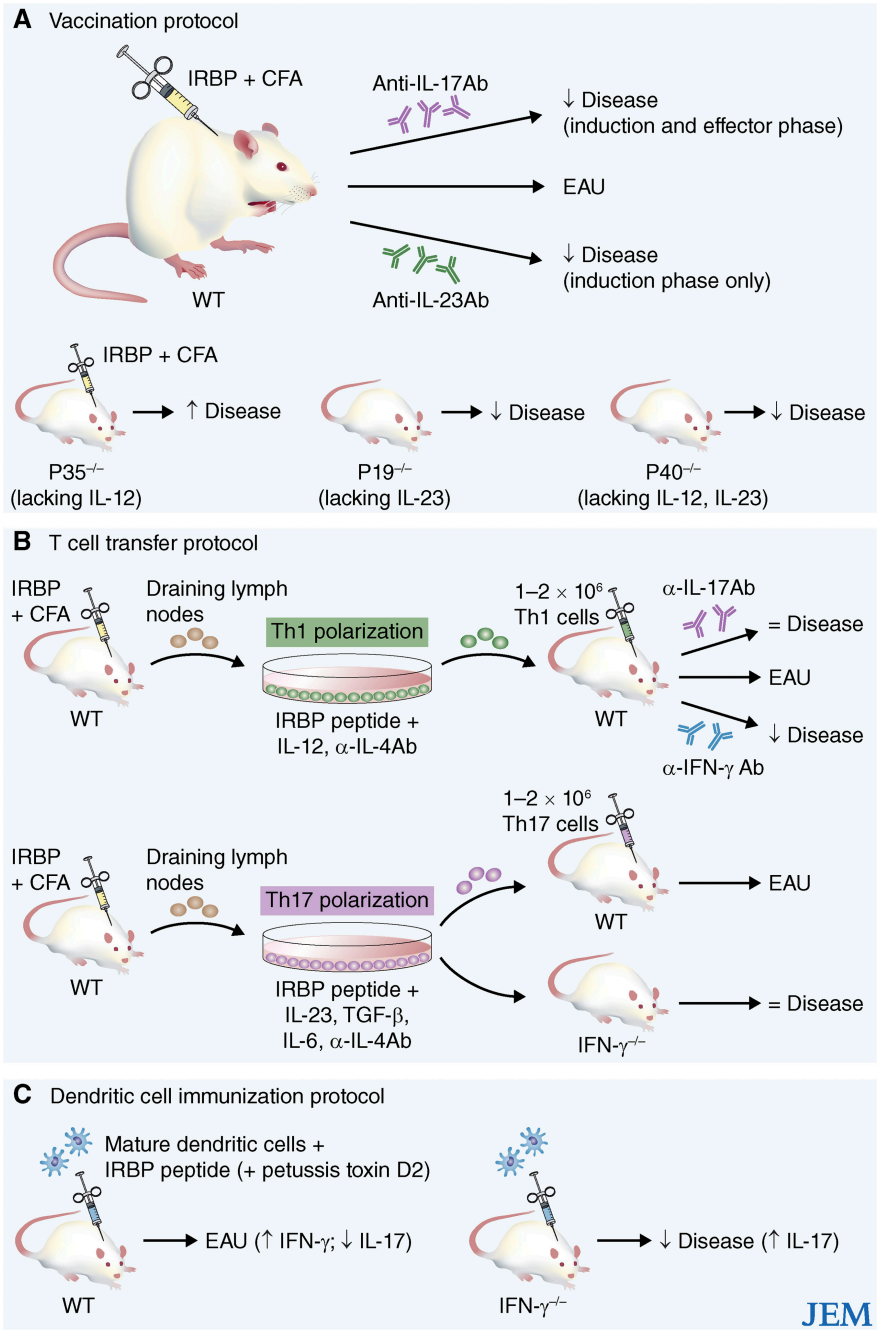

Figure 1. Th17 or Th1 cells can induce EAU depending on the method of disease induction. (A) Direct vaccination model. Disease was induced by immunizing mice with IRBP plus CFA. There was a significant reduction of EAU in p19 and p40 knockout mice, with a significant increase in EAU in p35 knockout mice compared with wild type. Antibody blockade of IL-17 reduced disease when given either during disease induction or after disease onset, whereas antibody blockade of IL-23 reduced disease only when administered during disease induction. (B) T cell transfer model. Transfer of Th1-polarized, IRBP-specific $CD4^+$ T cells induced EAU (top). In this model, blocking IL-17 had no effect on disease and blocking IFN-γ ameliorated disease. Transfer of Th17-polarized, IRBP-specific $CD4^+$ T cells induces EAU (bottom), and, in this model, disease was equivalent when cells were transferred into IFN-γ–deficient mice. (C) Dendritic cell immunization protocol. IRBP-pulsed mature dendritic cells were injected into mice, followed by pertussis toxin at day 2. In this model, disease was decreased in IFN-γ–deficient mice, despite an increased production of IL-17 in the central nervous system as compared with wild-type mice.

Th17 cells as protectors

Another issue that must be considered is that IL-17 would not have evolved if it only did harm. The protective side of IL-17 was demonstrated in a recent study of mycobacteria tuberculosis infection, in which IL-17 was required to recruit protective IFN-γ–producing $CD4^+$ T cells into the lung (26). In an asthma model, neutralization of IL-17 increased eosinophilic infiltration during the effector phase of disease, and administration of recombinant IL-17 diminished airway hyperreactivity and reduced the numbers of eosinophils and lymphocytes in bronchial lavage (27). In this model of asthma, IL-17 thus appears to be a negative regulator of established disease (27). How can we continue to call the Th17 pathway the critical mediator of immune-mediated tissue damage with such counter examples from autoimmunity, infectious disease, and allergic disease?

Th17 in mouse and in man

The ultimate significance of the Th17 pathway in human disease remains unclear, and we are only now clarifying the details of the Th17 pathway in humans. The first analyses of the Th17 pathway came from studies of experimental diseases in mice, and the first studies on the Th17 in man revealed significant differences. As Natalie Angier wrote in her elegant book *The Canon*, "Whether sizing up new acquaintances or seizing on novel ideas, we remain forever at the mercy of our first impressions" (28). In immunology (at least these days), our first impressions often come from mice. Again to quote Angier, we should analyze the source of our misconceptions, and then we "have a chance of amending, remodeling, or blowtorching them as needed, and replacing them with a closer approximation of science's approximate truths" (28).

The parallels between mouse and man first diverged in defining a role for transforming growth factor (TGF)-β in the differentiation of Th17 cells. In mice, IL-6 and TGF-β are required for the production of IL-17 (2). Two initial human studies, however, showed that IL-6 and IL-1β (produced by monocytes or conventional dendritic cells), but not TGF-β, were critical for the priming of Th17 responses (29, 30). In one of those studies, TGF-β suppressed IL-17 production (29). More recent data, however, revealed that TGF-β, IL-1β and IL-6, IL-21, or IL-23 (in serum-free conditions) could induce IL-17 production from naive human CD4 T cells from umbilical cord blood (31). TGF-β suppressed ROR-γt–induced IL-17 expression, but this suppression was relieved in the presence of inflammatory cytokines. Another study showed that TGF-β was essential, along with IL-23, IL-1β, and IL-6 for Th17 differentiation (32). Yet another showed that TGF-β enhanced IL-17 in peripheral T cells (33). At this point it appears that IL-1β and IL-6 drive IL-17A production from central memory $CD4^+$ T cells, whereas TGF-β and a constellation of other inflammatory cytokines promote the differentiation of naive $CD4^+$ T cells into Th17 cells (34).

The role of TGF-β is highly pleiotropic (35, 36). Local induction of TGF-β in mouse brain, for example, leads to induction of EAE (36), and its pharmacologic suppression reverses paralytic disease (37). TGF-β signaling in the brain leads to increased production of IL-6, which then enhances inflammation (37). TGF-β is elevated in chronic MS lesions, in which there is also intense production of IL-17 from astrocytes and oligodendroglia (38). Thus, TGF-β might promote IL-17 production during the chronic active phase of MS (9, 38).

Studies in humans have also revealed the existence of T cell clones in the intestines of patients with inflammatory bowel disease that produce both IL-17 and IFN-γ, and are thus designated Th1/Th17 cells. These dual producers can also be found in EAE lesions in mice (39) and express both the Th17-inducing transcription factor ROR-γt and the Th1-inducing transcription factor T-bet. The biological importance of these hybrid Th1/Th17 clones is as yet unclear.

Concluding remarks

Immunologists ought to be restrained in attributing too much to the Th17 pathway at this stage. The plentiful exceptions outlined in this commentary suggest that its signature function as the mediator of organ-specific tissue damage in autoimmunity and other forms of pathology should be refined. Exceptions always teach us something important, as we have learned from our evolving understanding of the Th1/Th2 paradigm (1). The Th17 pathway has many divergent roles in models of autoimmune, infectious, and allergic disease.

Indeed, IL-17 is not even a purely Th17 cytokine because it is also made by macrophages (40), astrocytes (41), oligodendroglia (41), uterine fibroids (42), and corneal epithelial cells on the surface of the eye (43). In fact, IL-17 was first cloned from mouse NKT cells (44). Finally, what drives Th17 is not altogether certain. Emerging data indicate that molecules such as osteopontin drive both Th1- and Th17-mediated tissue damage (22–25). We might thus be heading toward the conclusion that no single molecule or Th pathway dominates and that there is no hierarchical scheme at all.

It is difficult to understand how so many immunologists developed such exuberant enthusiasm for Th17 in the first place, placing it in a starring and paramount role for all immune-mediated tissue damage. One of the groups who was instrumental in the discovery and elucidation of this pathway recently reviewed the subject with a balanced perspective (2). They enumerated the multiplicity of "inconvenient truths" that befuddled this role for Th17 when they asked, "But are Th17 cells the only effector cells capable of inducing organ-specific autoimmunity? Mice deficient in T-bet and STAT-4, and thus lacking Th1 cells (45, 46), have overwhelmingly large numbers of Th17 cells (47, 48) and yet are resistant to EAE (47–49). Do those data suggest that Th1 cells are pathogenic and Th17 cells are not? The truth is probably somewhere in the middle. For many reasons, we support the idea that both Th1 and Th17 cells are capable of inducing autoimmunity" (2).

An emerging conclusion is that tissue damage and protection are nuanced and are governed by multiple/redundant molecular interactions that involve many cytokines, including the type I

IFNs, and other molecular cascades including, for example, the coagulation pathway (50). Thus, we should reserve our judgment about Th17 and not jump to conclusions as we did with the Th1/Th2 paradigm (1).

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