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CYTOKINE NETWORK AND ITS MANIPULATION IN RHEUMATOID ARTHRITIS

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ABSTRACT: Studies of inflammatory process in the inflamed synovium in rheumatoid arthritis (RA) have shown an intricate network of molecules involved in its initiation, perpetuation and regulation that balance the pro- and anti-inflammatory processes. This system is self-regulating through the action of anti-inflammatory and pro-inflammatory cytokines, cytokine receptor antagonists, and naturally occurring antibodies to cytokines. Inflammatory synovitis in RA appears to be the result of an imbalance in the cytokine network with either an excess production of pro-inflammatory cytokines or from inadequacy of the natural anti-inflammatory mechanisms. Using this knowledge the newer therapeutic approaches to RA and other inflammatory arthritides are being aimed at correcting this imbalance. Three most promising products appear to be the use of monoclonal antibodies to tumor necrosis factor-α (TNF-α), soluble TNF-α receptors, and interleukin-1 receptor antagonist. Other promising therapeutic agents that could regulate the cytokine network are in various stages of laboratory and clinical evaluation. These studies promise to yield therapeutic targets that could dramatically change the way inflammatory diseases would be treated in future.

Introduction :

Joint damage in rheumatoid arthritis (RA) is mediated through immunological mechanisms. However, for decades, the exact steps involved in the initiation and perpetuation of synovial inflammation and bone erosion remained a mystery. The subject has been extensively reviewed[1-11]. The application of molecular biology techniques to design monoclonal antibodies, soluble receptors, or receptor antagonists as therapeutic biologic agents made it possible to regulate the cytokine signals for the treatment of the diseases refractory to conventional therapies. A number of studies have looked at the levels of various cytokines in human synovial fluid and peripheral blood and production of these cytokines by the peripheral blood mononuclear cells. Animal models of RA have given a more in-depth insight into the effects of cytokines and cytokine blockade. The unifying observation of all these studies is that there is dysregulation of immune response and an abnormal cytokine profile in RA.

The basic pathology in the synovium of RA is hyperplasia, increased vascularity, and inflammatory cells infiltrate. The principal cells amongst these infiltrate are CD4+ T lymphocytes[8]. CD4+ T cells and other cells from the synovial membrane; synovial cells, other lymphocytes, macrophages, and fibroblasts, release a large number of cytokines with variable, sometimes synergistic, overlapping or antagonistic, effects[8,9]. However, for the sake of simplicity and better understanding, these can be differentiated into two groups on the basis of their action. The first group is pro-inflammatory (Table 1), including interleukin 1 (IL-1), tumor necrosis factor alpha (TNF-α), IL-8, IL-12, IL-15, IL-17, and IL-18. The second group, anti-inflammatory cytokines, is represented by soluble factors that down-modulate inflammation, namely IL-4, IL-10, IL-11, and IL-13, and soluble proteins, such as IL-1 receptor antagonist (IL-1Ra), soluble receptors for TNF and IL-1, and IL-18 binding protein. Certain cytokines like IL-6, interferon gamma (IFN-γ) and TGF β have

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Table 1: Pro-inflammatory and anti-inflammatory cytokines in the RA joint:

Pro-inflammatory cytokines	Anti-inflammatory cytokines
TNF-α, IL-1, IL-8, IFN-γ, IL-2, IL-12, IL-15, IL-17, IL-18	IL-4, IL-10, IL-13, IL-1Ra, IL-18BP, soluble TNF-receptor.

got bivalent activities[6-8]. An imbalance between pro- and anti-inflammatory cytokines is believed to play an important role in disease severity and joint damage in RA.

Cytokines are small peptides that mediate several fundamental biological processes like; inflammation, tissue repair, cell growth, fibrosis, angiogenesis and immune response. Any cell of the body upon activation can produce these peptides. Majority of these cytokines act locally (IL-6 is an exception, acts systemically) and mediate their intracellular signaling by binding to the high affinity receptors present on the cell membrane[9]. Naturally occurring cytokine inhibitors tightly regulate action of cytokines. There are many families of cytokines. Over one hundred molecules have already been identified and many more are in the process of being identified.

Role of cytokines in inflammation:

One of the earliest reports established that RA synovial cultures released more IL-1 than osteoarthritis synovial cultures[1]. However, the issue appeared complicated because many other cytokines were also up regulated in actively inflamed joints. By using monoclonal antibodies against a battery of key cytokines such as TNF-α, dramatic suppression of the production of IL-1 was demonstrated[1]. This observation was the first step towards understanding the coordinately regulated production of cytokines involved in causing inflammation in RA joint. Further studies established that suppression of TNF-α not only down regulated IL-1 production but also several other cytokines like granulocyte macrophage colony stimulating factor (GM-CSF), IL-6, and IL-9[2-4].

Cytokine imbalance in inflammation:

In the synovium of the inflamed joints there is a cytokine imbalance between the pro-inflammatory and the anti-inflammatory cytokines.

T cells are believed to play a key role in orchestrating the inflammatory response of the disease through the production of cytokines with different properties[6-8,10]. Interestingly, the CD4 + T-helper (Th) lymphocytes have two main phenotypes characterized by two distinct cytokine profiles namely Th1 and Th2 subsets (Table –2). A third subset called Th-0 appears to be the progenitor of these two subsets. Its cytokine profile is intermediate. Thus, the Th1 cells predominantly mediate the cell-mediated immune response (CMI) while the Th2 cells mediated the humoral immune response. This commitment is to a large extent driven by the cytokines present in the microenvironment during the phase of T cell activation. This key step will determine whether the acquired immune response is dominated by macrophage activation, cell-mediated immune response and pro-inflammatory activity or humoral immune response and anti-inflammatory activity. T cells stimulated in presence of TNF-α, IFN-γ and IL-12 develop into Th1 type of phenotype whereas those stimulated in presence of IL4, IL-10 and IL-6 develop into Th2 phenotype[6,8]. In RA, there is predominance of Th1 type of cytokine profile however; detection of IL-6 and IL-10 in the synovial compartment suggests a role of Th2 cytokines in the pathogenesis of RA as well.

Table 2: The phenotypes of T –helper cells (Th), their cytokine profiles and their biological action

Th phenotypes	Cytokine profiles	Action
Th1 lymphocytes	IFN-γ, IL-2, IL-12, 15, 17, 18, 23	Pro-inflammatory
Th2 lymphocytes	IL-4, IL-5, IL-10, IL-13	Anti-inflammatory

Among the various cytokines IL-1 and TNF- α have been characterized as the major pro-inflammatory cytokines in the inflamed joint in rheumatoid arthritis. They have overlapping actions including local inflammation, enhancing adhesive properties of the inflammatory cells, causing angiogenesis, and bone resorption[5-9]. Both of these cytokines are mainly

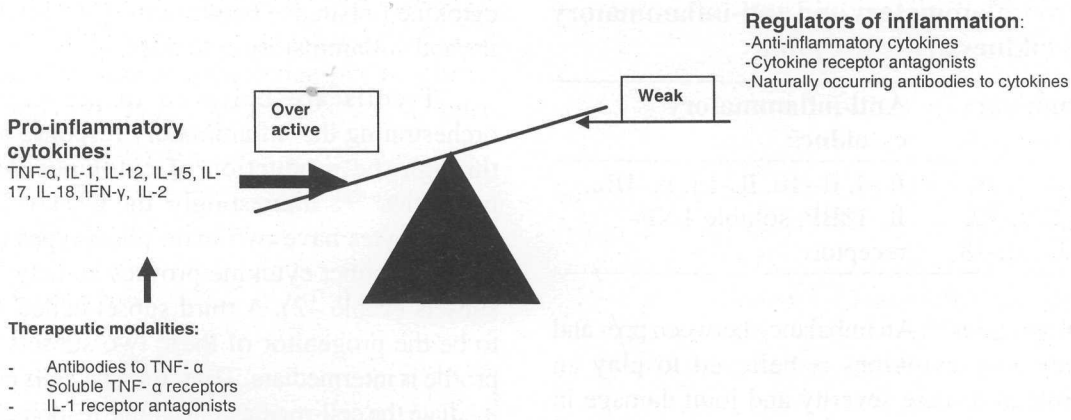

Figure 1 diagrammatically depicts the pro-inflammatory and regulatory cytokines in the inflamed synovium in RA along with some possible therapeutic targets.

produced by monocyte-macrophage lineage of cells. IL-1 is also produced by B cells, endothelial cells, activated T cells. These have been therefore the major targets for therapeutic manipulation. The mechanism of action of TNF-α on bone destruction has been clarified in animal model of mice transgenic for human TNF-α. These mice develop severe destructive joint disease. When these mice were crossed with *c-fos* deficient mice (mice that lack osteoclasts), the resultant progeny did not develop bone destruction despite developing arthritis and presence of severe inflammatory infiltrate in the joints[12,13]. In another strategy, treatment of TNF-α transgenic mice with osteoprotegrin completely blocked the bone loss[14]. Thus it is clear that TNF-α mediated bone erosion is dependent upon osteoclasts and osteoclast inhibition has a therapeutic potential in the management of RA.

IL-1 is a critical molecule that induces the activation of matrix metalloproteinases in chondrocytes in the joint cartilage and angiogenesis in the synovium. Interleukin 1 activity actually resides in each of its two molecules, IL-1α and IL-1β, which act by binding to membrane bound type I IL-1 receptor (IL-1R)[6]. This receptor requires IL-1R accessory protein (IL-1RAcP) for intracellular downstream signaling[15]. Type II receptors for IL-1, also known as decoy receptors, do not mediate any downstream signaling and are largely responsible for attenuating its response. Since IL-1 was documented to be the predominant cytokine in the synovial fluid in RA patients, strategies utilizing naturally occurring IL-1 inhibitors like IL-1Ra were tried in the patients. IL-1Ra binds to type I receptors and do not allow its binding with IL-1R AcP. However, the results were much below the expectations. The reason was postulated to be short half-life of IL-1Ra in *in vivo* settings. Search for newer IL-1 inhibition strategies led to interesting formulations, IL-1 trap (combination of soluble type IL-1R and soluble IL-1R AcP)[6,16]. This molecule has higher affinity for IL-1 and being a soluble form it does not allow IL-1 to bind to membrane bound type I IL-1R. Its protective efficacy in collagen induced arthritis model is proven. Role in human RA needs further study. Another strategy targeting IL-1 is trial of intracellular forms of IL-1Ra. One such study has reported that mice transgenic for IL-1Ra type I were protected from collagen-induced arthritis[17].

Th2 type of cytokines by virtue of; antagonizing the actions of Th1 type of cytokines, suppressing the production of pro-inflammatory cytokines, blocking the inflammatory cell emigration, stimulating the production of other anti-inflammatory molecules (e.g. IL-1 Ra) and inhibiting the release of matrix metalloproteinases may prevent joint damage in RA.

Other cytokines, chemokines and growth factors in synovial inflammation:

IL-6 is another important pro-inflammatory cytokine with several effects overlapping with that of IL-1 and TNF- α. It is known to act synergistically with IL-1 and

TNF-α to induce production of vascular endothelial growth factor (VEGF) by synoviocytes in RA. Anti-IL-6 receptor therapy, Tocilizumab, has been shown to reduce disease severity and the level of VEGF in sera of patients with RA[18].

Another important cytokine implicated in joint inflammation and destruction in RA is IL-17. It is a T-cell cytokine, acts synergistically with TNF-α and IL-1, leads to destructive arthritis in mice deficient in IL-1Ra and has got regulatory effect on osteoclastogenesis[19]. It induces increased secretion of IL-1 and TNF-α by monocytes/macrophages.

IL-18 is another major cytokine that has been shown to have strong pro-inflammatory activity and that synergizes in action with IL-1 and TNF-α. However, its effect is dependent upon IL-12. Stimulation with IL-12 leads to synthesis of β chain of IL-18 receptor, which makes it a functional receptor. IL-18 has also been demonstrated to be a chemotattractant for T-cells in the serum and for CD4+ T cells in the RA synovial fluid[6]. The action of IL-18 is regulated by natural endogenous inhibitor, IL-18 binding protein (IL-18 BP)[6,20,21]. Increased levels of IL-18 BP in the synovial compartment have been demonstrated to reduce the incidence and severity of collagen induced arthritis (CIA). Intra-articular IL-18BP therapy has systemic effect as well as evidenced in CIA[21].

IL-12 is one of the major cytokine that induces the Th1 phenotype of the T cells by inducing production of IFN-γ by T cells and NK cells. A new member of IL-12 family of cytokines is IL-23, which is essential for mediating the effect of IL-12[22]. Targeting IL-23 seems promising therapeutic potential.

Interleukin-15 (IL-15) is a pro-inflammatory, innate response cytokine that mediates pleiotropic effector function in RA synovitis. A phase I-II dose-escalation trial with HuMax-IL15, a human IgG1 anti-IL-15 monoclonal antibody, in patients with active RA showed substantial improvements in disease activity and improvement scores[23].

Recently, macrophage migration inhibitory factor (MIF) has been demonstrated to have a key role in the pathogenesis of RA. It regulates synovial cell proliferation and synergizes in action with IL-1 and TNF-α. In MIF knockout mice, severity of antigen-induced arthritis was much decreased and simultaneous to p53 overexpression and apoptosis in synovium[24].

In a murine CIA model, CXCL16 has been shown to play an important role in T cell accumulation and stimulation in RA synovium. Anti-CXCL16 monoclonal antibody significantly reduced the clinical arthritis score and reduced infiltration of inflammatory cells and bone destruction in the synovium of mice with CIA[25]. There are several additional molecules in the chemokine – monokine and growth factor family that have also been shown to be anti-inflammatory. These include IFN-γ inducible protein 10 (IP-10) and platelet factor 4 (PF4). Therefore, these could also be some possible therapeutic targets in RA.

There are several other cytokines that include IL-2, IL-5, IL-6, IL-17, and IFN-γ that are closely involved in inflammation and its regulation. Some of them could be important therapeutic targets. Similarly, there are several other adhesion molecules, chemokines and growth factors with regulatory role. Some of them may turn out to be important therapeutic agents.

The possible therapeutic targets:

The above discussion brings up the exciting theoretical possibility of modulating this network for therapeutic purposes in diseases like RA. Although there seem to be innumerable possible targets, studies indicate that the following sites of 'attack' are likely to bear the therapeutic importance:

- TNF –α blockage
- Interleukin-1 blockage
- Interleukin-6 blockage
- Anti osteoclastogenesis
- Anti-chemokines

Conclusion:

There is an intricate network of molecules involved in the initiation, perpetuation and regulation that balance the pro- and anti- inflammatory process in RA synovium. It appears that the inflammatory synovitis in RA is the

result of an imbalance in the cytokine network. This knowledge could be exploited for the manipulation of the cytokine network with the aim of correcting this imbalance. Although clinical remission is difficult to achieve even with anticytokine treatment (whatever experience we have till date), these drugs offer the potential to decrease disease activity and improve quality of life in a majority of RA patients, and it is conceivable that combinations of biological therapies may pave the path to even better success, which ultimately is remission or even cure.

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