Mechanisms of Disease

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CYTOKINE PATHWAYS AND JOINT INFLAMMATION IN RHEUMATOID ARTHRITIS

ERNEST H.S. CHOY, M.D.,
AND GABRIEL S. PANAYI, M.D., SC.D.

RHEUMATOID arthritis is a common chronic inflammatory and destructive arthropathy that cannot be cured and that has substantial personal, social, and economic costs. The long-term prognosis is poor: 80 percent of affected patients are disabled after 20 years,[1] and life expectancy is reduced by an average of 3 to 18 years.[2] The medical cost of rheumatoid arthritis averages \$5,919 per case per year in the United States[3] and approximately £2,600 per case per year in the United Kingdom.[4] Current slow-acting antirheumatic drugs have limited efficacy and many side effects. Moreover, they do not improve the long-term prognosis of rheumatoid arthritis.[1]

The inflammatory process is usually tightly regulated, involving both mediators that initiate and maintain inflammation and mediators that shut the process down. In states of chronic inflammation, an imbalance between the two mediators leaves inflammation unchecked, resulting in cellular damage. In the case of rheumatoid arthritis, this damage is manifested by the destruction of cartilage and bone.

Efforts to develop safer and more effective treatments for rheumatoid arthritis that are based on an improved understanding of the role of inflammatory mediators are beginning to bear fruit. Treatments such as etanercept, a soluble tumor necrosis factor α (TNF-α) type II receptor–IgG1 fusion protein, and infliximab, a chimeric (human and mouse) monoclonal antibody against TNF-α, have been approved by the Food and Drug Administration and the European Medicine Evaluation Agency for rheumatoid arthritis. These therapies could dramatically change the treatment and outcome of the disease.

PATHOGENESIS OF RHEUMATOID ARTHRITIS

The synovial membrane in patients with rheumatoid arthritis is characterized by hyperplasia, increased vascularity, and an infiltrate of inflammatory cells, primarily CD4+ T cells, which are the main orchestrator of cell-mediated immune responses. In genetic studies, rheumatoid arthritis is strongly linked to the major-histocompatibility-complex class II antigens HLA-DRB1*0404 and DRB1*0401.[5] The main function of HLA class II molecules is to present antigenic peptides to CD4+ T cells, which strongly suggests that rheumatoid arthritis is caused by an unidentified arthritogenic antigen.[6] The antigen could be either an exogenous antigen, such as a viral protein, or an endogenous protein. Recently, a number of possible endogenous antigens, including citrullinated protein, human cartilage glycoprotein 39, and heavy-chain–binding protein, have been identified.[7]

Cellular Mediators of Inflammation and Joint Damage

Antigen-activated CD4+ T cells stimulate monocytes, macrophages, and synovial fibroblasts to produce the cytokines interleukin-1, interleukin-6, and TNF-α and to secrete matrix metalloproteinases (Fig. 1) through cell-surface signaling by means of CD69 and CD11[8] as well as through the release of soluble mediators such as interferon-γ and interleukin-17. Interleukin-1, interleukin-6, and TNF-α are the key cytokines that drive inflammation in rheumatoid arthritis. Activated CD4+ T cells also stimulate B cells (Fig. 1), through cell-surface contact and through the binding of $\alpha_L\beta_2$ integrin, CD154 (CD40 ligand), and CD28, to produce immunoglobulins, including rheumatoid factor. The precise pathogenic role of rheumatoid factor is unknown, but it may involve the activation of complement through the formation of immune complexes. Activated CD4+ T cells express osteoprotegerin ligands that stimulate osteoclastogenesis (Fig. 1). Such activated T cells caused joint damage in an animal model of rheumatoid arthritis.[9]

These activated macrophages, lymphocytes, and fibroblasts, as well as their products, can also stimulate angiogenesis, which may explain the increased vascularity found in the synovium of patients with rheumatoid arthritis. Endothelial cells in the synovium are activated and express adhesion molecules that promote the recruitment of inflammatory cells into the joint. This process is enhanced by the release of chemokines, such as interleukin-8, by inflammatory cells in the joint. The detailed mechanisms of these complex cellular interactions remain elusive.

Soluble Mediators of Inflammation and Joint Damage

Monocytes, macrophages, fibroblasts, and T cells release numerous cytokines on stimulation. Most of these cytokines, including TNF-α and interleukin-1, can be detected in synovial fluid from patients with rheumatoid arthritis.[10] Both TNF-α and interleukin-1 are likely to have primary roles in the pathogenesis of rheumatoid arthritis. The serum and synovial concentrations of both cytokines are high in patients with active rheumatoid arthritis.[11,12] Furthermore, TNF-α and interleukin-1 are potent stimulators of mesenchymal

From the Department of Rheumatology, Guy's, King's, and St. Thomas' Hospitals School of Medicine, King's College, London. Address reprint requests to Dr. Choy at the Department of Rheumatology, King's College Hospital, East Dulwich Grove, London SE22 8PT, United Kingdom.

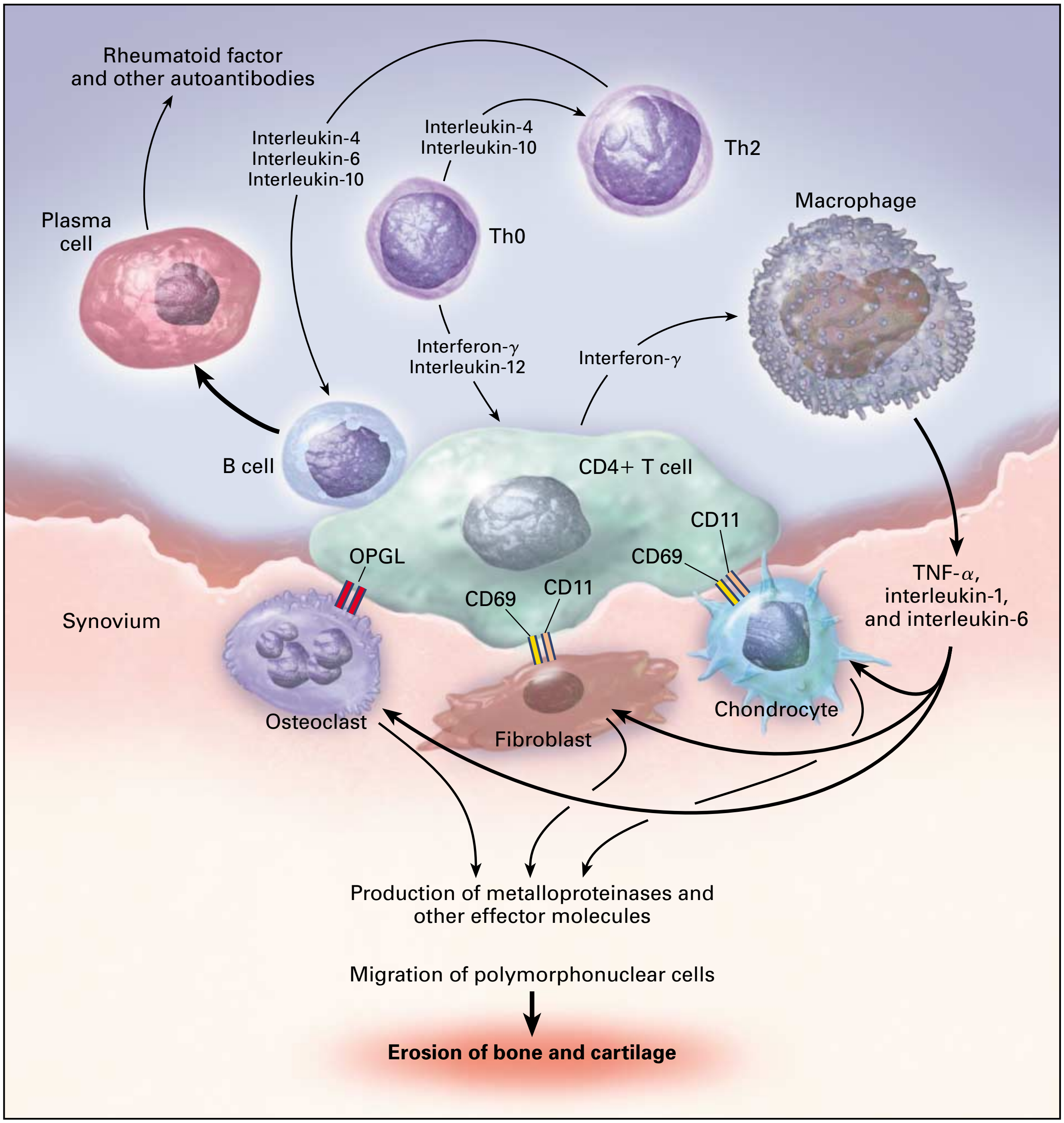


Figure 1. Cytokine Signaling Pathways Involved in Inflammatory Arthritis.

The major cell types and cytokine pathways believed to be involved in joint destruction mediated by TNF-α and interleukin-1 are shown. Th2 denotes type 2 helper T cell, Th0 precursor of type 1 and type 2 helper T cells, and OPGL osteoprotegerin ligand.

cells, such as synovial fibroblasts, osteoclasts, and chondrocytes, that release tissue-destroying matrix metalloproteinases.[13] Interleukin-1 and TNF-α also inhibit the production of tissue inhibitors of metalloproteinases by synovial fibroblasts.[13] These dual actions are thought to lead to joint damage. Perhaps by inducing the production of interleukin-11, TNF-α stimulates the development of osteoclasts, which are responsible for bone degradation.[14]

TNF-α

TNF-α is a potent cytokine that exerts diverse effects by stimulating a variety of cells. It is a soluble 17-kd protein composed of three identical subunits.

It is produced mainly by monocytes and macrophages, but also by B cells, T cells, and fibroblasts. Newly synthesized TNF-α is inserted into the cell membrane and subsequently released through the cleavage of its membrane-anchoring domain by a serine metalloproteinase.[15] Thus, TNF-α secretion might be suppressed by inhibitors of this enzyme.[16]

Perhaps the best-studied aspect of TNF-α is its ability to promote inflammation. TNF-α is an autocrine stimulator as well as a potent paracrine inducer of other inflammatory cytokines, including interleukin-1, interleukin-6, interleukin-8, and granulocyte–monocyte colony-stimulating factor.[17-19] TNF-α also promotes inflammation by stimulating fibroblasts to express adhesion molecules, such as intercellular adhesion molecule 1.[20] These adhesion molecules interact with their respective ligands on the surface of leukocytes, resulting in increased transport of leukocytes into inflammatory sites, including the joints in patients with rheumatoid arthritis.

TNF-α indirectly down-regulates inflammation by stimulating the release of corticotropin from the pituitary.[21] This hormone stimulates the adrenal cortex to release cortisol, which inhibits inflammation.

As an inflammatory cytokine, TNF-α has an important — perhaps dominant — role in rheumatoid synovitis. In cultures of synovial cells from patients with rheumatoid arthritis, blocking TNF-α with antibodies significantly reduced the production of interleukin-1, interleukin-6, interleukin-8, and granulocyte–monocyte colony-stimulating factor.[18] Hence, the blockade of TNF-α may have a more global effect on inflammation than the blockade of other cytokines present in high concentrations in synovial fluids, such as interleukin-1.

The results of studies in animals provide further evidence of the importance of TNF-α in rheumatoid arthritis. In transgenic mice that expressed a deregulated human TNF-α gene, an inflammatory and destructive polyarthritis similar to rheumatoid arthritis spontaneously developed.[22] Pretreatment of these animals with a monoclonal antibody against TNF-α prevented the development of arthritis. Blocking TNF-α with a soluble TNF-receptor fusion protein or with monoclonal antibodies also ameliorated disease activity in mice with type II collagen-induced arthritis.[23,24]

Interleukin-1

Interleukin-1 is a 17-kd protein that is mostly produced by monocytes and macrophages but is also produced by endothelial cells, B cells, and activated T cells.[25] The interleukin-1 signaling system is more complex than the TNF-α system. Interleukin-1 binds to two types of cell-surface receptors.[26,27] Only type I receptors have a cytoplasmic tail and are capable of intracellular signaling.[28] Type II receptors are decoy receptors: they bind circulating interleukin-1 but do not deliver any intracellular signals.[29] The type I receptor is found in low numbers on many cells, whereas the type II receptor is expressed primarily on neutrophils, monocytes, and B cells.[30] Soluble forms of both types of interleukin-1 receptor compete with cell-surface receptors, thereby decreasing interleukin-1–mediated activation of cells. In addition, a naturally occurring antagonist, interleukin-1–receptor antagonist, binds the type I receptor with high affinity without triggering a signal, thus providing another mechanism for the inhibition of interleukin-1 activity.[31] The biologic activity of interleukin-1 is dependent on the precise quantities of many interacting molecules.

Studies of arthritis in animals have strongly implicated interleukin-1 in joint damage. Injection of interleukin-1 into the knee joints of rabbits results in the degradation of cartilage,[32] whereas the injection of antibodies against interleukin-1 ameliorates collagen-induced arthritis in mice and decreases the damage to cartilage.[33] Macrophages in the synovial tissue of patients with rheumatoid arthritis appear to be an important source of interleukin-1.[34] Like TNF-α, interleukin-1 may cause damage by stimulating the release of matrix metalloproteinases from fibroblasts and chondrocytes.[13,35] The concentrations of interleukin-1–receptor antagonist are high in the synovial fluid of patients with rheumatoid arthritis, but not high enough to suppress inflammation.[36]

Interleukin-6

Interleukin-6 is a pleiotropic inflammatory cytokine produced by T cells, monocytes, macrophages, and synovial fibroblasts.[37] Originally identified as a factor that induces the final maturation of B cells into plasma cells, interleukin-6 is involved in diverse biologic processes, such as the activation of T cells, the induction of the acute-phase response, the stimulation of the growth and differentiation of hematopoietic precursor cells, and the proliferation of synovial fibroblasts.[37]

Antiinflammatory Cytokines

Whereas some cytokines initiate and maintain the inflammatory process, others dampen it. The two best-studied antiinflammatory cytokines are interleukin-10 and interleukin-4. In vitro, these cytokines cooperate to inhibit the production of inflammatory cytokines.[38,39]

Interleukin-10

Interleukin-10 is produced by monocytes, macrophages, B cells, and T cells. It inhibits the production of several cytokines, including interleukin-1 and TNF-α, and the proliferation of T cells in vitro.[40] Interleukin-10 can also reverse the cartilage degradation mediated by antigen-stimulated mononuclear cells from patients with rheumatoid arthritis.[38] Although interleukin-10 is found in the synovial fluid of patients with rheumatoid arthritis, the amount may be insufficient to suppress inflammation.[41]

Interleukin-4

Interleukin-4 is produced by CD4+ type 2 helper T cells and participates in the differentiation and growth of B cells.[40] In vitro, interleukin-4 inhibits the activation of type 1 helper T cells, and this, in turn, decreases the production of interleukin-1 and TNF-α and inhibits cartilage damage.[42] Interleukin-4 also inhibits the production of interleukin-6 and interleukin-8.[39] In cultures of synovium samples from patients with rheumatoid arthritis, interleukin-4 inhibited the production of interleukin-1 and increased the expression of interleukin-1–receptor antagonist, both of which actions should decrease inflammation.[36]

Joint Damage in Rheumatoid Arthritis

Rheumatoid arthritis is characterized by progressive joint damage that is mediated by several mechanisms (Fig. 1 and 2). Early erosion of cartilage and bone is associated with the formation of a proliferating pannus. The interface between pannus and cartilage is occupied predominantly by activated macrophages and synovial fibroblasts that express matrix metalloproteinases and cathepsins.

Interleukin-1 and TNF-α stimulate the expression of adhesion molecules on endothelial cells and increase the recruitment of neutrophils into the joints. Neutrophils release elastase and proteases, which degrade proteoglycan in the superficial layer of cartilage.[43] The depletion of proteoglycan enables immune complexes to precipitate in the superficial layer of collagens and exposes chondrocytes.[44] Chondrocytes and synovial fibroblasts release matrix metalloproteinases when stimulated by interleukin-1, TNF-α, or activated CD4+ T cells. Matrix metalloproteinases, in particular stromelysin and collagenases, are enzymes that degrade connective-tissue matrix and are thought to be the main mediators of joint damage in rheumatoid arthritis. In animals, activated CD4+ T cells stimulate osteoclastogenesis, and they may cause joint damage independently of interleukin-1 and TNF-α in patients with rheumatoid arthritis.

Summary

Rheumatoid arthritis is initiated by CD4+ T cells, which amplify the immune response by stimulating other mononuclear cells, synovial fibroblasts, chondrocytes, and osteoclasts. The release of cytokines, especially TNF-α, interleukin-1, and interleukin-6, causes synovial inflammation. Joint damage results from the degradation of connective tissue by matrix metalloproteinases and the stimulation of osteoclastogenesis by activated CD4+ T cells. Clearly, there are many possible therapeutic targets, but the inhibition of cytokines would seem to offer an especially useful approach to suppressing inflammation and preventing joint damage.

INHIBITION OF CYTOKINES

Given the complexity of cytokine interactions and the multiplicity of cytokine targets, the effectiveness and toxicity of cytokine-based interventions are difficult to predict. A variety of cytokine-based strategies are being explored for the treatment of inflammatory diseases. These include the neutralization of cytokines (by soluble receptors or monoclonal antibodies), receptor blockade, and the activation of antiinflammatory pathways by bioengineered versions of immunoregulatory cytokines (Fig. 3).

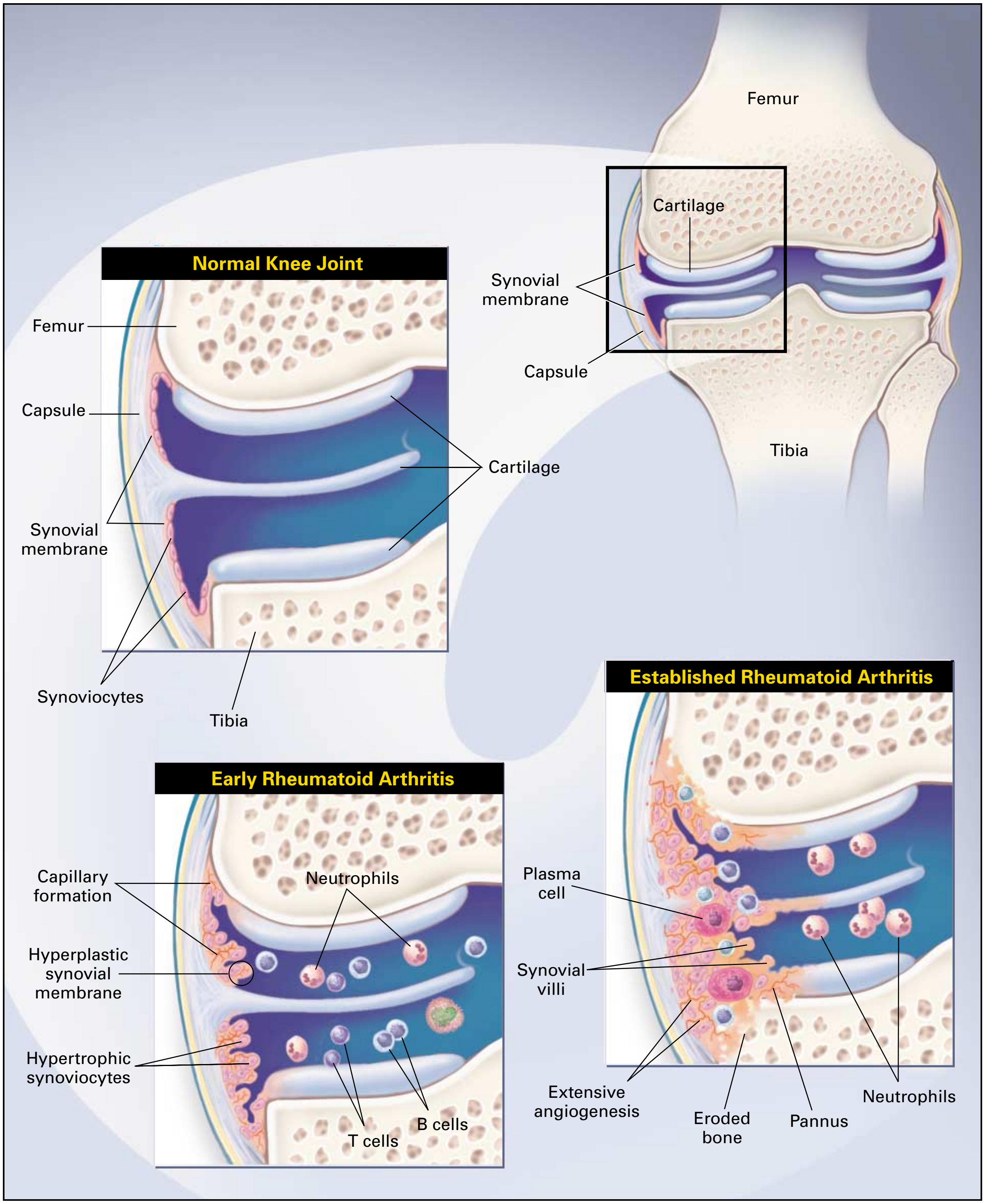
Neutralization of Cytokines

Soluble receptors have a physiologic role in neutralizing many cytokines, as exemplified by soluble TNF receptors. TNF-α binds to TNF receptors on the surface of many cells, including monocytes, macrophages, T cells, synovial fibroblasts, osteoblasts, and endothelial cells. There are two types of TNF receptors, p55 and p75, which are part of a large family of structurally related cell-surface receptors.[45,46] The cytoplasmic domains of the p55 and p75 receptors are quite different,[47] suggesting that they may activate different signal-transduction pathways. The p75 receptor is believed to have a primary role in stimulating the proliferation of T cells and in suppressing TNF-α–mediated inflammatory responses, whereas the p55 receptor appears to be critical in triggering host defense and inflammatory responses.[48,49]

Soluble forms of both p55 and p75 are part of a feedback loop that can modulate the inflammatory action of TNF-α. The transmembrane domain of both TNF receptors is susceptible to lysis by proteases, including TNF-α–converting enzyme, leading to the release of a soluble form of the receptor. Hence, both types of receptor are present in body fluids. Soluble TNF receptors are found in high concentrations in

Figure 2 (facing page). Pathogenesis of Rheumatoid Arthritis.

In the normal knee joint, the synovium consists of a synovial membrane (usually one or two cells thick) and underlying loose connective tissue. Synovial-lining cells are designated type A (macrophage-like synoviocytes) or type B (fibroblast-like synoviocytes). In early rheumatoid arthritis, the synovial membrane becomes thickened because of hyperplasia and hypertrophy of the synovial-lining cells. An extensive network of new blood vessels is formed in the synovium. T cells (predominantly CD4+) and B cells (some of which become plasma cells) infiltrate the synovial membrane. These cells are also found in the synovial fluid, along with large numbers of neutrophils. In the early stages of rheumatoid arthritis, the synovial membrane begins to invade the cartilage. In established rheumatoid arthritis, the synovial membrane becomes transformed into inflammatory tissue, the pannus. This tissue invades and destroys adjacent cartilage and bone. The pannus consists of both type A and type B synoviocytes and plasma cells.


Femur
Cartilage
Synovial membrane
Capsule
Tibia
Normal Knee Joint
Femur
Capsule
Synovial membrane
Cartilage
Synoviocytes
Tibia
Early Rheumatoid Arthritis
Capillary formation
Neutrophils
Hyperplastic synovial membrane
Hypertrophic synoviocytes
T cells
B cells
Established Rheumatoid Arthritis
Plasma cell
Synovial villi
Extensive angiogenesis
Eroded bone
Pannus
Neutrophils

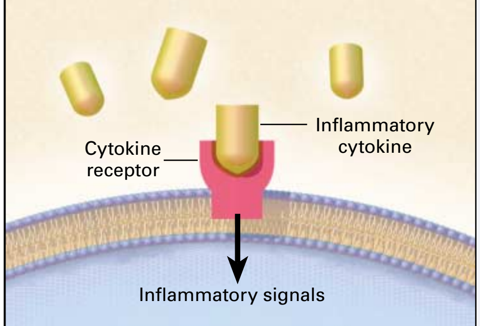
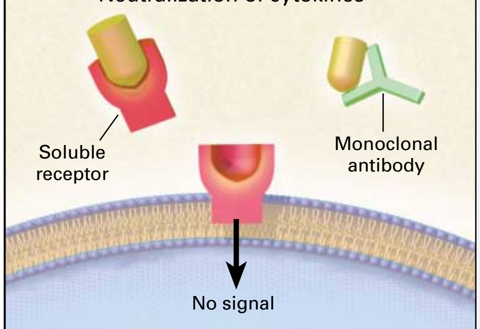
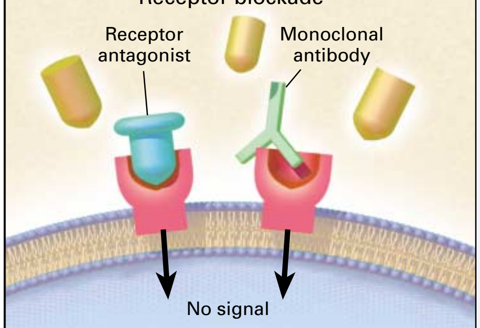
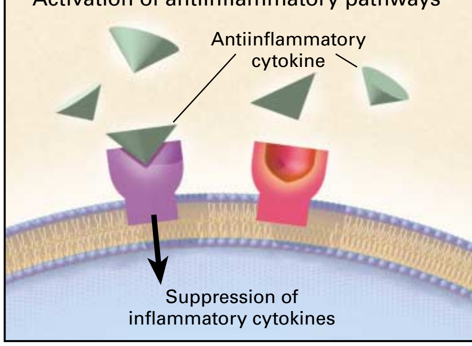
Cytokine–Receptor Interaction	Description	Examples
Normal interaction 	Binding of an inflammatory cytokine to its receptor leads to the production of inflammatory effector molecules.	Tumor necrosis factor α, interleukin-1, and interleukin-6
Neutralization of cytokines 	The cytokine is prevented from binding to its cell-surface receptor by soluble receptor, natural antagonists, or monoclonal antibody.	Soluble tumor necrosis factor–receptor fusion proteins (etanercept), soluble interleukin-1 receptor, monoclonal antibody against tumor necrosis factor (infliximab, D2E7, nerelimomab), and monoclonal antibody against interleukin-6
Receptor blockade 	The cytokine is unable to bind its receptor because of interactions with a receptor antagonist or a monoclonal antibody against the cytokine receptor.	Recombinant interleukin-1–receptor antagonist and monoclonal antibody against interleukin-6 receptor
Activation of antiinflammatory pathways 	Antiinflammatory cytokines inhibit the expression of inflammatory cytokine.	Interleukin-4 and interleukin-10

Figure 3. Methods of Blocking the Activity of an Inflammatory Cytokine.

the synovial fluid and serum of patients with rheumatoid arthritis.[50] Nevertheless, an excess of TNF-α relative to the concentration of soluble TNF receptors prolongs joint inflammation.

Treating patients with recombinant soluble cytokine receptors may help suppress inflammation. However, soluble receptors have short plasma half-lives, and repeated doses would be required to neutralize the effects of inflammatory cytokines. This limitation can be circumvented by conjugating soluble receptors with human Fc (a proteolytic fragment of IgG), which can extend the half-lives of these molecules to approximate those of immunoglobulin.[51] Another alternative is to polymerize TNF receptor or anti–TNF-α Fab′ with polyethylene glycol. This can reduce antigenicity and prolong the half-life in circulation. The efficacy of these constructs in patients with rheumatoid arthritis is currently being investigated.

Antibodies against cytokines are another approach to neutralizing cytokines. The type of antibody appears to be critical to its clinical efficacy. Murine monoclonal antibodies are antigenic and induce the production of antimouse antibodies in recipients.[52] Chimeric and humanized monoclonal antibodies are less immunogenic than murine monoclonal antibodies, and they are therefore more suitable as therapeutic agents.[53]

Receptor Antagonism

Blocking the ability of a receptor to bind its cytokine is another strategy to interrupt signal transduction. This can be accomplished with either natural receptor antagonists, such as interleukin-1–receptor antagonist, or antibodies against cytokine receptors. For such an approach to be successful, the amount of antagonist must be large enough to bind the majority of receptors for long periods.

Activation of Antiinflammatory Pathways

In addition to natural cytokine antagonists and soluble receptors, immunoregulatory cytokines such as interleukin-10 and interleukin-4 can suppress inflammation.[39,40,42] As is true for most cytokines, however, their effects are pleiotropic and not fully understood. For instance, the treatment of synovial-fluid macrophages with exogenous interleukin-10 increased the expression of cell-surface and soluble TNF receptors, an effect that could make cells more responsive to TNF-α and its inflammatory effects.[54] Furthermore, because cytokines are low-molecular-weight proteins or glycoproteins with short half-lives, maintaining therapeutic serum concentrations of antiinflammatory cytokines may be difficult and expensive. A potential solution would be to use gene therapy that would lead to continued synthesis of therapeutic antiinflammatory cytokines in the joints. In animal models of rheumatoid arthritis, the genes for interleukin-10 and interleukin-4 have been transfected by viral vectors into synovial fibroblasts in vitro. These fibroblasts were subsequently injected back into the joints, where they released the antiinflammatory cytokine, resulting in the suppression of inflammation and destruction of joints.[55,56]

CLINICAL TRIALS OF CYTOKINE INHIBITORS

Soluble Human Cytokine-Receptor Proteins

Etanercept

Etanercept is a fusion protein made up of two recombinant p75 soluble TNF receptors fused with the Fc portion of human IgG1. The dimeric structure of etanercept makes it approximately 1000 times as efficient as the monomeric soluble p75 TNF receptor at neutralizing TNF-α.[57]

In two placebo-controlled trials of 168 and 234 patients with rheumatoid arthritis, twice weekly subcutaneous injections of 25 mg of etanercept[58,59] resulted in significant improvement. The number of swollen joints decreased by approximately 50 percent from base line after six months of treatment.[58] Treatment with etanercept was well tolerated, and produced only minor reactions at the site of the injection. Synovial biopsies showed a statistically significant decrease in the numbers of T cells and plasma cells and in the amount of vascular-cell adhesion molecule 1 and the expression of interleukin-1 after one month of treatment.[60] Long-term, open-label studies have indicated that the efficacy of continued treatment with etanercept is sustained for at least 33 months, and no major adverse events have occurred.[61] Furthermore, the combination of etanercept and methotrexate was significantly more effective than methotrexate alone in a placebo-controlled trial of 89 patients with rheumatoid arthritis who had had a partial response to methotrexate.[62]

Etanercept is also effective in patients with juvenile rheumatoid arthritis.[63] In a randomized, placebo-controlled trial of 51 patients with juvenile polyarticular rheumatoid arthritis, 0.4 mg of etanercept per kilogram of body weight or placebo was injected subcutaneously twice weekly for four months or until a flare of the disease occurred. The total number of joints with active arthritis decreased by 58 percent from base line, and the range of motion of affected joints was increased by 80 percent.

In other studies, etanercept was better tolerated and more effective than methotrexate in patients with early rheumatoid arthritis.[64] There was less radiographic evidence of progression of rheumatoid arthritis in patients who were receiving etanercept than in patients who were receiving methotrexate.[64]

Monoclonal Antibodies against Cytokines

Infliximab

Infliximab is a chimeric IgG1 antibody against TNF-α. In a double-blind, placebo-controlled trial of 73 patients with rheumatoid arthritis, a single intravenous dose of 10 mg of infliximab per kilogram rapidly reduced the number of swollen joints as well as the serum concentration of C-reactive protein.[65] Clinically significant improvement was evident within a week after treatment was begun. Synovial-biopsy specimens, obtained before and four weeks after the beginning of treatment, showed significant reductions in the number of T cells and in the tissue content of vascular-cell adhesion molecule 1 and E-selectin.[66]

In another randomized, placebo-controlled trial of 101 patients with rheumatoid arthritis,[67] infliximab or placebo was given repeatedly, with or without methotrexate. Antibodies against infliximab developed in many patients after repeated treatment, but the incidence was reduced by concomitant treatment with methotrexate. Furthermore, a dose of 3 mg of infliximab per kilogram in combination with methotrexate was as efficacious as a dose of 10 mg per kilogram, with or without methotrexate. This finding was confirmed in a randomized, placebo-controlled trial of 428 patients with rheumatoid arthritis, in which the infliximab-treated patients had sustained clinical improvement for at least 30 weeks.[68]

Other Antibodies against TNF-α

D2E7 is a human antibody against TNF-α generated by phage-display technology,[69] whereas nerelimomab is a humanized monoclonal antibody against TNF-α that consists of the hypervariable regions of a murine monoclonal antibody against TNF-α grafted onto a human κ light chain and an IgG4 heavy chain.[70] Both these antibodies were effective in preliminary randomized, placebo-controlled trials in patients with rheumatoid arthritis.[69,70]

Cytokine-Receptor Blockers

Recombinant Interleukin-1–Receptor Antagonist

In a randomized, double-blind, placebo-controlled trial of 472 patients with rheumatoid arthritis, treatment with recombinant human interleukin-1–receptor antagonist[71] resulted in moderate clinical improvement and decreased the rate of progression of erosions, as assessed by radiography.[72] Reactions at the injection site were the most common adverse event. Recombinant human interleukin-1–receptor antagonist is currently being tested in combination with methotrexate.

A drawback to the therapeutic use of interleukin-1–receptor antagonist is its short (six-hour) half-life in plasma,[73] which necessitates frequent daily treatment with high doses to maintain a therapeutic effect. This problem is further compounded by the need for a large (10- to 1000-fold) excess of interleukin-1–receptor antagonist to block the effect of interleukin-1 in vitro and in vivo.[74] One way to circumvent these problems and achieve high local concentrations of interleukin-1–receptor antagonist may be by the use of gene therapy.[75] In animals, synovial fibroblasts transfected with the gene for human interleukin-1–receptor antagonist and then reinjected into joints produced interleukin-1–receptor antagonist in the synovium, with consequent clinical improvement.[76] A similar ex vivo gene-transfer strategy was used to introduce the gene for the interleukin-1–receptor antagonist into the joints of three patients with rheumatoid arthritis before they underwent total joint replacement. Subsequent removal and analysis of joint tissue indicated that this technique induced the intraarticular expression of the gene for the interleukin-1–receptor antagonist.[75]

Antibody against Interleukin-6 Receptor

An antibody against the receptor for interleukin-6 has shown efficacy in mice with collagen-induced arthritis.[77] A clinical trial of a humanized monoclonal antibody against the interleukin-6 receptor, which is theorized to have the same functional consequences as a monoclonal antibody against interleukin-6, is currently under way.

Recombinant Interleukin-10 and Interleukin-4

Recombinant interleukin-10[78] and interleukin-4[79] have been tested in patients with rheumatoid arthritis. The clinical efficacy of the treatments has been disappointing; the lack of efficacy may be due to the short half-life of these substances.

CONCLUSIONS

Although the cause of rheumatoid arthritis still eludes us, our improved understanding of the pathogenesis of the disease has opened the door to innovative therapies. By targeting molecules that are directly involved in the pathogenesis of rheumatoid arthritis, these therapies may be more efficacious and specific and less toxic in the short and long term than standard therapies. Radiologic evidence suggests that these new therapies, such as anticytokine therapy, may slow disease progression. Finally, the success of anticytokine therapy will also provide valuable insights into the initiation and progression of rheumatoid arthritis.

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