An update on the cytokine network in rheumatoid arthritis

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Purpose of review

To update the knowledge accumulated on the contribution of cytokines to rheumatoid arthritis and related animal models. Publications from the end of 2002 and 2003 period were analyzed for a selection.

Recent findings

A better understanding of the clinical results with tumor necrosis factor-α inhibitors has come from studies in treated patients. The expected effect of infliximab on the apoptosis of cells expressing tumor necrosis factor-α was not observed in synovium biopsy specimens. The mode of action of tumor necrosis factor-α on bone destruction has been clarified in gene-defective mice. Tumor necrosis factor-α acts through osteoclasts–an effect that is inhibited with osteoprotegerin. New interleukin-1 inhibitors with a potential for increased efficacy, such as interleukin-1trap, have been manufactured and are now being tested in rheumatoid arthritis. The list of cytokines of interest for therapeutic intervention has been growing rapidly. The results with animal models have provided clues to control arthritis with natural interleukin-18 inhibitors, such as interleukin-18 BP. Additional results have been accumulated that indicate the contribution of T cell subsets in inflammation and destruction through the production of interleukin-17. Synergistic interactions with other cytokines are critical in the interleukin-17 tuning effects. Macrophage inhibitory factor was described many years ago. Its comeback is based on properties of synoviocyte activation and proliferation.

Summary

Such findings are critical for a better understanding of response heterogeneity in patients treated with the cytokine inhibitors now on the market. New therapeutic approaches are been planned from these results.

Keywords

rheumatoid arthritis, inflammation, destruction, cytokines, treatment

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Abbreviations

IFN	interferon
IL	interleukin
MIF	migration inhibitory factor
MMP	matrix metalloproteinases
RA	rheumatoid arthritis
TLR	toll-like receptor
TNF	tumor necrosis factor

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Introduction

In recent years, a large body of results has clearly indicated that cytokines contribute to joint diseases [1••]. The role of cytokines in chronic inflammation has been clarified with clinical results obtained with inhibitors. From early results obtained in rheumatoid arthritis (RA), more recent studies have shown that the same cytokines are also involved in other types of arthritis, such as ankylosing spondylitis, and in many inflammatory diseases. The nonspecific effect of cytokines is indicated because the same findings have been obtained in diseases with different anatomic localizations.

However, the situation is far from being completely understood. Additional mechanisms have been identified to explain the efficacy and failures as well as the side effects. Some 20 years ago, the picture could be simplified with the identification of only two major cytokines, tumor necrosis factor (TNF)-α and interleukin (IL)-1, in the understanding of chronic inflammation. Today the list of cytokines, chemokines, and other factors reaches more than 100, making the choice of which one to target more difficult. At the same time, it remains to be understood how the inhibition of a single cytokine can still be clinically effective.

Here we will review the literature on the cytokine network in RA and related models published during the last part of 2002 and 2003. We will focus first on novel understandings obtained from clinical results with TNF-α and IL-1 inhibitors. Then we will consider cytokines, which could also become treatment targets.

Effects of tumor necrosis factor-α, interleukin-1 inhibitors, and interleukin-6 inhibitors

Clinical results with tumor necrosis factor-α inhibitors

The mode of action of infliximab, a chimeric monoclonal antibody, could differ from that of etanercept, a soluble p75 TNF-α receptor. It was suggested that monoclonal antibodies could recognize membrane-bound TNF-α, leading to the destruction of the TNF-α–expressing cells through classic pathway complement activation. This would not be the case with etanercept, able to bind only soluble TNF-α. However, when synovial biopsy specimens were compared before and at day 28 of infliximab treatment, an increase in the number of apoptotic cells defined with the TUNEL assay could not be detected. Examination showed a reduced number of cells in the biopsy specimens from treated patients, indicating an effect on cell migration [2•].

Various cytokines have been shown to amplify the production of TNF-α. Among these, IL-7 is a cytokine produced by synoviocytes, which was found to stimulate TNF-α production by synovial fluid mononuclear cells and very potently that of IFN-γ and TNF-α by synovial fluid CD4+ T cells [3•].

The mode of action of TNF-α on joint destruction has been clarified using transgenic mice that express human TNF-α. In this model, mice have a severe and destructive arthritis. They were crossed with c-fos–deficient mice, which completely lack osteoclasts and thus have osteopetrosis. In the resulting mutant mice, a TNF-α–dependent arthritis developed in the absence of osteoclasts. However, despite the presence of severe inflammatory changes, these mice were fully protected against bone destruction. These results indicate that TNF-α–dependent bone erosion is mediated by osteoclasts. Therefore, in addition to the use of anti-inflammatory therapies targeting cytokines, osteoclast inhibition could be beneficial for RA treatment [4••]. Indeed, treatment of human TNF-α transgenic mice with osteoprotegerin completely blocked TNF-α–mediated bone loss by increasing bone mineral density and bone volume. Moreover, bone formation was dramatically increased [5•].

Improvement of interleukin-1 inhibitors

Whereas the result with TNF-α inhibitors are in line with those obtained in animal models, the results with IL-1 inhibition have showed rather inferior effects. It was suggested that the lower effects of IL-1Ra in the clinic could be explained by its short half-life *in vivo* and by the need for a permanent presence of IL-1Ra in the circulation at high concentrations. Among other ways to inhibit IL-1 with endogenous inhibitors, soluble IL-1 receptors could be of interest. This applies not so much to the type I receptor as to the type II IL-1 receptor. The type I membrane-bound receptor is able to transduce the IL-1 driven signal, whereas the type II does not do so but is released as a soluble form, acting as a natural inhibitor. To lead to signal activation and transduction, the type I membrane receptor needs to be associated with the IL-1 receptor accessory protein. Such an association is not observed with IL-1Ra, explaining its lack of agonistic effect. On the basis of these findings, the administration of the sIL-1 receptor accessory protein showed a positive protective effect on joint destruction in the collagen arthritis model. To go further, a combination of both the soluble type I IL-1R and the sIL-1AcP led to the production of an IL-1 trap [6•]. Such a complex showed an increased affinity for IL-1. Its use in the collagen arthritis model led to a protective effect [7••]. It remains to be seen whether this complex will show the same efficacy in RA trials.

The IL-1Ra, as used as a treatment today, is a member of a growing family of endogenous IL-1 inhibitors. In particular, various intracellular forms of IL-1Ra have been isolated. These variants can still have a regulatory effect directly inside the cell, without interaction at the level of the membrane IL-1 receptor. Such a regulatory effect was indicated when mice transgenic for the intracellular IL-1Ra type I were protected from collagen-induced arthritis [8•].

In the spontaneous inflammatory arthritis of K/BxN T cell receptor transgenic mice, the effector phase of the disease is induced by anti–glucose 6 phosphate isomerase antibodies. It should be mentioned that the applications of these new concepts to human RA might be difficult because the same pathogenic antibodies in the mouse were not observed in various series of human RA [9•]. The roles of TNF-α and IL-1 have been evaluated by transferring arthrogenic serum into a panel of genetically deficient mice [10•]. To get the severe destructive arthritis, IL-1 proved to be absolutely necessary. TNF-α was also required, but less than IL-1, because disease developed in some of the TNF-α–deficient mice. However, there was no evidence of a role for TNF-α in bone destruction.

The administration of a toll-like receptor (TLR)-4 ligand, lipopolysaccharide, combined with arthrogenic serum (defined above) in IL-1 receptor-deficient mice resulted in acute joint swelling, but not in MyD88-deficient mice. Benign arthritis was observed in TLR-4 mutant mice [11•]. These results indicated the contribution of innate immunity via TLR-4. Because MyD88 is a common pathway for IL-1 and TLR-4 signaling, TLR-4 pathway may bypass the direct contribution of IL-1 in chronic joint inflammation.

Interleukin-1 is a critical factor for the activation of matrix metalloproteinases (MMP) in cartilage. Bcl-3 is a

member of the NF-kB family and a known regulator of NF-kB. It appears to be critical in the IL-1-induced MMP-1 transcription in chondrocytes, through an interaction with NF-kB [12]. ESE-1 is another transcription factor expressed in RA synovium. It is specifically induced in synovial fibroblasts, chondrocytes, osteoblasts, and monocytes/macrophages by IL-1β, TNF-α, or LPS. This induction is related to the translocation of the NF-kB family members p50 and p65 to the nucleus and the transactivation of the ESE-1 promoter via a high-affinity NF-kB binding site [13].

Synovium in RA is associated with neoangiogenesis, as observed in tumor growth and invasiveness. Using various IL-1 deficient mice, it was observed that IL-1-β and, to a lesser extent, IL-1-α, were required for *in vivo* angiogenesis and invasiveness of different tumor cells. Conversely, these effects were reduced with IL-1Ra [14••].

Interleukin-6 inhibition

More recently, IL-6 has been the target of RA treatment with an anti-IL-6 receptor antibody. Such treatment reduced VEGF production in RA patient serum. IL-6 acted synergistically with IL-1-β or TNF-α to induce VEGF production by RA synoviocytes. Such synergy with IL-1-β or TNF-α may be the mechanism by which IL-6 blockade effectively suppresses VEGF production in synovial fibroblasts [15].

More cytokines as therapeutic targets

Interleukin-17

Interleukin-17 is a T cell cytokine produced in the context of RA synovium. Although its effects alone are rather limited, IL-17 appears to be a potent actor in joint inflammation and destruction through additive and synergistic interactions with other proinflammatory cytokines [16•]. Such enhancing effects have been demonstrated mainly for TNF-α and IL-1. In addition, IL-17 increases IL-1 and TNF-α production by monocytes. Conversely, IL-17 production was found to be increased by monocyte products such as the new IL-23 [17•]. Accordingly, T cells through the production of IL-17 may regulate the proinflammatory status.

The production of IL-17 from activated T cells is required for the spontaneous development of destructive arthritis in mice deficient in IL-1Ra [18•]. IL-17 is part of the T cell–derived cytokines other than RANKL such as granulocyte-macrophage colony-stimulating factor and IFN-γ, which have powerful regulatory effects on osteoclastogenesis [19••].

Previously, IL-17 was shown to be a nitric oxide-producing cytokine. Such an effect leads to an inhibitory effect on proteoglycan synthesis [20]. In synoviocytes, IL-17 showed additive effects with IL-1-β and TNF-α on the expression of TSG-6, a hyaluronan-binding protein [21].

T cells regulate the expression of MMPs in human osteoblasts, including MMP-13. Under conditions of chronic inflammation, multiple T cell cytokines, including IL-17, synergize to induce high levels of MMP-13 via a mechanism that is dependent on activated p38 MAP kinase and is suppressed by activated ERK-1/2 [22].

Interleukin-18

IL-18 is one of the major cytokines, which induce a Th1 profile. Its effect is mediated by IL-12. Stimulation with IL-12 induces the β chain of the IL-18 receptor. This makes functional the IL-18 receptor, which is composed of the constitutive α chain and the regulated β chain. On mononuclear synovium cells, both receptors are expressed. Synoviocytes do not respond to IL-18 because the β chain is not expressed and cannot be induced by IL-12 [23•]. In RA synovium, expression of IL-18 has been associated with an increased expression of TNFα and IL-1, indicating the link between IL-18 and inflammation [24•]. IL-18 was found to be a chemoattractant for T cells and RA synovial CD4+ T cells responded to IL-18 by adopting a polarized morphology. Injection of IL-18 into mouse footpad led to the local accumulation of inflammatory cells [25•].

Such results suggest the control of IL-18 as treatment of joint inflammation. The high levels of IL-18 expression in RA joints are in contrast with the reduced IL-18 expression in RA peripheral blood mononuclear cells. Such low levels were increased by treatment with steroids [26].

The action of IL-18 is regulated by the endogenous release of IL-18BP, which binds to IL-18 with a high affinity as a decoy receptor. Intra-articular over-expression of IL-18BP significantly reduced incidence of collagen-induced arthritis in treated knee joints. Affected knee joints of IL-18BP-treated mice showed less severe arthritis, characterized by a reduction of inflammation and destruction of bone and cartilage. Local intra-articular IL-18BP treatment in both knees provided additional protection against CIA incidence and severity in distal paws, suggesting a systemic effect [27••]. Treatment of human synoviocytes with IFNγ increased IL-18BP, indicating a negative feedback loop via IL-18BP, which may limit IL-18 biologic activity in arthritis [28].

New interleukin-12 family members

IL-12 has been characterized as a major cytokine leading to the Th1 pathway at least in part through the production of IFNγ by T cells and NK cells. IL-18 acts in synergy with Il-12 to further increase such effects. Additional members of the IL-12 family can also contribute. IL-12 is composed of two subunits p35 and p40 whereas

the new IL-23 is made of the same p40 subunit combined with a new p19 subunit. It appears that IL-23 is in fact the key cytokine for the IL-12 effect. This was first shown for animal models of brain inflammation [29••]. Specific IL-23 inhibitors were able to reduce brain inflammation first thought to be related to an IL-12 effect. This case of mistaken identity appears to result from the use of inhibitors acting both on IL-12 and IL-23. As indicated above, IL-23 has been characterized as a potent inducer of IL-17 production by CD4 T cells [17•].

Macrophage migration inhibitory factor

Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine that may be of critical importance in the pathogenesis of RA [30••]. In particular, MIF may regulate RA synovial hyperplasia by acting on synoviocytes directly and via an involvement in the effects of IL-1β and TNFα. In addition, the effects of MIF on synoviocyte activation are independent of NF-kB, and dependent on ERK MAP kinase [31]. In MIF knockout mice, synoviocyte proliferation was decreased. The decrease in the severity of antigen-induced arthritis was associated with an increase in p53 expression and apoptosis in synovium without an obvious effect on proliferation. These results indicate a role for MIF in the regulation of p53 expression and p53-mediated events in the inflamed synovium [32]. These data suggest an important therapeutic potential for MIF antagonism in RA.

Such a link with joint inflammation has been linked to MIF gene heterogeneity. In patients with systemic-onset juvenile idiopathic arthritis, the -173 single-nucleotide G-to-C polymorphism of the MIF gene was associated with higher levels of MIF in serum and synovial fluid and moreover with a poor outcome [33].

Conclusion

Inhibition of cytokines has led to an important step in the treatment of chronic inflammation. Their nonspecific effects, once considered to be a limitation, allowed the use of the same inhibitors in different diseases. Today their mode of action, as well as that of their inhibitors, remains to be clarified to explain heterogeneity in patient response and tolerance. The identification of new therapeutic targets research may allow better understanding and treatment of these complex diseases.

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