Recent Advances in Immunopathophysiology of Interleukin-6: An Innovative Therapeutic Drug, Tocilizumab (Recombinant Humanized Anti-human Interleukin-6 Receptor Antibody), Unveils The Mysterious Etiology of Immune-Mediated Inflammatory Diseases

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Interleukin (IL)-6 cDNA was originally cloned as a terminal B cell differentiation factor into antibody-producing plasma cells. This revealed that it is a multifunctional cytokine that acts on a variety of cells. From the clinical viewpoint, it is especially important that IL-6 acts on hepatocytes to induce acute-phase reactants, including C-reactive protein, serum amyloid A protein, and fibrinogen, and to decrease serum albumin levels. Very recently, this cytokine has been found to enhance the synthesis of a peptide called hepcidin in the liver which regulates iron recycling, resulting in anemia due to hypoferrernia. It has also been shown that IL-6 is responsible for various clinical symptoms, including the appearance of autoantibodies, fatigue, anemia, anorexia, fever, and increases in the erythrocyte sedimentation rate, all of which develop in patients with various chronic autoimmune inflammatory diseases. In practice, blocking the IL-6 signaling pathway with a recombinant humanized anti-IL-6 receptor antibody, tocilizumab (TCZ), has dramatically improved all the signs and symptoms of these patients. A study in mice demonstrated that IL-6 promotes the development of a new type of T-helper cells called Th17 cells that impact the pathogenesis of autoimmune diseases. This suggests that TCZ is not only an antiinflammatory agent but also might affect basic autoimmunity. In this review, recent advances in the immunobiology of interleukin-6 related to immune-mediated diseases are discussed.

Key words interleukin-6 receptor; tocilizumab; humanized antibody; rheumatoid arthritis; T helper 17 cell; anemia of inflammation

1. INTRODUCTION

Although the etiology of most autoimmune diseases is not fully understood, it is believed that genetic background and environmental factors such as microbial infections, nutrition, and exposure to chemical compounds are involved. It is evident that immune-reactive cells including T cells, B cells, and macrophages play important roles in the pathogenesis of these autoimmune diseases. Recently, it has become obvious that several cytokines are responsible for the development and progression of these diseases. In particular, evidence has accumulated indicating that interleukin (IL)-6 is one of the major proinflammatory cytokines. It acts on a variety of cells, including immune-competent cells and hematopoietic cells, to cause proliferation and differentiation. Accordingly, IL-6 is a well-known multifunctional cytokine that has multiple biological activities. Thus hyperproduction of this cytokine possibly causes many clinical symptoms in inflammatory autoimmune diseases. The involvement of IL-6 in the pathogenesis of immune-mediated diseases was first suggested by the finding showing that a patient with cardiac myxoma produced large amount of IL-6 and had many symptoms similar to those of patients with chronic inflammatory diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Subsequently, it was found that patients with Castleman’s disease, RA, systemic-onset juvenile idiopathic arthritis (soJIA), and some other autoimmune inflammatory diseases exhibit similar symptoms that can be readily explained by overproduction of IL-6.

Based on these findings, IL-6 was thought to be a worthwhile and attractive therapeutic target for drug discovery and development. While many biopharmaceuticals targeting IL-6 have been developed, we started to develop a humanized anti-IL-6 receptor antibody [tocilizumab (TCZ)] for the treatment of patients with inflammatory autoimmune diseases, including RA and soJIA. In this review, recent advances in IL-6 immunobiology related to chronic autoimmune diseases and some results from clinical studies in patients with RA given TCZ are discussed.

2. IL-6 cDNA CLONING

IL-6 was originally called B cell stimulatory factor-2 (BSF-2), which differentiates activated B cells into antibody-producing plasma cells. In 1986, Hirano et al. cloned the cDNA coding for BSF-2. This revealed that BSF-2/IL-6 was identical to hybridoma/plasmacytoma growth factor and hepatocyte-stimulating factor that had been independently studied under different names. Subsequent studies showed that IL-6 is produced by various types of cells such as T cells, B cells, monocytes, macrophages, dendritic cells, fibroblasts, endothelial cells, glial cells, and several types of tumor cells and that IL-6 regulates the immune response and inflammation. IL-6 also acts on a variety of cell types and shows a wide range of biological functions, as described below.

3. IL-6 SIGNALING PATHWAY

The cDNA for the IL-6 receptor was cloned in 1988. This revealed that it had a very short cytoplasmic region lacking the kinase domains essential for a signaling pathway. For IL-6 signal transduction, another membranous protein,
a 130-kDa cell-surface glycoprotein called gp130, is necessary. 7,8 The IL-6 receptor is an 80-kDa polypeptide chain (IL-6R, IL-6Rα-chain, CD126), which is able to bind to IL-69 and gp130 (IL-6R β-chain, CD130) is unable to bind IL-6 but is responsible for signal transduction. When IL-6 binds to membrane-bound IL-6R (mIL-6R), the two molecules of gp130 are dimerized and form a trimer complex of IL-6, IL-6R, and gp130 leading to signal transduction. 7—10 A recent crystal structure study has demonstrated that two of each molecule associate to form a hexamer complex. 11,12

It should be noted that gp130 is expressed ubiquitously in all tissues, even in cells that lack detectable expression of IL-6R. 10 This suggests that gp130 is not merely a component of IL-6R and that it might function as a common signal transducer for various cytokines. Several different cytokines share gp130. Kishimoto's group and others reported that ciliary neurotropic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OM), IL-11, and cardiotropin-1 (CT-1) all use gp130 as a component of their receptors. 13—16 This explains why these cytokines have very similar activities (redundancy).

Importantly, the soluble IL-6 receptor (sIL-6R) that lacks transmembrane and cytoplasmic domains is present in the serum and synovial fluids. Once sIL-6R binds to IL-6, the complex becomes capable of associating with gp130 to transduce the IL-6 signal into cells. This means that the gp130-mediated IL-6 signaling pathway works even for cells that do not express IL-6R on their cell surface. This is called transsignaling.

4. IL-6 AND ITS PATHOGENIC ROLE IN INFLAMMATORY AUTOIMMUNE DISEASES

Acute inflammation is accompanied by an increase in the plasma concentration of many proteins, such as "acute-phase proteins," including C-reactive protein (CRP), fibrinogen, serum amyloid A (SAA) protein, and haptoglobin. These phenomena can be easily explained by the increase in the gene expression of IL-6, leading to increased synthesis of acute-phase proteins 7,18 in the liver. In contrast, IL-6 decreases the synthesis of albumin in the liver, resulting in hypoalbuminemia. 19 Moreover, in IL-6 knockout mice, it was shown that IL-6 is essential for the induction of the acute-phase reaction as well as for the antiviral antibody response. 20 We also confirmed that the injection of recombinant human IL-6 into cynomolgus monkeys increased the serum CRP level and the platelet count in the peripheral blood. 21

One of the recent advances regarding IL-6 is the discovery that it plays a critical role in the development of anemia of chronic inflammation. It has been shown that IL-6 induces hepcidin, which is an iron-regulatory peptide produced in the liver. Hepcidin binds to a transporter molecule called ferroportin and inhibits the secretion of iron by macrophages and the absorption of iron from the intestine. Thus excessive IL-6 causes hypoferrernia, which leads to anemia of chronic inflammation. 22—25

Another important activity of IL-6 is the induction of osteoclast differentiation, which may contribute to joint destruction in patients with RA. As reported by Tamura et al., 26 a cocktail of IL-6 and sIL-6R induces the differentiation of precursor cells into mature osteoclasts in mice. IL-6 also stimulates the expression of vascular endothelial growth factor (VEGF), 27 which is an essential factor for the neovascularization involved in hyperplasia of the synovial tissues in RA patients. Moreover, IL-6 also enhances the function of leptin, an anti-appetite hormone, resulting in the anorexia commonly seen in patients with chronic inflammatory diseases. It has also been reported that injection of IL-6 in cancer patients causes fever. This might be due to induction of cyclooxygenase-2, leading to the synthesis of prostaglandins. All these lines of evidence suggest that the production of excessive amounts of IL-6 is involved in various diseases, including chronic autoimmune inflammatory diseases. Patients with cardiac myxoma provided the first clinical evidence suggesting that IL-6 is responsible for the immunopathogenesis of chronic autoimmune inflammatory diseases. Cardiac myxoma is a benign heart tumor that arises from the atrium. Patients with cardiac myxoma exhibit a wide variety of autoimmune and inflammatory symptoms, including autoantibodies, fever, joint pains, and anemia. All these symptoms resolve after surgical removal of the tumor. The finding that cardiac myxoma cells produce a large amount of IL-6 strongly suggested that IL-6 is responsible for such autoimmune inflammatory symptoms. 28

In patients with Castleman's disease, it was reported that there is an abnormal overproduction of IL-6. 29 Affected lymph node cells overproduce IL-6, which explains symptoms such as high fever, anemia, fatigue, anorexia, acute-phase reactions, hypergammaglobulinemia, secondary amyloidosis, and massive plasma cell infiltration into affected lymph nodes. Finally, RA is another chronic inflammatory disease that preferentially affects the synovial joints. The inflamed synovium is characterized by infiltration of inflammatory cells such as macrophages and lymphocytes, leading to proliferation of synovial cells, angiogenesis, and irreversible destruction of cartilage and bone of the joints. The production of IL-6 is elevated in RA patients. 30,31 Moreover, IL-6 levels in sera are closely related to disease activity. 32 These findings readily explain almost all the symptoms seen in RA patients such as the increase in acute-phase protein (CRP and SAA) levels, 33 hypergammaglobulinemia, autoantibodies such as rheumatoid factor (RF) and anti-nuclear antibody, hypoalbuminemia, increase in erythrocyte sedimentation rate, increased platelet numbers, 34,35 and induction of osteoclasts. 36 Symptoms such as fever, fatigue, anemia, and anorexia can be also explained by the excessive production of IL-6.

Based on the above findings in patients with cardiac myxoma, RA, and Castleman's disease, we concluded that the blockade of IL-6 and its receptor interactions was a worthwhile, attractive, and promising new therapeutic approach for the treatment of chronic autoimmune inflammatory diseases.

5. PATHOGENIC ROLES OF IL-6 IN THE DEVELOPMENT OF AUTOIMMUNE DISEASES IN ANIMAL MODELS

To clarify the roles of IL-6 in the pathogenesis of experimental arthritis, IL-6-deficient mice were backcrossed into C57BL/6 mice for eight generations, and the histologic changes in the joints of antigen-induced arthritis were
compared between IL-6-deficient and wild-type littermate mice. Wild-type mice developed severe arthritis, whereas IL-6-deficient mice had little or no arthritis. It is noteworthy that in IL-6-deficient mice, the expression level of tumor necrosis factor (TNF) mRNA in synovial tissues was comparable to that in wild-type mice, indicating that IL-6 but not TNF is essential for disease development.

Collagen-induced arthritis in mice is an experimental arthritis model widely used for the evaluation of anti-arthritis agents. In these mice, elevated production of IL-6 was observed in the synovial tissues and the blockade of the IL-6 signaling pathway with antibody or gene knockout suppressed the development of arthritis. We reported that anti-mouse IL-6R antibody (MR16-1) inhibited the development of collagen-induced arthritis in mice when injected at the same time as antigen immunization or within 3 d after immunization. Splenic T cells responded to the correspondent antigenic stimulation to proliferate in the control mice. In contrast, this response was markedly inhibited in the MR16-1-treated mice. Antibody treatment also inhibited antibody production against collagen. Additionally, we performed collagen-induced arthritis studies in monkeys to determine whether tocilizumab could inhibit arthritis development. The results were similar to those obtained in mice studies.

Atsumi et al. established knockin mice with a mutation at position Tyr-759 in gp130 which is a binding site of the src homology 2 domain-bearing protein tyrosine phosphatase (SHP)-2, which develop arthritis due to insufficient clonal selection of T cells in the thymus leading to an increased number of autoreactive T cells and increased level of autoantibodies. Tyr-759 is also a binding site for a negative feedback regulator called SOCS3 in the gp130 signaling pathway. The results indicated that continuous signaling through gp130 may result in the development of autoimmune arthritis.

Another interesting murine arthritic model is SKG mice that spontaneously develop autoimmune arthritis as they age. T cells are essential for disease development, and synovial fluids of arthritic mice contain large amounts of IL-6. Sakaguchi et al. reported that deficiency of the IL-6 gene completely inhibited the development of arthritis, whereas 20% of TNF-α-deficient mice developed the disease, indicating that IL-6 but not TNF is essential for the development of arthritis. Recently, it has been reported that the injection of MR16-1 inhibits the development of arthritis in those mice.

Moreover, HTLV-1 tax transgenic mice are a genetically modified arthritis model resembling human RA and spontaneously develop arthritis as they age. They have high levels of IL-6 and IL-6 deficient mice do not develop arthritis, but TNF-deficient mice do.

SLE is a typical autoimmune disease, characterized by the production of autoantibodies to a variety of autoantigen such as nuclear antigens, leading to immune complex-mediated glomerulonephritis. It has been reported that B cells from SLE patients show a hyperresponse to cytokines and spontaneous production of immunoglobulins. IL-6 levels are elevated in the sera of patients with active, but not inactive, SLE. Increased IL-6 has also been detected in the urine and renal glomeruli of patients with lupus nephritis.

NZB and NZW F1 (B/WF1) mice spontaneously develop autoimmune disease that resembles human SLE, i.e., hyper-gammaglobulinemia, autoantibody production including anti-DNA antibody, immune complex-mediated glomerulonephritis, and death from renal failure. We and others previously reported that B cells from BWF1 mice in vitro show hyperresponsiveness to IL-6 and then produce anti-DNA antibody. We also found that BWF1 mice treated with anti-IL-6R antibody had dramatically decreased proteinuria and survived longer than control mice. In addition, anti-IL-6R antibody almost completely suppressed the production of pathogenic IgG anti-DNA antibody. This result suggests that IL-6 is essential for the production of anti-DNA autoantibody and the pathogenesis of murine SLE.

Atreya et al. and Yamamoto et al. reported that anti-IL-6R antibody suppressed the development of experimental colitis in mice, such as TNBS-induced, IL-10 knockout-induced, and CD45RBhigh CD4+ T cell-induced colitis. In mice treated with anti-IL-6R antibody, apoptosis of mucosal T cells was observed, suggesting that IL-6 might contribute to the survival of autoreactive T cells.

As mentioned above, IL-6 increases the synthesis of acute-phase reactants in the liver. SAA protein is one of those and its serum level becomes higher in patients with chronic autoimmune inflammatory diseases. To confirm the role of IL-6 in the development of secondary amyloidosis, Mihara et al. carried out an experiment to test whether MR16-1 could inhibit the deposition of amyloid A (AA) protein on the organ in mice. The result showed that the antibody inhibited the development of AA-amyloidosis. Hagiwara et al. investigated how IL-6 activates the transcription of AA gene expression in vitro. They found that IL-6 is a pivotal cytokine and TNF and IL-1 are secondary, although they also enhance the synthesis of AA synergistically with IL-6. Thus the addition of anti-IL-6R antibody (TCZ) almost completely suppressed the gene expression of AA, whereas blockade of the other two cytokines showed only weak partial inhibition.

These lines of evidence from animal models strongly support the above-mentioned hypothesis that IL-6 plays an important role in the pathogenesis of chronic autoimmune inflammatory diseases and is a worthwhile therapeutic target.

6. TOCILIZUMAB

On the basis of the above experimental and clinical results, we set out to develop an anti-IL-6 receptor blockade therapy. In collaboration with the MRC Collaborative Centre in London, mouse monoclonal antibody against human IL-6 receptor was humanized by means of complementarity-determining region (CDR) grafting technology. Humanization was completed perfectly and the activities of TCZ are equivalent to that of the original mouse antibody in terms of both IL-6R binding and the inhibition of IL-6 binding to IL-6R.

TCZ inhibits both mIL-6R- and sIL-6R-mediated signaling pathways. Inhibitory effects of TCZ on mIL-6R-mediated signal transduction was found in experiments using the human myeloma cell line KPMM2, which expresses mIL-6R and proliferates in response to IL-6. TCZ also shows inhibitory effects on sIL-6R-mediated signal transduction as examined using the human gp130-transfected mouse pro-B cell line BAF (BAF-h130).
7. TCZ CLARIFIED THE PATHOGENIC ROLES OF IL-6 IN SEVERAL AUTOIMMUNE INFLAMMATORY DISEASES

7.1. Clinical Response in Castleman’s Disease Patients The results of clinical studies in patients with multicentric Castleman’s disease have been reported by Nishimoto et al. After TCZ was administered, fever and fatigue immediately resolved, while anemia and serum levels of CRP, fibrinogen, and albumin quickly improved. In addition, lymphadenopathy and hypergammaglobulinemia were significantly alleviated. Importantly, the renal function abnormalities in patients with amyloidosis dramatically improved. The pathophysiologic significance of IL-6 in Castleman’s disease was thus confirmed, and blockade of IL-6 signaling by the anti-IL-6 receptor antibody was shown to be a potential new therapy for IL-6-related diseases.

7.2. Clinical Response in Systemic-Onset Juvenile Idiopathic Arthritis soJIA is an inflammatory disease characterized by spiking fever, pericarditis, skin rash, arthritis, splenomegaly, and hepatomegaly. Children with soJIA often show growth retardation and developmental abnormality. Relatively high-dose corticosteroids and/or immunosuppressive agents are commonly used to treat patients but they have insufficient efficacy. Serum IL-6 levels are elevated and correlated with disease activity. Yokota et al. reported that TCZ treatment dramatically reduced disease activity and improved the quality of life of children with the soJIA.

7.3. Clinical Response in RA Following the success of the treatment of Castleman’s patients, TCZ was used in RA patients.

In a phase I clinical study, it was reported that serum CRP and SAA levels were completely normalized as long as TCZ was detectable in the serum, indicating that IL-6 is essential for the production of CRP and SAA in vivo. TCZ was well tolerated and no serious adverse events were observed. Subsequently, multicenter, double-blind, randomized, placebo-controlled phase II trials were conducted in RA patients to investigate the safety and efficacy of TCZ treatment in both Japan and Europe. In Japan, 164 patients with refractory RA received 4 or 8 mg/kg of TCZ or placebo intravenously every 4 weeks for a total of 12 weeks, and the efficacy was assessed based on American College of Rheumatology (ACR) criteria. As reported by Nishimoto et al., TCZ significantly improved all measures of disease activity in the ACR core set and also improved laboratory findings such as hemoglobin levels, platelet counts, and serum levels of CRP, fibrinogen, SAA, albumin, and RF.

As also reported by Nishimoto et al., during long-term treatment (more than 15 months), serum IL-6 levels gradually decreased, becoming undetectable in some patients. This suggests that TCZ may not just be a simple anti-inflammatory agent but also may affect fundamental aspects of autoimmunity. Forty-four percent of patients in the TCZ groups showed an increase in total cholesterol level. However, the levels reached a plateau even when TCZ was administered repeatedly and remained constant close to the upper limit of the normal range. Since high-density lipoprotein (HDL) cholesterol levels also increased, the atherogenic index (total cholesterol−HDL cholesterol/HDL cholesterol) did not increase throughout the study period. No cardiovascular complications associated with increased total cholesterol were observed. Mild to moderate increases in serum liver enzymes were observed in 14 (12.8%) of 109 patients in the TCZ groups. The data indicate that TCZ treatment is generally well tolerated and shows clinical benefits.

As reported by Maini et al. in a phase II study conducted in the European CHARISMA study, a total of 359 patients with active RA and an inadequate response to methotrexate (MTX) therapy (MTX ≥10 mg/week for at least 6 months) were administered TCZ or placebo together with 10—25 mg/week of MTX or MTX placebo every 4 weeks for a total of 12 weeks. The patients received 2, 4, or 8 mg/kg of TCZ, either as monotherapy or in combination with MTX, or MTX monotherapy. As evaluated by the change in DAS28 from baseline, TCZ 8 mg/kg monotherapy and TCZ 8 mg/kg plus MTX both achieved significantly higher responses than MTX alone. However, there was no significant difference between TCZ 8 mg/kg monotherapy and TCZ 8 mg/kg plus MTX.

Recently, the results of several large-scale phase III trials have been published. A Japanese study was performed to investigate the efficacy and safety of TCZ in 306 patients with active RA. Patients in the TCZ group showed a significant delay in the radiographic progression of joint destruction compared with those in the disease-modifying antirheumatic drug (DMARD) group. In addition, ACR20, 50, and 70 responses were achieved by 89%, 70%, and 47%, respectively, of patients in the TCZ group, which was significantly better than the 35%, 14%, and 6% who achieved these responses in the conventional DMARD group (p<0.001). The overall incidences of adverse events were 89% and 82% in the TCZ and control groups, respectively. This trial showed that TCZ monotherapy is more efficacious than conventional DMARDs in delaying and stopping radiographic progression of joint destruction and in improving signs and symptoms.

More recently, the results of the first and second of five multinational phase III studies have provided further evidence that IL-6 receptor inhibition is likely to play a significant role in the treatment of RA. In the first multinational phase III study, the OPTION study, was a double-blind, randomized, controlled study in 623 patients with moderate to severe active RA refractory to MTX. Patients received 8 or 4 mg/kg of TCZ, or placebo i.v. every 4 weeks. All three groups also received MTX. The proportion of patients that achieved an ACR20 response at 24 weeks was significantly higher in the 8- and 4-mg/kg TCZ groups than in the placebo group. These data demonstrate that TCZ is effective and has a good safety and tolerability profile (Smolen et al. EULAR, 2007).

The second multinational phase III study, the TOWARD study, was a two-arm, randomized, double-blind study in 1216 patients with moderate to severe active RA and inadequate response to DMARDs. The study was conducted at 130 study sites in 18 countries, including the U.S.A. Patients received either TCZ 8 mg/kg or placebo intravenously every 4 weeks in combination with stable antirheumatic therapy, including traditional DMARDs but excluding biologics. Compared with patients treated with traditional DMARDs alone, a greater proportion of patients treated with TCZ plus traditional DMARDs achieved significant improvement in disease signs and symptoms at 24 weeks when assessed by the
standard ACR score assessment method (Press release by Roche).

All the results of these above-mentioned clinical studies clearly indicated the benefits of using TCZ to block IL-6 signaling in the treatment of patients with autoimmune-mediated inflammatory diseases, including RA, soJIA, and Castleman’s disease.

8. RECENT ADVANCES IN IL-6 RESEARCH

Because the effects of TCZ therapy in patients with several autoimmune inflammatory diseases, including RA patients, have been so dramatic, they suggest that the overproduction of IL-6 is deeply involved in the pathogenesis and progression of these diseases. As mentioned above, excessive production of IL-6 can readily explain almost all of the symptoms seen in patients. For example, blockade of IL-6 signaling by TCZ causes dramatic improvement of anemia, which is beneficial for maintaining and improving patient quality of life. This effect could be the result of the inhibition of the production of hepcidin (an iron-regulatory peptide secreted by liver cells) or the recovery of signal transduction via the erythropoietin (EPO) receptor. The EPO receptor and IL-6R share the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway. Since excessive IL-6 signaling induces expression of suppressors of cytokine signaling (SOCS), which are intracellular negative feedback factors that inhibit the JAK-STAT pathway, TCZ may down-regulate these factors, resulting in increased EPO signaling over time.

Another mechanism of the activity of TCZ may be that blockade of IL-6 signaling decreases the synthesis of VEGF, resulting in the inhibition of angiogenesis in the synovial tissues and inhibition of the hyperplasia of the synovium. Construction of new vessels is necessary for the supply of oxygen and nutrition to the growing tissue and thus may contribute to hyperplasia of synovial tissues. There are higher VEGF levels in the serum and synovial fluids in RA patients and the levels correlate with disease activity and radiographic progression of the joints. Nakahara et al. showed that VEGF production was increased when synovial cells were cultured in the presence of IL-6 and sIL-6R. IL-6 seemed to be a pivotal cytokine for VEGF production, since anti-IL-6R antibody strongly inhibited VEGF production in the cultured cells, while inhibitors of both IL-1 and TNF were less inhibitory. More importantly, in patients with RA administered TCZ, serum VEGF levels dramatically decreased to normal.

Yet another possible mechanism is that the activation/differentiation of osteoclasts may contribute to the prevention of joint destruction. Tamura et al. reported that IL-6, together with sIL-6R, enhanced the differentiation of bone marrow-derived osteoclast precursor cells to mature osteoclasts by stimulating osteoblasts in mice. Recent progress in osteoimmunology has shown that osteoclasts are derived from synovial macrophages. Cytokines are involved in the formation of osteoclasts and some synovial cells, for example, Th17 cells (described below) express RANKL on their cell surface.

Finally, one of the most notable advances is related to the discovery that IL-6 promotes the development of a newly identified type of T-helper cell, the Th17 cells, that affect the pathogenesis of autoimmune diseases. Until recently, it was believed that there are only two types of T-helper cells: Th1 and Th2. However, considerable evidence has accumulated indicating that a new type of cells, called Th17 cells, might play an important role in the pathogenesis of autoimmune diseases. Th17 cells produce IL-17, which is a cytokine recruiting other immune cells to peripheral tissues leading to the enhancement of inflammation. As reported by Mangan et al., transforming growth factor-beta (TGFβ)-deficient mice have reduced numbers of Th17 cells. Similarly, Bettelli et al. showed that TGFβ-transgenic mice had increased numbers of Th17 cells and more severe autoimmune disease. These results clearly demonstrate that TGFβ is essential for the induction of Th17 cells. But more important papers recently published have shown that IL-6 promotes the development of Th17 cells and that anti-IL-6 antibody almost completely inhibited Th17 cell differentiation, even in the presence of TGFβ. Moreover, it is also reported that a cocktail of TGFβ and IL-6 decreased regulatory T cells, although TGFβ itself induces the differentiation of regulatory T cells. These findings suggest that there may be a new dichotomy in helper T-cell differentiation, and IL-6 might be a crucial polarizing factor to increase Th17 cells and to inhibit regulatory T cells, leading to autoimmunity. IL-6, together with TGFβ, is involved in the differentiation of this particularly pathogenic T cell lineage, and it has already been found that blockade of IL-6 signaling results in suppression of the development of Th17 cells in mice.

Although the results obtained in animal studies should be considered with caution when applied to humans, it is possible that TCZ is more than just an antiinflammatory agent but inhibits the pathogenesis of RA by its effects on the underlying etiology of the disease.

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