REVIEW ARTICLE

MECHANISMS OF DISEASE

Interleukin-17 and Type 17 Helper T Cells

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In 1986, Mosmann and Coffman introduced the concept of distinct types of helper T cells, which was based on the types of cytokines that T cells produce when they are stimulated to differentiate. They named these lymphocytes type 1 helper T cells (Th1 cells) and type 2 helper T cells (Th2 cells).[1] Th1 cells produce large quantities of interferon-γ, induce delayed hypersensitivity reactions, activate macrophages, and are essential for the defense against intracellular pathogens (Fig. 1). Th2 cells produce mainly interleukin-4 and are important in inducing IgE production, recruiting eosinophils to sites of inflammation, and helping to clear parasitic infections (Fig. 1). These distinctions allowed the assignment of a specific functional phenotype to helper T cells based on the effector cytokines that they produce. The production of effector cytokines underlies the term "effector helper T cells."

ORIGINS AND FUNCTIONS OF Th17 CELLS

HELPER T-CELL SUBGROUPS

More recently, T cells were shown to produce cytokines that could not be classified according to the Th1–Th2 scheme. Interleukin-17 was among these cytokines,[2] and the T cells that preferentially produce interleukin-17, but not interferon-γ or interleukin-4, were named Th17 cells.[3,4] Since these T cells constitute a distinct lineage, we now have three types of effector helper T cells: Th1, Th2, and Th17[5] (Fig. 1).

The mechanism of induction and the effector functions of this new class of effector helper T cells are just beginning to be understood. Their function in clearing specific types of infectious organisms, their role in inducing inflammation, and the molecular events that cause them to differentiate are the focus of important studies in immunology. Like Th1 and Th2 cells, Th17 cells produce a group of distinctive cytokines — interleukin-17 (also called interleukin-17A), interleukin-17F, interleukin-22, and interleukin-21 — all of which participate in orchestrating a specific kind of inflammatory response (Table 1).

DIFFERENTIATION OF Th17 CELLS

We will first describe Th17 cells in mice, since the first discoveries involving these cells were made in mice. Although there are major analogies to the development of Th17 cells in humans, some differences have been observed. Cytokines produced by cells of the innate immune system govern the differentiation of helper T cells. The cells of the innate immune system are the first line of defense against pathogens; their pattern-recognition receptors, which are not specific for any particular epitope, allow them to respond to a wide variety of microbial invaders by producing cytokines that activate T cells of the adaptive immune system. Interferon-γ and interleukin-12 drive naive T cells into the Th1 pathway, whereas interleukin-4 initiates the differentiation of naive T cells into Th2 cells[6] (Fig. 2). At the molecular

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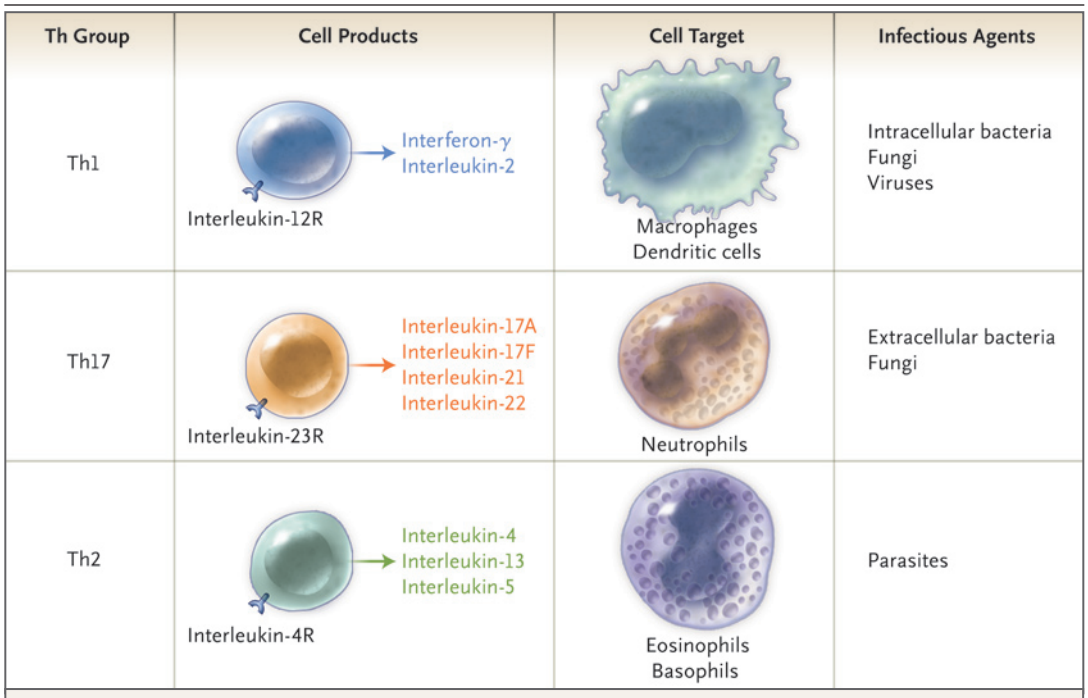

Figure 1. Helper T-Cell (Th) Subgroups and Effector Functions.
The cytokine profile (including key cytokine receptors as denoted by R), the effector cell type that is activated, and the corresponding types of infections are shown for each Th subgroup.

level, the differentiation of Th1 and Th2 cells requires lineage-specific transcription factors: T-bet for Th1 cells[7] and GATA3 and c-Maf for Th2 cells.[8,9] These factors activate the hallmark Th1 and Th2 cytokine genes, *IFN-γ* and *IL-4*, respectively (Fig. 2).

Interleukin-12 is also important for the differentiation of Th1 cells. It has two subunits, p35 and p40. Another protein, p19, which has no activity of its own, combines with the p40 subunit of interleukin-12 to form a unique heterodimeric cytokine called interleukin-23.[10] Thus, interleukin-12 and interleukin-23 have in common the p40 subunit, but they also have unique subunits, p35 (interleukin-12) and p19 (interleukin-23). In studies of genetically deficient mice that specifically lacked interleukin-23 or interleukin-12, the loss of interleukin-23 made the animals highly resistant to the development of autoimmunity and inflammation, whereas the loss of interleukin-12 did not.[11,12] These results suggest that it is not interleukin-12 and Th1 cells that are required for the induction of autoimmune-mediated inflammation but rather interleukin-23. They also suggest that T cells that differentiate under the influence of interleukin-23 are key players in the induction of autoimmunity. This concept is supported by experiments in which the induction of inflammation and autoimmunity in mice was made possible by injecting interleukin-17–producing T cells that had been induced to differentiate and proliferate in vitro by interleukin-23.[13] Thus, it appears that the interleukin-23–Th17 axis is a predominant pathway to the induction of autoimmune disease.

Interleukin-23 can expand a population of Th17 cells in vitro even when they are rendered genetically deficient in the master transcription factors of Th1 and Th2 cells[3,4]; this observation confirms that Th17 cells are a lineage that is distinct from Th1 and Th2 cells. The finding that interleukin-23 is a differentiating cytokine for Th17 cells poses a major conceptual problem, however, because naive T cells do not express receptors for interleukin-23; thus, highly purified naive T cells cannot differentiate into Th17 cells in the presence of interleukin-23.[14]

The problem took a new turn when three independent groups simultaneously discovered that a combination of transforming growth factor β (TGF-β) plus interleukin-6 induced the differentiation of naive T cells into Th17 cells.[14-16] This

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Table 1. Sources and Functions of Key Cytokines.*

Cytokine	Main Cell Source	Function
Interferon-γ	Th1 cells, natural killer cells, natural killer T cells	Cell-mediated immunity; control of intracellular pathogens; inhibition of Th17 pathway
Interleukin-1	Monocytes, other cells	Proinflammatory cytokine; induction of Th17 cells
Interleukin-4	Th2 cells, natural killer T cells	Antibody-mediated immunity; control of parasitic infections; antiinflammatory effect by inhibition of interleukin-1, TNF, and interleukin-6 production by monocytes; inhibition of Th17 pathway
Interleukin-6	Monocytes, other cells	Induction of acute-phase proteins; effects on B cells; induction of Th17 cells
Interleukin-8	Monocytes, other cells	Major chemokine for neutrophils
Interleukin-12	Monocytes, dendritic cells	Induction of Th1 pathway; acts in synergy with interleukin-18
Interleukin-17	Th17 cells, natural killer cells, natural killer T cells	Proinflammatory cytokine; control of extracellular pathogens; induction of matrix destruction; synergy with TNF and interleukin-1
Interleukin-18	Monocytes, dendritic cells	Induction of Th1 pathway; acts in synergy with interleukin-12
Interleukin-21	Th17 cells	Amplification of Th17 pathway in autocrine fashion
Interleukin-22	Th17 cells	Induction of epithelial-cell proliferation and of antimicrobial proteins in keratinocytes
Interleukin-23	Monocytes, dendritic cells	Th17 expansion and stabilization
Interleukin-25	Th2 cells	Interleukin-17 family member; induction of Th2-associated cytokines; inhibition of interleukin-1 and interleukin-23
TGF-β	Many cells	Induction of Foxp3+ regulatory T cells in the absence of interleukin-6; together with interleukin-6, interleukin-21, and interleukin-1β, induction of Th17 cells
TNF	Monocytes, dendritic cells	Proinflammatory cytokine; acts synergistically with interleukin-17

* TGF-β denotes transforming growth factor β, and TNF tumor necrosis factor.

finding was surprising, since TGF-β had been classified as an immunosuppressive cytokine, not as an inducer of T-cell differentiation. Furthermore, naive T cells that are exposed to TGF-β alone express forkhead box P3 (Foxp3), the master transcription factor that induces regulatory T cells — T cells that suppress inflammation and inhibit autoimmunity.[17] A relevant finding is that interleukin-6 is a potent inhibitor of TGF-β–driven induction of Foxp3+ regulatory T cells.[16] Interleukin-6 not only suppresses the generation of these cells, but together with TGF-β, it also forces naive T cells to express interleukin-17 and to become Th17 cells. Thus, Th17 cells and Foxp3+ regulatory T cells are reciprocally related: TGF-β induces naive T cells to develop into suppressor regulatory T cells, whereas interleukin-6 switches the transcriptional program initiated by TGF-β in a way that induces the development of Th17 cells.

Th17 cells express a unique transcription factor, ROR-γt,[18] which induces transcription of the *IL-17* gene in naive helper T cells and is required for the development of interleukin-17 producing cells in the presence of interleukin-6 and TGF-β.[19] ROR-γt must act in cooperation with other transcription factors, including ROR-α, signal transducer and activator of transcription 3 (STAT3), IRF-4, and runt-related transcription factor 1 (Runx1), for full commitment of precursors to the interleukin-17 lineage.[20-23] Activation of ROR-γt also causes expression of the receptor for interleukin-23, indicating that interleukin-23 acts on T cells that are already committed to the Th17 lineage. Exposure of developing Th17 cells to interleukin-23 not only enhances the expression of interleukin-17 but also induces interleukin-22 and suppresses interleukin-10 and interferon-γ, which are not normally associated with the Th17 phenotype.[24] Thus, interleukin-23 is essential for stabilizing the Th17 phenotype.

The interferon-γ and interleukin-4 produced

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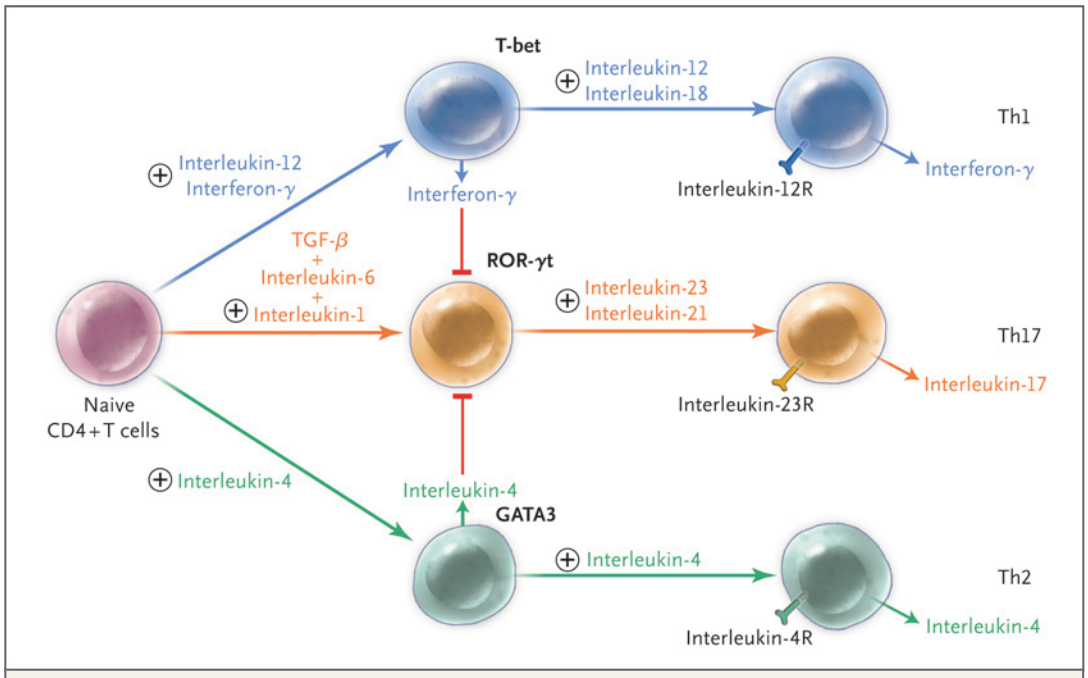

Figure 2. Differentiation of Mouse Th17 Cells.

Naive mouse T cells can differentiate into one of three effector helper T-cell (Th) subgroups. Each pathway is under the control of a different set of cytokines. The Th17 pathway is under the control of transforming growth factor β (TGF-β) plus interleukin-6 and interleukin-1 or TGF-β plus interleukin-21 followed by interleukin-23. This pathway is inhibited by interferon-γ and interleukin-4. The transcription factor (T-bet, ROR-γt, or GATA3) characteristic of each pathway is shown. R denotes receptor.

by Th1 and Th2 cells, respectively, amplify the differentiation of these cells in an autocrine loop. Interleukin-17, by contrast, is neither a growth factor nor a differentiation factor for Th17 cells; thus, it cannot amplify Th17 responses. However, a member of the interleukin-2 cytokine family — interleukin-21, which is produced in large amounts by mature Th17 cells — can, together with TGF-β, amplify Th17-cell differentiation[25-27] (Fig. 2); in the absence of interleukin-21, the expansion of Th17 cells is defective. In short, there is also an autocrine loop for Th17 cells, but in this loop, TGF-β and interleukin-21 are major factors.

HUMAN Th17 CELLS

Initially, TGF-β plus interleukin-6 were not considered to be differentiation factors for human Th17 cells. On the contrary, it was thought that the generation of human Th17 cells from naive precursors was inhibited by TGF-β and promoted by interleukin-6 plus interleukin-1β.[28,29] The studies underlying these ideas, however, did not use genuinely naive T cells as a starting population and did not control for endogenous sources of TGF-β such as serum and platelets. When naive T cells from cord blood were cultured in serum-free medium, the generation of Th17 cells as a result of the interaction between TGF-β and an "inflammatory" cytokine was confirmed in human T cells.[30,31] It appears that TGF-β plus interleukin-21,[30] TGF-β plus a combination of interleukin-6 and interleukin-23, or interleukin-6 plus interleukin-21[31] can induce the expression of ROR-c, the human counterpart of murine ROR-γt (Fig. 3).

As with Th1 and Th2 cells, no single surface marker is specific for Th17 cells. However, coexpression of the chemokine receptors CCR4 and CCR6[32] or expression of CCR2 in the absence of CCR5[33] appears to define human Th17 cells. (Chemokines induce chemotactic responses in neighboring cells that display receptors for chemokines, of which there are four main types: CXC, CC, CX3C, and XC.) Some memory helper T cells produce both interferon-γ and interleukin-17,[34] and these cells express CXCR3 in addi-

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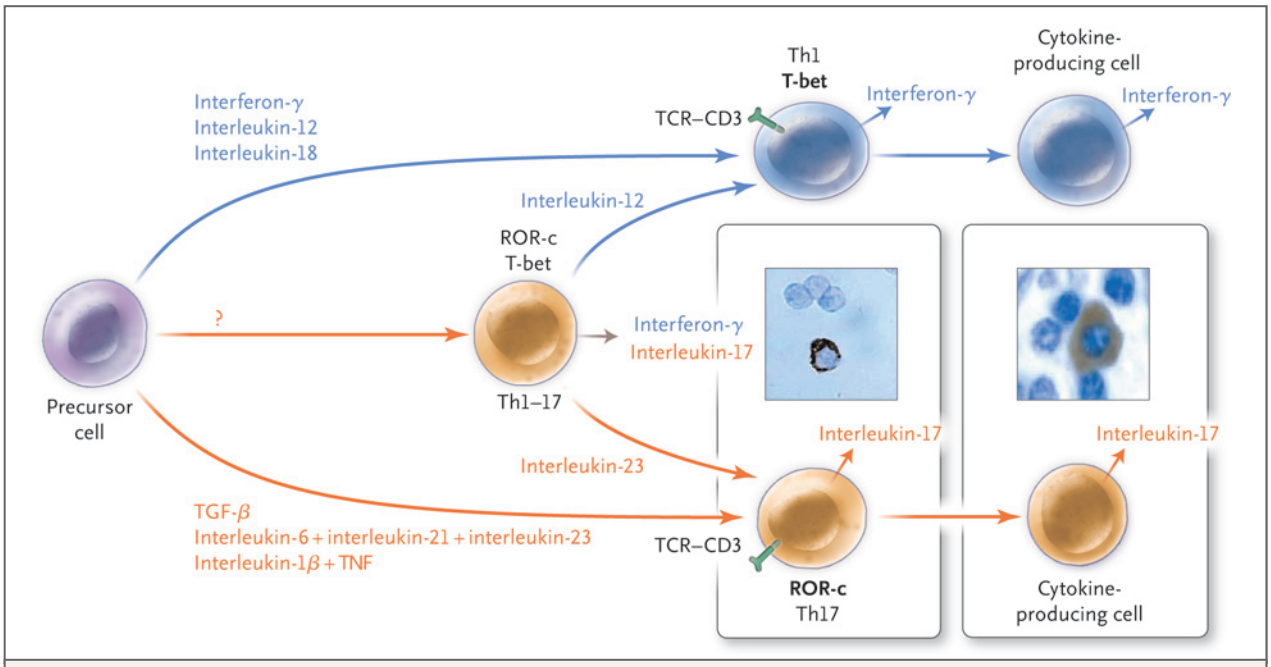

Figure 3. Differentiation of Human Th17 Cells.

Key cytokines for the development of human Th17 cells are transforming growth factor β (TGF-β) plus interleukin-6, interleukin-21, and the inflammatory cytokine interleukin-1, followed by interleukin-23. In addition to the classic Th1 and Th17 subgroups, a mixed Th1–Th17 subgroup has been identified, which expresses both T-bet and ROR-c. In inflammatory tissues, fully differentiated cytokine-producing cells have been observed. The micrographs show immunohistochemical staining of the cytoplasm for antibodies against interleukin-17 (brown) in human blood CD4+ T cells activated in vitro for 24 hours and a plasma-cell–like cell in a section of rheumatoid synovium. These cell have lost their T-cell receptor (TCR) and the CD3 complex. TNF denotes tumor necrosis factor.

tion to CCR4 and CCR6. They also appear to express both the T-bet and ROR-c transcription factors. In reactive lymph nodes and inflamed tissues, large cells with a resemblance to plasma cells produce interleukin-17 (Fig. 3), suggesting that Th17 cells acquire an activated phenotype at the tissue site.[35]

INTERLEUKIN-17 AND Th17 CELLS IN DISEASE

RESPONSES TO INFECTIOUS AGENTS

Th17 cells can rapidly initiate an inflammatory response that is dominated by neutrophils (Fig. 1); indeed, acute inflammation in which neutrophils are prominent is typical of Th17-driven inflammation. Immunity mediated by Th17 cells is particularly important at epithelial and mucosal surfaces, as indicated by the pattern of expression of their chemokine receptors and effector cytokines.[36,37]

A number of pathogens induce mainly Th17 responses (Fig. 1). They include gram-positive *Propionibacterium acnes*, gram-negative *Citrobacter rodentium*, *Klebsiella pneumoniae*, bacteroides species and borrelia species, *Mycobacterium tuberculosis*, and fungi such as *Candida albicans*.[14,38-42] To rid the body of fungi and certain extracellular bacteria requires inflammation of the type engendered by Th17 cells. The role of interleukin-17 and Th17 cells in clearing infections has been shown in the hyper-IgE syndrome, in which a mutation in *STAT3*, one of a family of transcription activators, nullifies the ability to mount Th17 responses. Patients with this disorder have recurrent *C. albicans* and *Staphylococcus aureus* infections in the skin and lungs.[43,44]

THE INTERLEUKIN-23—Th17 PATHWAY IN CHRONIC INFLAMMATION AND AUTOIMMUNITY

Unregulated Th17 responses or overwhelming interleukin-17 production from T cells and other sources is associated with chronic inflammation and severe immunopathologic conditions. Interleukin-17 was first shown to induce interleukin-6 in fibroblasts[2] and in cultured synoviocytes in

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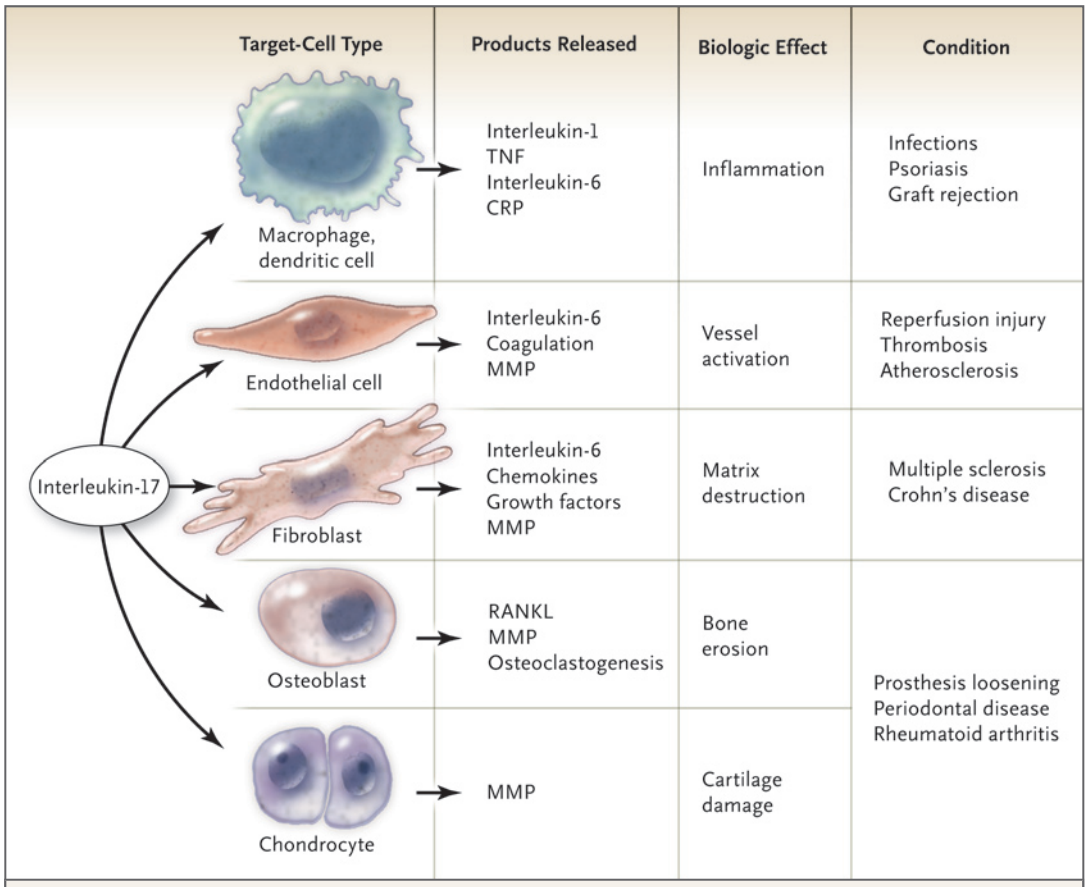

Figure 4. Effects of Interleukin-17 on Cell Functions and Its Role in the Pathophysiology of Diseases.
For each key effect of interleukin-17, the target-cell type involved and the products released in response to interleukin-17 are shown. Each biologic effect is linked to examples of conditions in which an association with the presence of interleukin-17 has been observed. CRP denotes C-reactive protein, MMP matrix metalloproteinase, RANKL receptor activator of nuclear factor-κB ligand, and TNF tumor necrosis factor.

patients with rheumatoid arthritis[45] (Fig. 4). Most parenchymal cells express interleukin-17 receptors[46] (Table 2), and signaling through these receptors induces target cells to produce proinflammatory factors such as interleukin-6, interleukin-1, tumor necrosis factor (TNF), CXCL8 (interleukin-8), and matrix metalloproteinases.[2,3,56] Through the production of matrix proteinases, interleukin-17 can also destroy extracellular matrix and cause bone resorption. In bone, interleukin-17 stimulates osteoblasts to express the receptor activator of nuclear factor-κB (RANK) ligand (RANKL).[57] Such osteoblasts can activate osteoclasts, which express the membrane protein RANK, a receptor for RANKL, at their surface. Th17 cells also express RANKL, but they may not activate osteoclasts by a RANKL–RANK interaction. Rather, secretion of interleukin-17 by Th17 cells and induction of RANKL on cells such as osteoblasts that support the activation of osteoclasts appear to be required for bone loss. Through the RANKL–RANK system, interleukin-17 may have a role in rheumatoid arthritis, periodontal disease, and loosening of joint prostheses.[58] In rheumatoid arthritis, the production of TNF, interleukin-1, and interleukin-17 by synovial cells is predictive of joint destruction.[59]

Interleukin-6 is both a target of interleukin-17 and a differentiation factor for Th17 cells. By inducing the production of interleukin-6 or interleukin-1β, interleukin-17 activates a positive feedback loop that commits naive T cells to the Th17 lineage. Moreover, by inducing chemokine production, Th17 cells attract numerous effector

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Table 2. Receptors of Th17-Associated Cytokines.*

Receptor and Its Structure, Distribution, and Function	Reference
Interleukin-17A receptor	
Interleukin-17RA, the cognate receptor for interleukin-17A, is highly expressed on hematopoietic cells and expressed at lower levels on osteoblasts, fibroblasts, and endothelial and epithelial cells	Yao et al.[2]
Human interleukin-17RC binds human interleukin-17A with high affinity, but mouse interleukin-17RC does not bind mouse interleukin-17A	Kuestner et al.[47]
Human interleukin-17RA and interleukin-17RC can form a heterodimer that binds human interleukin-17A	Toy et al.[48]
Interleukin-17RA appears to be part of the functional interleukin-25 receptor (a heterodimer consisting of interleukin-17RA and interleukin-17RB)	Rickel et al.[49]
Interleukin-17F receptor	
Interleukin-17RC, the cognate receptor for interleukin-17F, is expressed at low levels on hematopoietic cells and at high levels on nonhematopoietic cells	Toy et al.[48]
Human interleukin-17RA–interleukin-17RC heterodimers can bind human interleukin-17F	Toy et al.[48]
Interleukin-21 receptor	
This receptor is a heterodimer consisting of the common cytokine-receptor γ chain (γ_c) and interleukin-21R	Leonard and Spolski[50]
γ_c is expressed on lymphoid cells	Takeshita et al.[51]
Interleukin-21R is restricted to hematopoietic cells (but not only lymphoid cells) with highest levels of expression on B cells, but also on T cells, natural killer cells, and some populations of myeloid cells	Parrish-Novak et al.[52]
Interleukin-22 receptor	Kotenko et al.[53]
This receptor is a heterodimer of interleukin-22R1 and interleukin-10R2	
Interleukin-10R2 is ubiquitously expressed on hematopoietic and nonhematopoietic cells	Moore et al.[54]
Interleukin-22R1 is expressed on a variety of epithelial and parenchymal tissues (skin, liver, kidney, pancreas, intestine, lung)	Wolk et al.[55]

* Some Th17 cytokines, such as interleukin-21, might exclusively target lymphoid cells, whereas the Th17-associated effector cytokines interleukin-17, interleukin-17F, and interleukin-22 have widespread effects on many tissues.

T cells into inflamed tissue; acting in synergy with TNF and interleukin-1β, interleukin-17 is a potent inducer of the chemokine CCL20, which is strongly chemotactic for lymphocytes, including Th17 cells. These Th17 cells are drawn to sites of interleukin-17–driven inflammation through CCR6, the receptor for CCL20, which is detected on Th17 cells.[32] In addition, chemokines such as interferon-inducible protein-10 (IP-10), a member of the CXC chemokine family, attract other immune cells such as Th1 cells and monocytes into inflamed tissues.[41]

There is evidence that, apart from rheumatoid arthritis,[59] Th17 cells are involved in psoriasis,[60] multiple sclerosis,[61] and inflammatory bowel disease.[62] They may also participate in the development of corticosteroid-resistant asthma.[63,64] Genetic studies have linked certain sequence variants of the interleukin-23–receptor gene to susceptibility to Crohn's disease, psoriasis, and psoriatic arthritis.[62,65,66]

The predominant T-cell population that can be isolated from the skin lesions of patients with psoriasis has a Th17 phenotype,[67] which accords with the attraction of inflammatory cells to epithelial tissues by CCL20–CCR6 signaling. In preclinical models of inflammatory hyperkeratosis, the pathogenic role of interleukin-22 production by Th17 cells, driven by interleukin-23, has been shown conclusively.[68]

In multiple sclerosis, the role of Th17 cells, if any, has been difficult to explore. *IL-17* and *IL-6* are among the most highly expressed genes in brain lesions in patients with the disease,[69] and elevated levels of interleukin-17 have been detected in serum and cerebrospinal fluid from patients with multiple sclerosis.[61] In patients with multiple sclerosis in whom lesions are restricted

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to the optic nerves and spinal cord, the levels of interleukin-17 and interleukin-8 (CXCL8) in serum and cerebrospinal fluid are higher than in conventional multiple sclerosis,[70] and the level of interleukin-17 in the cerebrospinal fluid correlates with the extent of spinal lesions as measured by means of magnetic resonance imaging.[70] An in vitro study suggested that Th17 cells have the capacity to breach the blood–brain barrier and infiltrate the parenchyma of the central nervous system.[71] The expression of the p19 chain of interleukin-23 is increased in monocyte-derived dendritic cells in blood samples from patients with multiple sclerosis, and this increase correlates with an augmented capacity of the dendritic cells to induce the production of interleukin-17 by T cells.[72]

THERAPEUTIC POTENTIAL

Targeting the interleukin-6 receptor with a monoclonal antibody (e.g., tocilizumab, a humanized monoclonal antibody against the receptor) and preempting the interleukin-1 receptor with an interleukin-1–receptor antagonist (e.g., anakinra, a recombinant human interleukin-1–receptor antagonist) are two effective approaches to the treatment of rheumatoid arthritis and other autoimmune inflammatory diseases.[73,74] Given that interleukin-6 regulates the balance between Th17 and regulatory T cells,[75,76] it is possible that blocking interleukin-6–induced intracellular signals by a monoclonal antibody against the interleukin-6 receptor ameliorates the function of regulatory T cells, thereby bringing the immune system into physiologic balance.

Since interleukin-23 enhances interleukin-17 production and induces production of other effector cytokines in Th17 cells, inhibition of interleukin-23 is another way to control Th17 cells. Treatment with a monoclonal antibody against p40, a polypeptide common to interleukin-12 and interleukin-23 (e.g., treatment with ustekinumab), has been shown to have efficacy in psoriasis and Crohn's disease.[77,78] In Crohn's disease, the antibody caused a local reduction of the levels of interleukin-12 and interleukin-23. However, since it neutralizes both interleukin-12 and interleukin-23, the effects cannot be attributed specifically to the interleukin-23–Th17 axis. Nevertheless, studies of a psoriasis-like skin disease and preclinical models of inflammatory bowel disease in mice suggest that interleukin-23–driven inflammation dominates these models of psoriasis and Crohn's disease rather than the interleukin-12–interferon-γ axis.[67,68,79,80]

The most direct way to control the biologic effects of Th17 cells would be to target the effector cytokines that they produce. Monoclonal antibodies against interleukin-17 or the interleukin-17 receptor and a soluble interleukin-17 receptor (Table 2) have been developed for clinical application. Phase 2 trials of a monoclonal antibody against interleukin-17 (AIN457) for psoriasis, rheumatoid arthritis, Crohn's disease, and psoriatic arthritis are under way. So far, inhibitors of interleukin-21 and interleukin-22 have been tested only in preclinical models of autoimmune diseases,[81,82] and we will have to await further results to determine whether these inhibitors are clinically useful.

Some cytokines have anti–interleukin-17 properties and control the development of Th17 cells. Interleukin-4, for example, inhibits the production and functions of interleukin-17,[3] and interleukin-25, which is produced by Th2 cells, also inhibits the production of interleukin-17 by downregulating interleukin-23, interleukin-1, and interleukin-6.[83] Treatment with interleukin-25 can suppress autoimmune inflammation of the brain in mice.[83] In the inflamed central nervous system, resident microglial cells are the major source of interleukin-25.

Another cytokine, interleukin-27, a member of the interleukin-12–interleukin-23 family and a heterodimer of p28 and EBI3 (a glycoprotein related to p40), specifically inhibits the development of Th17 cells.[84,85] In addition, interleukin-27 participates in the induction and differentiation of Tr1 cells, which resemble regulatory T cells and produce interleukin-10 and interferon-γ. The interaction with Tr1 cells may allow interleukin-27 to suppress inflammation indirectly.[86-88]

Future treatments could target the effector functions of Th17 cells. Interleukin-17 induces the production of interleukin-1 and TNF-α. Interleukin-1 and TNF-α may not directly block the generation of Foxp3+ regulatory T cells; however, they inhibit the functions of regulatory T cells. This phenomenon may explain the recurrence of immunoinflammatory disease when treatment with TNF inhibitors is discontinued.[89] A combination of interleukin-17 and TNF inhibitors, administered either simultaneously or sequentially,

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might better control inflammation and might even restore the function of regulatory T cells[90,91] (see figure in the Supplementary Appendix, available with the full text of this article at NEJM.org).

CONCLUSIONS

In 1995, the newly discovered interleukin-17 was thought to be of minimal importance because it lacked immediate effects on T cells and B cells.[57] Interest in this molecule began to emerge when its role in inducing inflammation was established. Now, there is agreement that interleukin-17 has an important role in providing protection against infection and in inducing and maintaining chronic inflammatory diseases.

Molecules involved in the induction of Th17 cells and their effector functions (i.e., interleukins 6, 17, 21, 22, and 23) have been identified, and this knowledge will allow the rational development of strategies for modulating Th17 cells. The reciprocal relationship between regulatory T cells and Th17 cells suggests possibilities for shifting the balance between them in a manner that restores the function of regulatory T cells in autoimmune diseases.

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