Commentary

Towards cytokine insight in sight

In a recent paper in the *Lancet*,[1] antibodies that neutralise the cytokine, tumour necrosis factor α (TNF-α), were reported to produce marked and somewhat sustained relief of symptoms in the immune mediated disease rheumatoid arthritis. This report lends hope that the neutralisation of cytokines may eventually be of therapeutic value in inflammatory eye diseases including uveitis, keratitis, scleritis, corneal transplant rejection, cystoid macular oedema, and possibly fibrotic or angiogenic diseases including diabetic retinopathy, proliferative vitreoretinopathy, macular degeneration, pterygium, and fibrosis after surgery to reduce intraocular pressure.

In order to consider the challenges and potential of cytokine inhibition, it is necessary to review several principles about cytokines and cytokine function.

Cytokines are proteins that cells use for communication. The cells in the immune system utilise cytokines extensively. The cytokines include an expanding family of at least 15 interleukins, the tumour necrosis factors, chemokines, colony stimulating factors, interferons, and a variety of growth factors such as transforming growth factor β (TGF-β). Lipids, nitric oxide, and peptides are usually not considered cytokines although these substances, too, are involved in cellular communication.

The rationale to target cytokines is simple. Cytokines are essential for the function of the immune system. Many diseases result from a pathological immune response. Therefore, interrupting the cytokine communication will result in diminished inflammation. Furthermore, a variety of cytokines including interleukin-1 (IL-1), TNF-α, IL-6, IL-8, IL-2, and granulocyte macrophage colony stimulating factor can be directly injected into the eye with significant inflammation resulting.[2] On the other hand the direct injection of IL-10 or TGF-β may be anti-inflammatory.

Several basic principles with regard to cytokine function may help us to understand the complexity of the challenge in interfering with cytokine control. First of all cytokines are pleiotropic. This means that they have may targets and regulate many genes. For example, among other functions, IL-1 stimulates fibroblast growth, increases collagen synthesis, causes bone resorption, is cytotoxic for some tumour cells, is chemotactic for lymphocytes, stimulates prostaglandin synthesis, causes basophil histamine release, induces fever, and stimulates synthesis of other cytokines.

Secondly, cytokines often share functions – that is, they are redundant. For example, both IL-1 and TNF can activate lymphocytes, act as pyrogens, cause muscle cachexia, induce the acute phase protein synthesis, activate endothelial cells, cause fibroblast proliferation, and induce tumour necrosis.

Thirdly, cytokines function within a network. Consequently the antagonism of a single cytokine may alter many downstream effects. For example, vascular endothelial growth factor (VEGF) has recently been implicated as a major contributor to angiogenic disease such as diabetic retinopathy.[3] VEGF can be regulated in some cells by IL-1.[4]

Fourthly, most effects of cytokines are local rather than systemic. In general, cytokines are not intended to act at a distant site as would an endocrine hormone. Cytokines can stimulate the cell that produces the cytokine, so called autocrine stimulation, or they may stimulate adjacent cells, so called paracrine stimulation. In theory, cytokines may never need to be secreted and may stimulate cells by surface contact or by binding to intracellular receptors. This poses a great challenge with regard to their pharmacological inhibition.

Finally, it is an oversimplification to label cytokines as simply proinflammatory or anti-inflammatory. For example, many of the effects of endotoxin in inducing a sepsis-like state have been attributed to TNF and inhibition of TNF can prevent sepsis in experimental animals.[5] However, in some circumstances injection of TNF can also prevent fatal effects from Gram negative infection or endotoxin.[6] The cytokines are a finely regulated system with a critical amount in a critical setting being desirable. The elusive goal for future pharmacotherapy will be to inhibit precisely the right amount in the critical microenvironment.

A number of strategies could be used to inhibit cytokines including neutralising antibodies to the cytokine or its receptor, natural inhibitors, soluble receptors, antisense RNAs, or inhibitors of cytokine synthesis. A large portion of the anti-inflammatory effects of corticosteroids may come from their ability to inhibit cytokine synthesis. Several of the cytokine antagonists include a natural antagonist to IL-1, the IL-1 receptor antagonist, and inhibitors of IL-1 and TNF have had disappointing therapeutic value in human trials for Gram negative sepsis or rheumatoid arthritis. The major exception is the rheumatoid arthritis study cited above. The cytokines themselves have currently enjoyed greater commercial success. For example, some of the interferons may be of value for certain malignancies and chronic viral infections,[7] the colony stimulating factors are useful for haematological cytopenias, and IL-1 or TNF may have some benefit in treating specific cancers. β Interferon is used in the treatment of multiple sclerosis.[8]

Endotoxin from Gram negative bacteria will induce the synthesis of many cytokines provoking a cascade not unlike the complement cascade or the coagulation cascade. Endotoxin can be given to the footpad of a rat with resultant marked cellular infiltration of the uveal tract, especially the anterior segment. Although this inflammation is likely to be cytokine dependent, cytokine inhibitors of IL-1 and TNF have been disappointing in this animal model.[9 10] However, the growth factor, TGF-β, and the cytokine, IL-10, have each shown a significant ability to inhibit the cellular infiltrate characteristic of this model.[11] In other animal models of inflammation outside the eye, TNF may be therapeutic or it may worsen the disease depending upon the timing of its administration.[12]

Several exciting new developments have recently been reported with regard to understanding the physiology of cytokines. A metalloproteinase seems to be a critical step in the synthesis of TNF and several pharmaceutical firms have produced an inhibitor of this enzyme.[13] The synthesis of several cytokines appears to be dependent upon the intracellular activation of an enzyme which is known as a mitogen activated protein kinase (MAP kinase). Recently, a family of inhibitors for this enzyme has been described.[14]

These inhibitors have the potential to block the synthesis not only of one but of whole groups of cytokines. This approach may be ultimately more successful than the inhibition of a single cytokine in view of the redundancy of the communication system and the potential for cytokines to have effects without ever being secreted from the cell. The recent creation of genetically altered mice which are incapable of synthesising a specific cytokine or a cytokine receptor is an invaluable advance towards the elucidation of essential functions of cytokines.[15]

Uveitis encompasses a variety of different diseases. It is probable that the therapeutic approach for one form of uveitis is not the optimal approach for another. The simple inhibition of the cytokine network may result in undesirable adverse events or even a worsening of inflammation. As the complexity and integration of the cytokine network becomes more fully understood, the success in manipulating the cytokine system for therapeutic advantage will ultimately be realised.

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