The Various Roles of Th17 cells and Th17-related Cytokines in Pathophysiology of Autoimmune Arthritis and Allied Conditions

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Abstract

There is an increasing amount of evidence suggesting the importance of CD4^{+} T cells, particularly IL-17-producing helper T cells (Th17), in the pathology of rheumatoid diseases such as rheumatoid arthritis. In various mouse models, arthritis has been reported to be markedly decreased because of IL-17 deficiency. Genetic polymorphisms in Th17 and Th17-related cytokines have also been reported in association with human rheumatoid diseases. This review summarizes the role of Th17 in mouse and human joint pathology and discusses the role of Th17 cells in the pathology of rheumatoid arthritis, psoriasis, psoriatic arthritis, and Behcet's disease. Th17 cells play a significant role in the main pathology of these diseases. They are involved in the onset of arthritis and articular bone destruction due to osteoclastogenesis in rheumatoid arthritis. They are also involved in acanthosis and parakeratosis of the skin in psoriasis and migration and activation of neutrophils in Behcet's disease. Therefore, Th17 cells may have significant potential to function as therapeutic targets for these diseases.

Keywords: IL-17-producing helper T cells (Th17); Regulatory T cells (Treg); Rheumatoid arthritis; Psoriasis; Behcet's disease

Abbreviations: IL: Interleukin; Th17: IL-17-producing helper T cells; RA: Rheumatoid Arthritis; Th cells: Helper T cells; IFN: Interferon; CIA: Collagen-Induced Arthritis; TGF-β: Transforming Growth Factor β; ROR: Retinoic acid receptor-related Orphan Receptor; STAT: Signal Transducer and Activator of Transcription; Treg: Regulatory T cells; nTreg: Naturally occurring regulatory T cells; iTreg: inducible Treg cells; Foxp3: Forkhead box P3; Tfh: Follicular helper CD4 T cells; G-CSF: Granulocyte Colony-Stimulating Factor; TNF-α: Tumor Necrosis Factor-α ; NK: Natural Killer; RANK: Receptor Activator of Nuclear Factor κB; RANKL: Receptor Activation of Nuclear Factor-κB Ligand; DMARD: Disease-Modifying Antirheumatic Drug; SpA: Spondyloarthropathy; ACR: American College of Rheumatology; FMF: Familial Mediterranean Fever

Introduction

Helper T cells (Th cells), which can be called the control tower of the acquired immune system, are classified into two types according to the cytokines they produce [1]. Th1 cells mainly produce interferon-γ (IFN-γ), while Th2 cells produce interleukin IL-4 and IL-5. Although both differentiate from naive Th cells, the former initiates activation of macrophages and cytotoxic T cells and is involved in the elimination of cell parasites, whereas the latter is mainly involved in the elimination of extracellular parasites via antibody production by the innate immune response. IFN-γ produced by Th1 cells suppresses differentiation into Th2 cells; conversely, Th2 cytokines block differentiation into Th1 cells. In other words, these cells have exclusive properties. Once the immune response balance in a living organism leans toward either Th1 or Th2, this tendency is increasingly reinforced via positive feedback.

This process can also be applied to undesirable immune responses (broadly termed allergies) in living organisms because the Th1 response is considered to be responsible for delayed hypersensitivity reactions and organ-specific autoimmune diseases while the Th2 response is thought to be responsible for systemic autoimmune diseases.

Inconsistencies in the Th1/Th2 Hypothesis

RA is the most common autoimmune disease and was first proposed as a Th1-type disease in the 1990s. In fact, IFN-γ, the representative Th1 cytokine, and IL-12, which is necessary for differentiation to Th1 cells, are being increasingly detected in specimens from RA patients [2,3]. However, phenomena that cannot be explained by this hypothesis have been indicated, with reports of barely any IFN-orbeing detected in RA synovium [4,5]. Also, a study indicated that IFN-γ administration was effective in RA treatment [6,7]. This clinical study continued into the 1990s, but results eventually indicated that the effects were insufficient because no statistically significant improvements were observed [8,9]. The use of IFN-γ, which has various side effects such as fever and depression, in RA treatment is therefore not recommended. However, if RA was truly a Th1 disease, IFN-γ administration should actually worsen symptoms in RA patients. Furthermore, collagen-induced arthritis (CIA), said to be an animal model of RA, worsened in IFN-γ receptor-deficient mice [10,11] and IFN-γ knockout mice [12].

Furthermore, Takayanagi et al. focused on research in osteoclasts, which are multinucleated cells differentiated from macrophages and involved in bone resorption, and reported in 2000 that even trace amounts of IFN-γ strongly suppressed osteoclast differentiation [13]. These results suggest that if RA is a Th1 disease, osteoclast differentiation would be suppressed and bone destruction would be less likely. However, bone destruction is actually a significant clinical problem in RA. Therefore, the Th1/Th2 cell mechanism is an important theme in the field of immunology. However, while various evidences have been collected from mouse models and human clinical studies and from the viewpoint of osteoimmunity, numerous inconsistencies have been reported.

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Th 17 Discovery in Arthritis Pathology

IL-17 has been detected in the synovial fluid of RA patients and was reported in 1999 as a cytokine that promotes osteoclast differentiation [14]. Also, CIA was reportedly attenuated in IL-17-deficient mice [15]. In 2005, a new IL-17-producing Th cell subset, called Th17 cells, was reported [16-18]. Th17 cells characteristically produce IL-17A, IL-17F, IL-21, and IL-22, and they undergo induced differentiation from naive CD4+ T cells with transforming growth factor beta (TGF-β) and IL-6 or IL-21. IL-1β and IL-23 also play important roles in proliferation and survival, whereas IL-6, IL-21, and IL-23 induce expression of retinoic acid receptor-related orphan receptor-γt (RORγt), which acts as the master regulator of Th17 via phosphorylation of signal transducer and activator of transcription 3 (STAT3), a transcription factor.

Th17 cells were first detected in mice as a new subset of CD4+ helper T cells. However, they do not produce IFN-γ or IL-4; therefore, they are not Th1 or Th2 cells. It was subsequently clarified that the same Th17 cells detected in mice were also present in humans. Interestingly, an analysis of IL-17-deficient mice [19] indicated that specific infectious diseases and autoimmune pathologies such as autoimmune arthritis [20], experimental autoimmune encephalomyelitis, and psoriasis [21], which were previously thought to be regulated by Th1 cells, may actually be regulated by Th17 cells.

The mouse Th17-specific transcription factor RORγt cooperates with STAT3 and induces IL-23 receptors, which play an important role in Th17 support and amplification and promote IL-17 transcription. In addition, Th17 differentiation is promoted by the forced expression of RORγt [22].

Th17 cells have been widely recognized as an independent helper T cell lineage because IFN-γ produced by Th1 cells and IL-4 produced by Th2 cells both suppress Th17 differentiation, and, like T-bet in Th1 cells and transacting T-cell-specific transcription factor in Th2 cells, the Th17-specific transcription factor RORγt was also subsequently identified.

Human Th17 Cells

Th17 cells were subsequently reported in humans, and it has been confirmed that human Th17 cells also express the mouse RORγt ortholog, RAR-related orphan receptor C [23]. Since the discovery of Th17 cells, vigorous research has been conducted on their mechanism of differentiation, and it appears that cytokine signals necessary for Th17 differentiation differ between humans and mice [24]. Differentiation of mouse Th17 cells is induced by the exposure of naive CD4T cells to antigens in the presence of TGF-β and IL-6. Although differentiation induced by IL-23 was also initially indicated, it currently appears that IL-23 is involved in maintaining the proliferation and function of Th17 cells. However, IL-23 plays an important role in human Th17 cell differentiation, and IL-23 and IL-1β are also often induced along with antigen stimulation of naive CD4T cells. There is no fixed definitive opinion regarding the role of TGF-β in human Th17 cell differentiation because some reports stated that TGF-β was unnecessary or suppressed differentiation, while others found that TGF-β was essential to human Th17 cell differentiation. Despite the fact that Th17 cell differentiation is suppressed by IFN-γ produced by Th1 cells, even when the first report of human Th17 cells was made, the existence of CD4T cells, which simultaneously produce IFN-γ and IL-17 in living organisms, was discovered [25]. In fact, IL-17 is reportedly generated from Th1 clones and, prior to the discovery of Th17, was considered to be a cytokine originating from Th1 cells. Moreover, it has recently been found that human Th17 cells transform into Th1 cells following IL-12 stimulation [26]. Transformation of human regulatory T cells (Treg) cells into Th17 cells has also been indicated [27]. This instability in form and nature of Th17 cells is currently the subject of vigorous research, and its importance within living organisms should soon be clarified.

Th17-related Cytokines

IL-17 is an inflammatory cytokine that acts on a diverse range of cells and induces the production of chemokines such as granulocyte colony-stimulating factor (G-CSF) and IL-8. It also causes strong inflammation, particularly because of the induction of neutrophils. IL-17A is a homodimer glycoprotein comprising polypeptides with a molecular mass of 21 kDa. IL-17 is a family of interleukins (IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F) coded by six genes that have been identified by subsequent homology searches [28]. As explained below, IL-17 is important in phylaxis. It is known that the aforementioned IL-17-producing CD4+ helper T (Th17) cells play an important role in various inflammatory and autoimmune diseases and are garnering attention as possible therapeutic targets.

IL-17A acts on a wide range of cells, including fibroblasts, epithelial cells, vascular endothelial cells, and macrophages, and induces the inflammatory cytokine tumor necrosis factor-α (TNF-α) and chemokines such as G-CSF and CXCL8 (IL-8). Therefore, it promotes granulocyte synthesis and neutrophil activation and migration to inflamed sites, thus promoting further inflammation. Previous studies have clarified that in addition to inflammatory disorders, allergic reactions, and defense mechanisms against bacterial infections, IL-17A plays an important role in the pathology of various autoimmune diseases such as RA.

IL-17A and IL-17F have the greatest homology within the IL-17 family (50% at the amino acid level), and both are produced by the same Th17 cells and share the same receptors. Because IL-17A and IL-17F are secreted by disulfide-bonded homodimers and heterodimers, they are thought to have identical bioactivities. In fact, like IL-17A, IL-17-F is known to induce IL-1 and IL-6, inflammatory cytokines such as TNF-α, chemokines such as CXCL1, and the expression of matrix metalloproteinase and antimicrobial peptides, through which it is involved in inflammation induction and defense against bacterial infections [28]. However, there are functional differences between IL-17F and IL-17A because IL-17F has an inflammatory threshold lower than that of IL-17A and because 1L-17F induces the production of different cells [29].

As mentioned above, IL-17 cytokines are produced by activated Th17 cells. However, it has become clear that various cells other than the Th17 cell subset also produce IL-17A and IL-17F. In addition to CD8+ T cells, γδT, and natural killer (NK) T cells, IL-17A and IL-17F are produced by lymphoid tissue inducer (LTi)-like cells, neutrophils, monocytes, and NK cells of the innate immune system [30]. IL-17A and IL17F are also produced by Paneth cells and intestinal epithelial cells, respectively, both of which are nonimmune cells [29]. In order to increase our understanding of the onset mechanisms of autoimmune diseases and phylaxis mechanisms of various pathogens, it is important to understand the roles of IL-17A and IL-17F produced by other cells in the formation, role, and differentiation mechanisms of Th17 cells.

Th17 cells also produce IL-22, but many IL-22-producing T cells do not produce IL-17 and do not belong to either the Th1 or Th2 subset. Recently, IL-22-producing cells have been named Th22 cells [31] and are thought to be particularly involved in skin inflammation. IL-22 is

also produced from cells other than T cells. Endogenous IL-22 plays an important role in proliferation of synoviocytes, inflammation, and promoting osteoclastogenesis.

While IL-21 is a product of Th17 cells, even in humans, it also acts on Th17 differentiation [32]. However, IL-21-producing T cells are not limited to the Th17 subset [33]. Follicular T cells involved in antibody production are particularly important IL-21-producing cells. IL-21 is essential in the development of arthritis by mechanisms dependent on follicular Th cells development, autoreactive B cell maturation, RANKL induction of CD4 T cells, and fibroblast –like synoviocytes, and osteoclastogenesis promotion (Table 1).

Regulatory T cells (Treg)

We have focused on Th17 cells and outlined how various cytokines are involved in different stages of inflammation in arthritis. Because Th17 cells produce various cytokines that act in many target cells, simple targeting therapy for Th17 related cytokine, such as anti-IL-17 neutralizing therapy, may cause insufficient effect. Therefore, development of the method of targeting Th17 cell therapy is expected most. The therapy utilizing Treg (regulatory T cells), which can suppress various immune response including Th17-related inflammation, is one of hopeful way.

The immune system swiftly recognizes exogenous antigens and eliminates them while remaining tolerant to auto-tissue. The immune system is diversely composed of T cell and B cell antigen receptors, and it can recognize various exogenous antigens and auto-antigens. Dangerous self-reactive T cells or B cell clones that recognize auto-antigens are removed by a negative selection mechanism while the thymus and bone marrow are in the undeveloped stage. However, these self-reactive clones do not exhibit a perfect regulatory mechanism, and peripheral self-reactive lymphocytes still exist in mature healthy animals [34]. Recent studies have revealed that Treg cells are endogenous immunosuppressors that exert inhibitory control over proliferation and activation of self-reactive T cells in addition to maintaining immunological self-tolerance.

Naturally occurring regulatory T (nTreg) cells are usually produced in the thymus and exhibit various regulatory activities over immune responses such as infection, tumor immunity, and graft-specific immune tolerance. nTreg cells strongly express CD25 molecules (IL-2 receptor α-chain) as specific cell surface markers [35]. They also specifically express cytotoxic T lymphocyte-associated antigen 4, glucocorticoid-induced tumor necrosis factor receptor-related protein, $\alpha_E\beta_7$-integrin, folate receptor 4 [36], and neuropilin-1 and specifically and constantly express the transcription factor forkhead box P3(FoxP3) [37]. Retroviruses can force the expression of FoxP3 in normal T cells

and bring about the same function as Treg cells. Therefore, it appears that *FoxP3* is the master regulatory gene for Treg cell generation, differentiation, and regulatory function.

Furthermore, naive T cells also express FoxP3 in the peripheries on receiving antigen stimulation in the presence of TGF-β, indicating possible Treg cell differentiation in the peripheries [38]. These cells are called inducible Treg cells (iTreg cells). However, FoxP3 expression by TGF-β-induced iTreg cells is unstable and temporary. Moreover, previously known iTreg cells include type 1 Treg cells, which produce large quantities of IL-10, and Th3 cells, which produce large quantities of TGF-β.

Th17/Treg cell Balance Control

Treg cells exhibit a wide range of immunosuppressive activities and exert inhibitory control over various immune responses in addition to autoimmunity. Meanwhile, Th17 cells play an important role in autoimmune diseases, bacterial infections, and tumor immunity. While these T cell subsets have conflicting inflammatory and anti-inflammatory functions, TGF-β is essential for differentiation and is dependent on the presence or absence of IL-6. Furthermore, the transcription factors FOXP3 and RORγt determine the differentiation of Treg and Th17 cells, respectively. Protein level interaction is thought to occur between these two transcription factors, and the concept of Th17/Treg cell balance is currently attracting attention. The mechanism of Treg and Th17 cell differentiation has been clarified, and artificial control of Th17/Treg cell balance may enable the regulation of various immune disorders, including autoimmune pathology, tumor immunity, and specific infectious diseases (Figure 1).

While RORγt is strongly induced when IL-6 or IL-21 is simultaneously present with TGF-β, expression of the Treg cell-specific transcription factor FoxP3 is suppressed. In the initial stages of these differentiation processes, FoxP3 and RORγt are simultaneously expressed, although FoxP3 suppresses RORγt, which in turn inhibits IL-17 production [39]. That is, IL-6 and IL-21 obstruct differentiation to iTreg cells by suppressing FoxP3 expression and promoting Th17 differentiation. FoxP3 and RORγt are competitive and suppress one another.
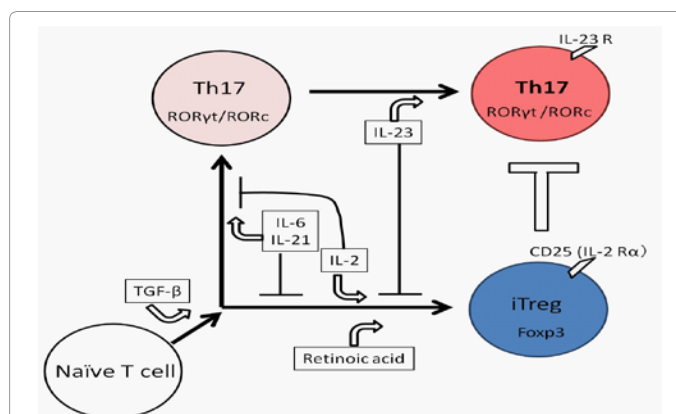
Treg cells are involved in immunity tolerance, whereas Th17 cells are involved in inflammatory pathophysiology, such as autoimmune pathophysiology. Treg cells are also functionally reciprocal T cell populations. However, some commonalities have been observed in the differentiation mechanisms of Treg and Th17 cells, such as the involvement of TGF-β-induced differentiation. As shown, many factors reportedly control Treg/Th17 differentiation. If it is possible to control this positive/negative immune response balance, it may also be possible to control various immune diseases.

Figure 1: Treg cells and Th17 cells.

Cytokine	Target cells	Function
IL-17A/F	neutrophil, macrophage, endothelial cell osteoclast synoviocyte	Recruitment to site of inflammation, activation, and migration Promotion of osteoclastogenesis Induction of proinflammatory cytokine
IL-22	keratinocyte synoviocyte synovial fibroblast	Induction of β-defensins, promotion of epidermal hyperplasia Proliferation Induction of RANKL, promotion of osteoclastogenesis
IL-21	B cell T cell CD4 T cells and fibroblast-like synoviocyte	Antibody class switching Autoreactive B cell maturation Tfhdevelopment RANKL induction

Table 1: Th17 cytokines and their relation to arthritis pathology.

In IL-2- or IL-2R subunit-deficient mice, T cells proliferate and cause the onset of fatal conditions such as splenoma, lymphoma, and enteritis [40]. Abnormalities in nTreg cells are also involved in activated induced cell death abnormalities [41,42]. IL-2 is essential to nTreg cell homeostasis, and, in IL-2 deficient mice, lack of peripheral nTreg cells is thought to cause self-tolerance failure.

Meanwhile, IL-2 not only plays an important role in nTreg homeostasis but also suppresses Th17 differentiation via STAT5 [43]. Th17 proliferation and activation is also thought to cause autoimmune pathology in IL-2-deficient mice. Therefore, IL-2 is involved in Treg cell homeostasis while suppressing differentiation into Th17 cells.

IL-23 is involved in the maintenance and proliferation of Th17 cells, acts on cells differentiating into Th17 cells, and potentiates RORγt. Th17 cells only induced by IL-6 and TGF-β actually produce IL-10 and suppress inflammation. However, because intrinsic Th17 effector activity is induced by IL-23 [44], IL-23 is clearly strongly related not only to Th17 maintenance but also to effector functions of Th17 cells in immune diseases. There are also reports of IL-23-induced inhibition of iTreg cell induction independent of Th17 cells, thus causing inflammatory enteritis [45].

Retinoic acid is a metabolite of vitamin A, and it strongly induces iTreg cell differentiation, suppresses Th17, and plays an important role in regulating TGF-β-inducible Treg/Th17 cell differentiation [46]. Retinoic acid also suppresses RORγt activity and blocks Th17 differentiation as a result of iTreg cell differentiation and strong FoxP3 induction. Promotion of iTreg cell differentiation by retinoic acid may play an important role in tolerance to inflammatory diseases of the digestive tract [47].

IL-17 and Th17 in Animal Arthritis Models

Various mouse autoimmune models, including those of type II CIA, are believed to occur because of long-term Th1 autoimmune responses, which have been indicated by disease resistance, particularly in IL-12 p40-deficient mice. However, in recent years, this has been reported to be caused by a deficiency in IL-23, which shares the p40 subunit with IL-12 [48]. IL-17 production was markedly decreased in IL-23-deficient mice regardless of normal Th1 responses. Furthermore, the importance of IL-17 was clarified by reports showing that CIA symptoms became milder in IL-17-deficient mice and with anti-IL-17 antibody administration [15,49]. However, it must be noted that IL-17 produced by TCRγδ T cells is involved in mouse CIA pathophysiology [50]. Reportedly, Th17 and IL-17 also play important roles in spontaneous arthritis in SKG mice with variations in zeta-chain (T cell receptor)-associated protein kinase, which is involved in T cell antigen receptor signal transmission, and mice lacking IL-1Ra, which is an endogenous IL-1 inhibitor [20,51].

Bone Destruction and Th17 cells in RA

Th17 cells significantly induced osteoclast differentiation in co-cultures of osteoblasts and bone marrow cells. Th17 cells from IL-17-deficient mice weakly exhibit osteoclast differentiation function. IL-17 induces receptor activation of nuclear factor-κB ligand (RANKL) expression in synovial cells, and Th17 cells induce RANKL expression in osteoblasts via IL-17 production [52]. While Th17 cells cause localized inflammation, produce IL-17, and induce RANKL in synovial fibroblasts, Th17 cells also express RANKL. Therefore, Th17 cells induce osteoclasts and are involved in bone destruction.

Th17 and Related Cytokines in Human RA

In addition to inducing the production of various inflammatory cytokines and chemokines, IL-17 also induces joint inflammation and destruction in RA, including cartilage degeneration through protein fusion enzyme production and osteoclast induction through increased RANKL expression (Figure 2). However, no remarkable IL-17 production is observed in RA. IL-17 production in human RA was detected by measuring IL-17 mRNA and IL-17 protein in synovial tissue and fluid, but it was barely observed in osteoarthritis (OA), which was used as a control [53]. However, these increases in IL-17 concentrations were not remarkable, and many papers have reported IL-17 remaining at the same level [14,54-58]. IL-17 expression in synovial tissue has also been reported as a possible prognostic factor of joint destruction [59]. Moreover, IL-17 has been detected in serum, albeit in small amounts, and shown to be present in higher levels in RA patients than in healthy subjects [60]. Although Th17 cells appear in the peripheral blood of RA patients and healthy subjects at the same frequency, some reports have found no correlation to RA disease activity [61,62], while others have reported increased levels of Th17 cells in RA patients [63]. The Th17 cell ratio in synovial fluid in RA is also low, with overwhelmingly high levels of Th1 [61,64]. Although we previously stated that various cells other than Th17 produce IL-17, it has been reported that immunohistochemical analysis of local sites in RA joints revealed few IL-17-producing T cells (Th17), most of which were mastocytes [30]. Furthermore, expression of the chemokine receptor CCR6 is a characteristic of Th17 cells that is common to both humans and mice [65]. Also, Th17 cells naturally produce the CCR6 ligand, CCL20, which appears to be a positive feedback mechanism. A correlation between CCR6 polymorphisms and RA has also been reported [66]. Therefore, there is no unified view concerning IL-17 expression in RA, but the possibility remains that it plays an important
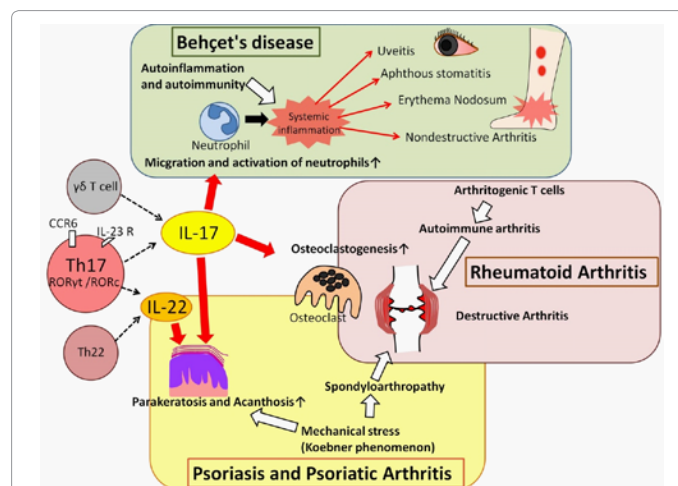
Arthritis can occur in any one of these diseases, but the role of Th17 cells and Th17-related cytokines in arthritis appears to differ according to disease. In RA, Th17 cells may play an important role in the initial development of arthritis and bone destruction caused by the induction of osteoclast formation, causing subsequent arthritis mutilans, which is characteristic of RA. In psoriasis, Th17 and Th22 cells promote the cutaneous pathophysiology of acanthosis and parakeratosis while inducing osteoclastogenesis in joints and progression to osteoclastic arthropathy. Meanwhile, in Behcet's disease, Th17 and IL-23 abnormalities are involved in neutrophil migration and activation and form the basis of the various pathophysiologies observed in Behcet's disease, which exhibits a principally neutrophilic pathophysiology and sometimes appears to cause the onset of arthritis.

Figure 2: The role of Th17 cells in rheumatoid arthritis (RA), psoriasis, and Behcet's disease.

role in the onset and initial phases of the disease because increased levels have been confirmed in disease-modifying antirheumatic drug (DMARD)-naive cases (before administering DMARDs) [67] and cases with CCR6 polymorphisms.

In human clinical trials, blockade of IL-17 using a humanized anti-IL-17 monoclonal antibody has been investigated in patients with RA. Although the efficacy of anti-IL-17 therapy is considered inferior than that of other anti-cytokine therapy, such as TNF-α, AIN457 and LY2439821 improved clinical signs of RA with no strong adverse effects, supporting the benefits of anti-IL-17 antibodies in RA [68,69].

However, it is a certain fact that IL-17 is crucial activators of host defense. A number of pathogens induce Th17 responses, and Th17 cells can rapidly initiate an inflammatory response that is dominated by neutrophils. Consequently, long-term use of anti-IL17 antibody may cause increased susceptibility to infections.

Investigations on IL-23 have not yet confirmed a correlation between RA and IL-23R polymorphisms [70]; furthermore, the clinical effects of anti-IL-12/23p40 neutralizing antibodies have not been clarified. Therefore, it appears that these have little relation with RA pathophysiology. In groups of RA patients with bone erosion in particular, IL-23p19 was detected in serum and synovial fluid. This was reported to correlate to IL-17 concentration [71]. Serum IL-23 increases have been reversed by the administration of anti-TNF-α, with no changes in IL-17 concentrations [72]. Meanwhile, Brentano et al. reported that IL-23p19 expression increased more in synovial membranes in RA than in synovial membranes in OA; however, p40 was barely expressed because it was produced as an IL-23 protein [73]. A study by Hillyer et al. also reported that IL-23 was barely secreted from synovial cells, whereas it was detected in cell lysates. In addition, when anti-IL-23R antibodies were actually added to a synovium cell culture *in vitro*, TNF-α and IL-1β production was inhibited. This inhibition was significantly different from that induced by control antibodies [56]. Although no significant inhibition of Il-6 production was observed and the overall results appeared weak, these results suggest the potential of IL-23 as a therapeutic target for RA. Synovial fibroblast proliferation and increased MCP-1 production are known physiological effects of IL-22; these effects may be involved in RA pathogenesis. Osteoclast induction has also been demonstrated in mice [74]. While it has been shown that IL-22-producing T cells were increased in the peripheral blood of RA patients [67], Ikeuchi et al. observed IL-22 expression in RA synovial membranes. However, many of these were synovial fibroblasts and macrophages, and barely any co-staining was observed for T cell markers and IL-22 [75].

Reportedly, the IL-2/IL21 loci are risk factors for RA [76]. Because high IL-21 concentrations have been detected in the synovial fluid and serum of RA patients [77], and because IL-21 is produced by follicular helper T cells, it can be a potential therapeutic target for RA.

Psoriasis, Psoriatic Arthritis (PsA), and Th17 cells

Psoriasis is a common inflammatory keratosis characterized by inflammation, telangiectasia, and hyperproliferation and differentiation abnormalities in epidermal cells. It is sometimes complicated by arthropathy. Evaluations of T cell inhibitory treatment in human psoriasis patients has revealed that T cells play a particularly important role in psoriasis pathophysiology. Because T cell activity inhibitors such as cyclosporine, IL-2 toxin, and alefacept (human LFA-3 fusion protein) have been successful in psoriasis treatment, it is clear that T cells are deeply involved in psoriasis pathophysiology. Many previous reports

have stated that analyses of skin lesions from human psoriasis patients have indicated the importance of the Th17/IL-23 axis in psoriasis [78]. Interestingly, IL12B, IL23R, and IL23A have been identified as psoriasis disease-susceptibility genes, but gene polymorphisms themselves suggest genetic predisposition to the IL-23/Th17 axis [79,80]. Th17 cells also secrete IL-22 in addition to IL-17, and increased levels of IL-17 and IL-22 have been reported at psoriatic sites [81-84]. In particular, Th22 cells are thought to be involved in inflammatory pathophysiology of the skin. IL-23 cytokines are essential to effector Th17 function and maintenance. Dermal myeloid dendritic cells produce IL-23 and Il-23p19 for the induced activation of Th17, which is involved in the formation of lesion sites in psoriasis [85-89].

Cytokines, including IL-22, IL-9, and IL-20, which are produced by Th17 and Th22 cells, activate STAT3, an epidermal keratinocyte, and encourage migration and proliferation while suppressing differentiation [82,90-92]. In human clinical trials, the administration of ustekinumab and briakinumab, which are IL-12/23 p40 monoclonal antibodies, led to a dramatic improvement in psoriasis [93-96]. Furthermore, IL-23 concentration decreased along with a decrease in psoriatic clinical symptoms after narrow-band ultraviolet-B (NB-UVB) treatment or TNF-α inhibition, suggesting that excessive IL-23 production is related to active psoriasis [97,98].

The success of anti-IL-12/23p40 antibodies against psoriasis is because of the inhibition of the IL-23/Th17 axis. Likewise, TNF-α inhibitors act on IL-23 production by dermal myeloid dendritic cells and inhibit IL-23/Th17 signaling [99,100].

From an immunological viewpoint, PsA is more similar to spondyloarthropathy (SpA) than RA, and it is caused by microbial infections, activation of innate immunity, and enthesis mechanical stress. Just as in the dermis of psoriasis skin lesions, CD4$^+$ activated T cells significantly infiltrate the synovial membranes of PsA-inflamed joints [101]. Fibroblasts and T cells in PsA synovial fluid induce osteoclastogenesis, resorption, and joint destruction via interactions between receptor activator of nuclear factor κB (RANK), its ligand RANKL, TNF-α, and IL-7 [102]. As mentioned previously, IL-12/23p40 antibodies have been dramatically successful against psoriasis. A phase II clinical trial investigating the effects of the IL-12/23p40 antibody, ustekinumab, on arthritic diseases, indicated a significant difference in the American College of Rheumatology (ACR) symptom criteria ACR20, ACR50, and ACR70 [103]. This supports the pathological roles of IL-23 in osteoclastogenesis potentiation and bone erosion potentiation in PsA joint sites. Therefore, immune responses via IL-17 and IL-23 appear to play important roles in PsA.

Th17 and Behcet's Disease Pathophysiology

Behcet's disease is marked by systemic inflammation of an unknown origin and recurrent aphthous ulceration of the oral mucosa, eyes, skin, and vulva. It is a chronic disease with repeated episodes of relapse and remission, and acute and subacute polyarthritis occurs in half of all reported cases. Although Behcet's disease resembles the clinical features of other autoinflammatory diseases, the involvement of specific autoantibodies or autoantigen-reactive T cells has not been clarified. There are also treatment modalities that are common between autoinflammatory diseases and Behcetse disease, such as Il-1β inhibition.

In autoinflammatory diseases, excessive IL-1β secretion induces inflammation; therefore, IL-1β inhibitors present possible treatments. In Behcet's disease, increased serum IL-1β has been confirmed in

active and inactive stages and effectively treated with IL-1β inhibitors [104,105]. In fact, the efficacy of gevokizumab, a monoclonal antibody for IL-1β, has been demonstrated for Behcet's disease [106]. Therefore, Il-1β is anticipated to become a viable treatment target for refractory Behcet's disease.

Colchicine is also an effective treatment for both disease groups. It has been shown to be effective not only against Behcet's disease but also in 80%–90% of familial Mediterranean fever (FMF) cases [107]. Inhibition of neutrophil migration is a representative mechanism of colchicine action; however, of all the autoinflammatory diseases characterized by neutrophil hyperfunctioning, colchicine is only effective against FMF. Therefore, while Behcet's disease appears to mainly manifest via autoinflammatory pathophysiology, the effectiveness of T cell immunosuppressants such as cyclosporine and tacrolimus against lesions of the eye, intestinal tract, and central nervous system in Behcet's disease have suggested characteristics of an autoimmune disease involving T cells. Although Behcet's disease is considered a Th1 autoimmune disease because of increased concentrations of Th1-dominant cytokines, the role of Th17 has recently been investigated. As mentioned previously, IL-1le of Th17 has recently creased ssants such as cyclosporinhA recent, large-scale genomic analysis indicated that IL-10 and IL23R polymorphisms were disease-susceptibility genes for Behcet's disease [108].

Th17 cells express the IL-23 receptor (IL-23R), and IL-17 production is promoted by IL-23 stimulation [109].

A previous human studies have shown that higher IL-23, IL-17, and IL-23 p19 mRNA in sera of BD patients with uveitis. Serum IL-23 values correlate with worsened uveitis in Behcet's disease, and enhanced IL-23 p19 mRNA expression has also been observed in erythema nodosum-like lesions of BD patients [110-113].

More recently, the efficacy of neutralizing humanized anti-IL-17A monoclonal antibody, AIN457, were investigated in patients with uveitis [73]. This treatment improved symptoms of uveitis. Collectively, IL-23/IL-17 pathway is associated with the active inflammation and immunological aberrations of BD..

Functional modification by *IL23R* polymorphisms has been indicated in hyperfunctioning of T cells. Moreover, IL-17 is strongly involved in neutrophil migration, and excessive IL-17 concentrations are believed to enhance neutrophilic function.

In the context of enhanced innate immunity (autoinflammatory pathophysiology), Behcet's disease appears to reflect a diverse range of pathophysiologies, including autoimmune diseases caused by many factors. Th17 and IL-17 maintain abnormally high concentrations of serum IL-1β and IL-17 in the context of *IL-17*-related genetic polymorphisms. Against this backdrop, Th17 and IL-17 may be strongly involved in the enhancement of neutrophilic function, which is the main pathophysiological feature of Behcet's disease.

Conclusion

This paper primarily considered the role of Th17 cells in arthritis on the basis of evidence from human and mouse studies. The role of Th17 in human arthritis differed according to illness. In RA, Th17 and Th17-related cytokines likely play important roles in bone destruction by osteoclasts in early-stage and chronic arthritis. In psoriasis, mainly Th17 and Th22 promote acanthosis and parakeratosis while osteoclastogenesis is induced in the joints and bone destruction progresses. Meanwhile, in Behcet's disease, Th17 and

IL-23 abnormalities are involved in neutrophil migration, activation, and inflammation, which are hallmarks of the disease. Interestingly, Th17 cells likely play an important role in the main pathophysiology (bone destruction in RA, cutaneous inflammation in psoriasis, and neutrophilic inflammation in Behcet's disease) of each of these three diseases. Therefore, Th17-targeted therapy can likely improve the essential pathophysiology of these diseases.

Notably, Treg cells inhibit immunity and are reciprocal to Th17 cells; therefore, control of this balance poses an additional potential therapy. However, there are still many unclear aspects regarding the nature of human Th17 and Treg cells. While both have plasticity, they cannot be explained simply as those found in mice. Nonetheless, the differentiation and functional mechanisms of Treg and Th17 cells will be further clarified in the future. If it is possible to control their balance, it is anticipated that effective treatment strategies will emerge not only for arthritis but also for other immune diseases, cancers, and infectious diseases.

References

1. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL (1986) Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 136: 2348-2357.

2. Bucht A, Larsson P, Weisbrot L, Thorne C, Pisa P, et al. (1996) Expression of interferon-gamma (IFN-gamma), IL-10, IL-12 and transforming growth factor-beta (TGF-beta) mRNA in synovial fluid cells from patients in the early and late phases of rheumatoid arthritis (RA). Clin Exp Immunol 103: 357-367.

3. Morita Y, Yamamura M, Nishida K, Harada S, Okamoto H, et al. (1998) Expression of interleukin-12 in synovial tissue from patients with rheumatoid arthritis. Arthritis Rheum 41: 306-314.

4. Husby G, Williams RC Jr (1985) Immunohistochemical studies of interleukin-2 and gamma-interferon in rheumatoid arthritis. Arthritis Rheum 28: 174-181.

5. Firestein GS, Zvaifler NJ (1987) Peripheral blood and synovial fluid monocyte activation in inflammatory arthritis. ii. low levels of synovial fluid and synovial tissue interferon suggest that gamma-interferon is not the primary macrophage activating factor. Arthritis Rheum 30: 864-871.

6. Peddinani MV, Savery F, Hang LM (1986) Human leukocyte interferon in the treatment of rheumatoid arthritis. Clin Ther 9: 39-43.

7. Veys EM, Mielants H, Verbruggen G, Grosclaude JP, Meyer W, et al. (1988) Interferon gamma in rheumatoid arthritis--a double blind study comparing human recombinant interferon gamma with placebo. J Rheumatol 15: 570-574.

8. Cannon GW, Pincus SH, Emkey RD, Denes A, Cohen SA, et al. (1989) Double-blind trial of recombinant gamma-interferon versus placebo in the treatment of rheumatoid arthritis. Arthritis Rheum 32: 964-973.

9. Cannon GW, Emkey RD, Denes A, Cohen SA, Saway PA, et al. (1993) Prospective 5-year followup of recombinant interferon-gamma in rheumatoid arthritis. J Rheumatol 20: 1867-1873.

10. Manoury-Schwartz B, Chiocchia G, Bessis N, Abehsira-Amar O, Batteux F, et al. (1997) High susceptibility to collagen-induced arthritis in mice lacking IFN-gamma receptors. J Immunol 158: 5501-5506.

11. Vermeire K, Heremans H, Vandeputte M, Huang S, Billiau A, et al. (1997) Accelerated collagen-induced arthritis in IFN-gamma receptor-deficient mice. J Immunol 158: 5507-5513.

12. Chu CQ, Song Z, Mayton L, Wu B, Wooley PH (2003) IFNgamma deficient C57BL/6 (H-2b) mice develop collagen induced arthritis with predominant usage of T cell receptor Vbeta6 and Vbeta8 in arthritic joints. Ann Rheum Dis 62: 983-990.

13. Takayanagi H, Ogasawara K, Hida S, Chiba T, Murata S, et al. (2000) T-cell-mediated regulation of osteoclastogenesis by signalling cross-talk between RANKL and IFN-gamma. Nature 408: 600-605.

14. Kotake S, Udagawa N, Takahashi N, Matsuzaki K, Itoh K, et al. (1999) IL-17 in

synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. J Clin Invest 103: 1345-1352.

15. Nakae S, Nambu A, Sudo K, Iwakura Y (2003) Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. J Immunol 171: 6173-6177.

16. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, et al. (2005) IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med 201: 233-240.

17. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, et al. (2005) Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol 6: 1123-1132.

18. Park H, Li Z, Yang XO, Chang SH, Nurieva R, et al. (2005) A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol 6: 1133-1141.

19. Nakae S, Komiyama Y, Nambu A, Sudo K, Iwase M, et al. (2002) Antigen-specific T cell sensitization is impaired in IL-17-deficient mice, causing suppression of allergic cellular and humoral responses. Immunity 17: 375-387.

20. Hirota K, Hashimoto M, Yoshitomi H, Tanaka S, Nomura T, et al. (2007) T cell self-reactivity forms a cytokine milieu for spontaneous development of IL-17+ Th cells that cause autoimmune arthritis. J Exp Med 204: 41-47.

21. Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, et al. (2007) Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. Nature 445: 648-651.

22. Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, et al. (2006) The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell 126: 1121-1133.

23. Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, Sallusto F (2007) Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. Nat Immunol 8: 942-949.

24. de Jong E, Suddason T, Lord GM (2010) Translational mini-review series on Th17 cells: development of mouse and human T helper 17 cells. Clin Exp Immunol 159: 148-158.

25. Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, et al. (2007) Phenotypic and functional features of human Th17 cells. J Exp Med 204: 1849-1861.

26. Boniface K, Blumenschein WM, Brovont-Porth K, McGeachy MJ, Basham B, et al. (2010) Human Th17 cells comprise heterogeneous subsets including IFN-gamma-producing cells with distinct properties from the Th1 lineage. J Immunol 185: 679-687.

27. Koenen HJ, Smeets RL, Vink PM, van Rijssen E, Boots AM, et al. (2008) Human CD25highFoxp3pos regulatory T cells differentiate into IL-17-producing cells. Blood 112: 2340-2352.

28. Iwakura Y, Ishigame H, Saijo S, Nakae S (2011) Functional specialization of interleukin-17 family members. Immunity 34: 149-162.

29. Ishigame H, Kakuta S, Nagai T, Kadoki M, Nambu A, et al. (2009) Differential roles of interleukin-17A and -17F in host defense against mucoepithelial bacterial infection and allergic responses. Immunity 30: 108-119.

30. Hueber AJ, Asquith DL, Miller AM, Reilly J, Kerr S, et al. (2010) Mast cells express IL-17A in rheumatoid arthritis synovium. J Immunol 184: 3336-3340.

31. Eyerich S, Eyerich K, Pennino D, Carbone T, Nasorri F, et al. (2009) Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. J Clin Invest 119: 3573-3585.

32. Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, et al. (2008) IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature 454: 350-352.

33. Evans HG, Suddason T, Jackson I, Taams LS, Lord GM (2007) Optimal induction of T helper 17 cells in humans requires T cell receptor ligation in the context of Toll-like receptor-activated monocytes. Proc Natl Acad Sci U S A 104: 17034-17039.

34. Sakaguchi S, Ono M, Setoguchi R, Yagi H, Hori S, et al. (2006) Foxp3+ CD25+ CD4+ natural regulatory T cells in dominant self-tolerance and autoimmune disease. Immunol Rev 212: 8-27.

35. Sakaguchi S (2000) Regulatory T cells: key controllers of immunologic self-tolerance. Cell 101: 455-458.

36. Yamaguchi T, Hirota K, Nagahama K, Ohkawa K, Takahashi T, et al. (2007) Control of immune responses by antigen-specific regulatory T cells expressing the folate receptor. Immunity 27: 145-159.

37. Hori S, Nomura T, Sakaguchi S (2003) Control of regulatory T cell development by the transcription factor Foxp3. Science 299: 1057-1061.

38. Chen W, Jin W, Hardegen N, Lei KJ, Li L, et al. (2003) Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. J Exp Med 198: 1875-1886.

39. Zhou L, Lopes JE, Chong MM, Ivanov II, Min R, et al. (2008) TGF-beta-induced Foxp3 inhibits T(H)17 cell differentiation by antagonizing RORgammat function. Nature 453: 236-240.

40. Suzuki H, Kündig TM, Furlonger C, Wakeham A, Timms E, et al. (1995) Deregulated T cell activation and autoimmunity in mice lacking interleukin-2 receptor beta. Science 268: 1472-1476.

41. Malek TR, Yu A, Vincek V, Scibelli P, Kong L (2002) CD4 regulatory T cells prevent lethal autoimmunity in IL-2Rbeta-deficient mice. Implications for the nonredundant function of IL-2. Immunity 17: 167-178.

42. Setoguchi R, Hori S, Takahashi T, Sakaguchi S (2005) Homeostatic maintenance of natural Foxp3(+) CD25(+) CD4(+) regulatory T cells by interleukin (IL)-2 and induction of autoimmune disease by IL-2 neutralization. J Exp Med 201: 723-735.

43. Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, et al. (2007) Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity 26: 371-381.

44. McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, et al. (2007) TGF-beta and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T(H)-17 cell-mediated pathology. Nat Immunol 8: 1390-1397.

45. Izcue A, Hue S, Buonocore S, Arancibia-Cárcamo CV, Ahern PP, et al. (2008) Interleukin-23 restrains regulatory T cell activity to drive T cell-dependent colitis. Immunity 28: 559-570.

46. Mucida D, Park Y, Kim G, Turovskaya O, Scott I, et al. (2007) Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Science 317: 256-260.

47. von Boehmer H (2007) Oral tolerance: is it all retinoic acid? J Exp Med 204: 1737-1739.

48. Murphy CA, Langrish CL, Chen Y, Blumenschein W, McClanahan T, et al. (2003) Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. J Exp Med 198: 1951-1957.

49. Lubberts E, Koenders MI, Oppers-Walgreen B, van den Bersselaar L, Coenen-de Roo CJ, et al. (2004) Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion. Arthritis Rheum 50: 650-659.

50. Roark CL, French JD, Taylor MA, Bendele AM, Born WK, et al. (2007) Exacerbation of collagen-induced arthritis by oligoclonal, IL-17-producing gamma delta T cells. J Immunol 179: 5576-5583.

51. Nakae S, Saijo S, Horai R, Sudo K, Mori S, et al. (2003) IL-17 production from activated T cells is required for the spontaneous development of destructive arthritis in mice deficient in IL-1 receptor antagonist. Proc Natl Acad Sci U S A 100: 5986-5990.

52. Sato K, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, et al. (2006) Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J Exp Med 203: 2673-2682.

53. Chabaud M, Durand JM, Buchs N, Fossiez F, Page G, et al. (1999) Human interleukin-17: A T cell-derived proinflammatory cytokine produced by the rheumatoid synovium. Arthritis Rheum 42: 963-970.

54. Singh R, Aggarwal A, Misra R (2007) Th1/Th17 cytokine profiles in patients with reactive arthritis/undifferentiated spondyloarthropathy. J Rheumatol 34: 2285-2290.

55. Raza K, Falciani F, Curnow SJ, Ross EJ, Lee CY, et al. (2005) Early rheumatoid arthritis is characterized by a distinct and transient synovial fluid cytokine profile of T cell and stromal cell origin. Arthritis Res Ther 7: R784-795.

56. Hillyer P, Larché MJ, Bowman EP, McClanahan TK, de Waal Malefyt R, et al. (2009) Investigating the role of the interleukin-23/-17A axis in rheumatoid arthritis. Rheumatology (Oxford) 48: 1581-1589.

57. Stamp LK, Easson A, Pettersson L, Highton J, Hessian PA (2009) Monocyte derived interleukin (IL)-23 is an important determinant of synovial IL-17A expression in rheumatoid arthritis. J Rheumatol 36: 2403-2408.

58. Kohno M, Tsutsumi A, Matsui H, Sugihara M, Suzuki T, et al. (2008) Interleukin-17 gene expression in patients with rheumatoid arthritis. Mod Rheumatol 18: 15-22.

59. Kirkham BW, Lassere MN, Edmonds JP, Juhasz KM, Bird PA, et al. (2006) Synovial membrane cytokine expression is predictive of joint damage progression in rheumatoid arthritis: a two-year prospective study (the DAMAGE study cohort). Arthritis Rheum 54: 1122-1131.

60. Cho ML, Yoon CH, Hwang SY, Park MK, Min SY, et al. (2004) Effector function of type II collagen-stimulated T cells from rheumatoid arthritis patients: cross-talk between T cells and synovial fibroblasts. Arthritis Rheum 50: 776-784.

61. Yamada H, Nakashima Y, Okazaki K, Mawatari T, Fukushi JI, et al. (2008) Th1 but not Th17 cells predominate in the joints of patients with rheumatoid arthritis. Ann Rheum Dis 67: 1299-1304.

62. Jandus C, Bioley G, Rivals JP, Dudler J, Speiser D, et al. (2008) Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondylarthritides. Arthritis Rheum 58: 2307-2317.

63. Shen H, Goodall JC, Hill Gaston JS (2009) Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. Arthritis Rheum 60: 1647-1656.

64. Ito Y, Usui T, Kobayashi S, Iguchi-Hashimoto M, Ito H, et al. (2009) Gamma/delta T cells are the predominant source of interleukin-17 in affected joints in collagen-induced arthritis, but not in rheumatoid arthritis. Arthritis Rheum 60: 2294-2303.

65. Hirota K, Yoshitomi H, Hashimoto M, Maeda S, Teradaira S, et al. (2007) Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model. J Exp Med 204: 2803-2812.

66. Kochi Y, Okada Y, Suzuki A, Ikari K, Terao C, et al. (2010) A regulatory variant in CCR6 is associated with rheumatoid arthritis susceptibility. Nat Genet 42: 515-519.

67. Colin EM, Asmawidjaja PS, van Hamburg JP, Mus AM, van Driel M, et al. (2010) 1,25-dihydroxyvitamin D3 modulates Th17 polarization and interleukin-22 expression by memory T cells from patients with early rheumatoid arthritis. Arthritis Rheum 62: 132-142.

68. Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, et al. (2010) Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. Sci Transl Med 2: 52ra722.

69. Genovese MC, Van den Bosch F, Roberson SA, Bojin S, Biagini IM, et al. (2010) LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: A phase I randomized, double-blind, placebo-controlled, proof-of-concept study. Arthritis Rheum 62: 929-939.

70. Chang M, Saiki RK, Cantanese JJ, Lew D, van der Helm-van Mil AH, et al. (2008) The inflammatory disease-associated variants in IL12B and IL23R are not associated with rheumatoid arthritis. Arthritis Rheum 58: 1877-1881.

71. Kim HR, Kim HS, Park MK, Cho ML, Lee SH, et al. (2007) The clinical role of IL-23p19 in patients with rheumatoid arthritis. Scand J Rheumatol 36: 259-264.

72. Kageyama Y, Kobayashi H, Kato N (2009) Infliximab treatment reduces the serum levels of interleukin-23 in patients with rheumatoid arthritis. Mod Rheumatol 19: 657-662.

73. Brentano F, Ospelt C, Stanczyk J, Gay RE, Gay S, et al. (2009) Abundant expression of the interleukin (IL)23 subunit p19, but low levels of bioactive IL23 in the rheumatoid synovium: differential expression and Toll-like receptor-(TLR) dependent regulation of the IL23 subunits, p19 and p40, in rheumatoid arthritis. Ann Rheum Dis 68: 143-150.

74. Geboes L, Dumoutier L, Kelchtermans H, Schurgers E, Mitera T, et al. (2009) Proinflammatory role of the Th17 cytokine interleukin-22 in collagen-induced arthritis in C57BL/6 mice. Arthritis Rheum 60: 390-395.

75. Ikeuchi H, Kuroiwa T, Hiramatsu N, Kaneko Y, Hiromura K, et al. (2005) Expression of interleukin-22 in rheumatoid arthritis: potential role as a proinflammatory cytokine. Arthritis Rheum 52: 1037-1046.

76. Daha NA, Kurreeman FA, Marques RB, Stoeken-Rijsbergen G, Verduijn W, et al. (2009) Confirmation of STAT4, IL2/IL21, and CTLA4 polymorphisms in rheumatoid arthritis. Arthritis Rheum 60: 1255-1260.

77. Niu X, He D, Zhang X, Yue T, Li N, et al. (2010) IL-21 regulates Th17 cells in rheumatoid arthritis. Hum Immunol 71: 334-341.

78. Maeda S, Hayami Y, Naniwa T, Ueda R (2012) The Th17/IL-23 Axis and Natural Immunity in Psoriatic Arthritis. Int J Rheumatol 2012: 539683.

79. Elder JT, Bruce AT, Gudjonsson JE, Johnston A, Stuart PE, et al. (2010) Molecular dissection of psoriasis: integrating genetics and biology. J Invest Dermatol 130: 1213-1226.

80. Harper EG, Guo C, Rizzo H, Lillis JV, Kurtz SE, et al. (2009) Th17 cytokines stimulate CCL20 expression in keratinocytes in vitro and in vivo: implications for psoriasis pathogenesis. J Invest Dermatol 129: 2175-2183.

81. Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, et al. (2008) Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol 128: 1207-1211.

82. Wolk K, Witte E, Wallace E, Döcke WD, Kunz S, et al. (2006) IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. Eur J Immunol 36: 1309-1323.

83. Nograles KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Fariñas M, et al. (2008) Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. Br J Dermatol 159: 1092-1102.

84. Chan JR, Blumenschein W, Murphy E, Diveu C, Wiekowski M, et al. (2006) IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. J Exp Med 203: 2577-2587.

85. Di Cesare A, Di Meglio P, Nestle FO (2009) The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol 129: 1339-1350.

86. Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, et al. (2004) Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. J Exp Med 199: 125-130.

87. Lowes MA, Chamian F, Abello MV, Fuentes-Duculan J, Lin SL, et al. (2005) Increase in TNF-alpha and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). Proc Natl Acad Sci U S A 102: 19057-19062.

88. Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, Abello MV, Novitskaya I, et al. (2009) Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. J Invest Dermatol 129: 79-88.

89. Zaba LC, Krueger JG, Lowes MA (2009) Resident and "inflammatory" dendritic cells in human skin. J Invest Dermatol 129: 302-308.

90. Boniface K, Bernard FX, Garcia M, Gurney AL, Lecron JC, et al. (2005) IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. J Immunol 174: 3695-3702.

91. Sa SM, Valdez PA, Wu J, Jung K, Zhong F, et al. (2007) The effects of IL-20 subfamily cytokines on reconstituted human epidermis suggest potential roles in cutaneous innate defense and pathogenic adaptive immunity in psoriasis. J Immunol 178: 2229-2240.

92. Wolk K, Haugen HS, Xu W, Witte E, Waggie K, et al. (2009) IL-22 and IL-20 are key mediators of the epidermal alterations in psoriasis while IL-17 and IFN-gamma are not. J Mol Med (Berl) 87: 523-536.

93. Kimball AB, Gordon KB, Langley RG, Menter A, Perdok RJ, et al. (2011) Efficacy and safety of ABT-874, a monoclonal anti-interleukin 12/23 antibody, for the treatment of chronic plaque psoriasis: 36-week observation/retreatment and 60-week open-label extension phases of a randomized phase II trial. J Am Acad Dermatol 64: 263-274.

94. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, et al. (2008) Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 371: 1665-1674.

95. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, et al. (2008) Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 371: 1675-1684.

96. Krueger GG, Langley RG, Leonardi C, Yeilding N, Guzzo C, et al. (2007) A

human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 356: 580-592.

97. Piskin G, Tursen U, Sylva-Steenland RM, Bos JD, Teunissen MB (2004) Clinical improvement in chronic plaque-type psoriasis lesions after narrow-band UVB therapy is accompanied by a decrease in the expression of IFN-gamma inducers -- IL-12, IL-18 and IL-23. Exp Dermatol 13: 764-772.

98. Gottlieb AB, Chamian F, Masud S, Cardinale I, Abello MV, et al. (2005) TNF inhibition rapidly down-regulates multiple proinflammatory pathways in psoriasis plaques. J Immunol 175: 2721-2729.

99. Zaba LC, Cardinale I, Gilleaudeau P, Sullivan-Whalen M, Suárez-Fariñas M, et al. (2007) Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. J Exp Med 204: 3183-3194.

100. Zaba LC, Suárez-Fariñas M, Fuentes-Duculan J, Nograles KE, Guttman-Yassky E, et al. (2009) Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. J Allergy Clin Immunol 124: 1022-10.e1-395.

101. Veale D, Yanni G, Rogers S, Barnes L, Bresnihan B, et al. (1993) Reduced synovial membrane macrophage numbers, ELAM-1 expression, and lining layer hyperplasia in psoriatic arthritis as compared with rheumatoid arthritis. Arthritis Rheum 36: 893-900.

102. Mori G, Cantatore FP, Brunetti G, Oranger A, Colaianni G, et al. (2007) Synovial fluid fibroblasts and lymphocytes support the osteoclastogenesis in human psoriatic arthritis. Ann N Y Acad Sci 1117: 159-164.

103. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, et al. (2009) Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet 373: 633-640.

104. Düzgün N, Ayaşlioğlu E, Tutkak H, Aydintuğ OT (2005) Cytokine inhibitors: soluble tumor necrosis factor receptor 1 and interleukin-1 receptor antagonist in Behçet's disease. Rheumatol Int 25: 1-5.

105. Botsios C, Sfriso P, Furlan A, Punzi L, Dinarello CA (2008) Resistant Behçet disease responsive to anakinra. Ann Intern Med 149: 284-286.

106. [No authors listed] (2011) Deal watch: XOMA and Servier to develop anti-IL-1Î² antibody for inflammatory diseases. Nat Rev Drug Discov 10: 166.

107. Chae JJ, Aksentijevich I, Kastner DL (2009) Advances in the understanding of familial Mediterranean fever and possibilities for targeted therapy. Br J Haematol 146: 467-478.

108. Mizuki N, Meguro A, Ota M, Ohno S, Shiota T, et al. (2010) Genome-wide association studies identify IL23R-IL12RB2 and IL10 as Behçet's disease susceptibility loci. Nat Genet 42: 703-706.

109. Miossec P, Korn T, Kuchroo VK (2009) Interleukin-17 and type 17 helper T cells. N Engl J Med 361: 888-898.

110. Leng RX, Chen GM, Pan HF, Ye DQ (2010) The role of IL-23/IL-17 axis in the etiopathogenesis of Behçet's disease. Clin Rheumatol 29: 1209.

111. Habibagahi Z, Habibagahi M, Heidari M (2010) Raised concentration of soluble form of vascular endothelial cadherin and IL-23 in sera of patients with Behçet's disease. Mod Rheumatol 20: 154-159.

112. Chi W, Zhu X, Yang P, Liu X, Lin X, et al. (2008) Upregulated IL-23 and IL-17 in Behçet patients with active uveitis. Invest Ophthalmol Vis Sci 49: 3058-3064.

113. Lew W, Chang JY, Jung JY, Bang D (2008) Increased expression of interleukin-23 p19 mRNA in erythema nodosum-like lesions of Behçet's disease. Br J Dermatol 158: 505-511.