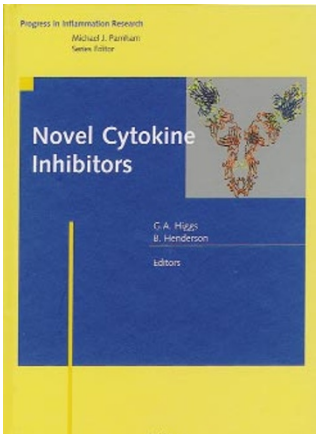
The Goldilocks tale of cytokines: Getting it right



Novel Cytokine Inhibitors
by G. Higgs and B. Henderson
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This latest volume in the Progress in Inflammation Research series edited by Higgs and Henderson comes at a time when the therapeutic potential of anti-cytokine drugs are being realized in spectacular fashion. Recombinant protein therapies utilizing two different approaches to inhibiting tumour necrosis factor (TNF) activity, soluble TNF-receptor fusions and anti-TNF monoclonal antibodies, are approved for use in rheumatoid arthritis and inflammatory bowel disease, chronic inflammatory conditions with a wealth of data implicating TNF in disease pathogenesis. The efficacy of these biological drugs seems to exceed or equal anything else in the current armamentarium, combining disease-modifying activity with rapid onset of action. Testimonies of patients and their physicians border on the miraculous. Clinical trials of inhibitors of interleukin-1 (IL-1), IL-4, IL-5, IL-6 and IL-8 are underway for various diseases presumed to be cytokine-driven.

These developments are comprehensively covered here. The contributors have been drawn from academic and biotech ranks (in particular, Celltech Chiroscience, with several TNF inhibitors in its pipeline), offering a balanced perspective. The pros and cons of monoclonal antibodies (high antigenicity, ligand specificity) and soluble receptors (low antigenicity, broader activity) are discussed, but as the authors admit, the proof of the pudding awaits clinical trials.

A strong feature of the book is the detailed presentation of alternative approaches to inhibiting cytokine activity. Although less advanced towards clinical application, these strategies take advantage of the impressive knowledge base accumulated in the last 10–20 years on regulation of cytokine gene expression, processing, secretion and receptor signalling.

Nascent efforts using antisense oligonucleotides to downregulate cytokine and cytokine-receptor expression are reviewed. Several cytokines require processing for secretion or release of membrane-bound forms, fingering the responsible proteinases as potential targets of anti-cytokine therapy. The precursors of IL-1β and IL-18 are cleaved into active forms by the cysteine protease caspase-1. Peptide inhibitors modeled on the cytokine precursor clea-vage sites may have sufficient specificity to leave the related caspases involved in apoptotic pathways unmolested. The discovery of the TNF-α converting enzyme or TACE (tumour necrosis factor-α converting enzyme) and the solution of the TACE crystal structure are covered briefly. Structure-based drug design should hasten development of specific inhibitors for this processing pathway.

The development of specific tyrosine kinase inhibitors as novel immunosuppressants represents an approach that targets cell-signalling pathways upstream of cytokine secretion. Most of the efforts in this area have been aimed at improving the biochemical selectivity of small molecule candidates. The recent clinical success of STI571, a BCR/Abl tyrosine kinase inhibitor with overlapping activity against c-kit (stem-cell factor receptor), in Philadelphia-chromosome-positive chronic myelogenous leukemia, demonstrates that absolute specificity is not always a rigid requirement for clinical activity. Inhibitors of the low K_m cAMP-specific phosphodiesterase-4 also inhibit cytokine production. Restricted expression of PDE4 in inflammatory cells and T-lymphocytes has led to clinical trials of PDE4 inhibitors in asthma and rheumatoid arthritis. Signalling pathways downstream of cytokine receptors, such as p38 mitogen-activated protein kinase (MAPK), also participate in stimulation of cytokine production. Significant progress has been achieved in developing specific inhibitors of p38 MAPK by optimizing lead compounds and structure-based drug design.

Pitfalls in the clinical development of anti-cytokine therapy are not neglected. The affinity of the trimeric interaction of TNF-like ligands and membrane-associated receptors greatly exceeds that achieved to date with single-chain soluble receptors. Fusion of human IgG Fc chains to the soluble TNF-R1 receptor created a dimer with increased affinity for TNF. Multi-subunit receptors, such as for IL-2 and IL-6, may be more resistant to engineering soluble receptors with high affinity. A further complication is observed with the naturally occurring soluble IL-6Rα that retains biological activity by functionally associating with the membrane bound IL-6Rβ receptor. The initial optimism, based on animal studies and supporting clinical results, for anti-cytokine therapy of septic shock, is covered in detail, as well as the disappointing results of clinical trials for anti-TNF and anti-IL-1 interventions.

The septic shock trials provide a reminder of the double-edged nature of cytokines. Systemic release of inflammatory cytokines such as TNF, IL-1 and IL-6, is deleterious, with morbid complications of refractory hypotension, acute respiratory distress syndrome and multi-organ failure. However, there is substantial evidence that localized cytokine release is required for effective immune responses against infectious organisms and, in all likelihood, malignancies. Anti-TNF monoclonal antibodies increase infectious complications, and exogenous TNF is protective in an animal model of localized infection, caecal ligation and puncture.

Brian Henderson ends the book on a hopeful note with a cogent discussion of adaptive mechanisms used by microorganisms to evade cytokine-mediated immunity. Ultimately, learning from microbial invaders how to manipulate the cytokine network to advantage may be the best approach to design novel anti-cytokine therapies for the multitude of inflammatory diseases that plague mankind. □

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