CYTOKINE INHIBITORS

edited by

Gennaro Ciliberto
Rocco Savino

Istituto di Ricerche di Biologia Molecolare P. Angeletti
Rome, Italy

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Preface

Cytokines play important physiological roles in cell-to-cell communication, development, and differentiation. It is well known that cell differentiation in the hemopoietic and immune systems depends on the complex interplay and sequential action of several members of this heterogeneous group of polypeptides, which have in common that they are produced in small quantities, often only upon exogenous stimuli, and in most cases act over a short distance in a paracrine or autocrine fashion. The differentiation-inducing activity of cytokines has opened up new avenues toward the therapy of hematological and immune disorders. Industrial investments on the part of biotech and pharmaceutical companies have been enormous over the past years, and many recombinant molecules are now marketed or used in advanced clinical trials for the treatment of primary or secondary anemia, granulocytopenias, thrombocytopenias and bone marrow transplantation protocols. Similarly, molecules acting as stimulators of immune functions, such as interferons, have found a wide market in the therapy of chronic hepatitis, cancer, and multiple sclerosis. It has to be stressed that the therapeutic utilization of these recombinant molecules has so far been only partially exploited due to a combination of factors, which include elevated production costs, limited half-life in vivo, and lack of efficient and safe systems for selective delivery of the desired therapeutic amount to the site of action.

Besides those cases in which exogenous cytokines can be used therapeutically either to substitute for or to potentiate physiological functions, there are contrasting cases in which it is desirable to block the activity of an endogenously overproduced cytokine. Research over the past ten years has clearly indicated that imbalanced cytokine production plays an important pathogenetic role in several inflammatory, chronic autoimmune diseases, and sometimes

facilitates cancer growth. Thus, blocking the activity of a central molecule can result in the improvement of clinical and biochemical parameters.

While it is clear that blocking cytokine function is necessary to cure several pathological conditions, it is also evident that this is difficult to achieve. Naturally soluble cytokine antagonists, with the exception of a very limited number of cases, do not exist. Thus, ad hoc drug-discovery strategies have to be devised in order to obtain potent and specific cytokine blocking agents. Potency is an absolute requirement to counteract the activity of the endogenous cytokine, which is produced in microgram-per-day amounts in several pathologies and is fully active at picomolar levels. Specificity is also difficult to achieve, given the high degree of redundancy in the use of common receptors and/or signaling pathways. Finally, while several cytokine blocking agents in the form of recombinant proteins (monoclonal antibodies, soluble receptors, receptor antagonists) have been successfully generated over the years, they suffer from several major limitations, some of them identical to those encountered for wild-type cytokine delivery, i.e., the need for parenteral administration and the elevated costs of production. In addition, we face new problems, the most important being the potential immunogenicity of these nonnatural molecules. In order to overcome these hurdles, there is strong pressure to develop small-molecular-weight inhibitors.

Cytokine antagonists can be obtained at least at three general levels: 1) blockade of cytokine production, 2) inhibition of cytokine-induced assembly of a functionally competent receptor complex, 3) interference with cytokine signaling inside target cells. All these approaches have now become more feasible thanks to our greater understanding of both the intracellular signaling pathways and the structural determinants responsible for cytokine–receptor interaction. In many instances the 3-D structure of cytokines and their relevant receptors has been solved, as was that of intracellular tyrosine kinases. This knowledge is of enormous help in the molecular modeling and drug design of selective inhibitory compounds. Once a given target is identified, the search for its inhibitors can be undertaken using different strategies: random screening of libraries of compounds, molecular design, or a combination of the two. Furthermore, the technical improvements and the widespread diffusion of combinatorial chemistry are speeding up these steps enormously. We are thus experiencing a moment of high creativity and progress in this field, marked by frequent, important breakthroughs.

The aim of this book is to provide a comprehensive and updated overview of the field of cytokine inhibitors at the beginning of the third millennium. Several chapters illustrate cases of naturally produced or in vitro engineered polypeptide cytokine-blocking agents. In particular, some chapters

(Chapter 1, Dinarello and Fantuzzi; Chapter 2, van Deventer and van der Poll; Chapter 3, Bendtzen et al.; Chapter 9, Naka et al.; and Chapter 10, Starr) give clear examples of the homeostatic function of cytokine inhibition and indirectly substantiate a therapeutic approach oriented to potentiating a natural response of the organism, when required. In the group of ''first-generation'' recombinant cytokine inhibitors the most successful clinical examples are tumor necrosis factor antagonists (Chapter 4, Hitraya and Schaible), which have reached the market during the past year and promise to become prominent tools in the therapy of chronic inflammatory conditions over the next decade. One case is also shown of how the detailed knowledge of the interaction between a cytokine and a multimeric receptor complex has led to the rational design of potent and selective receptor antagonists (Chapter 8, Vernallis). Chapter 5, Murali et al.; Chapter 6, Moss et al.; Chapter 7, Proudfoot-Fichard et al.; Chapter 11, Lipson et al.; and Chapter 12, Gum and Young, illustrate various examples and approaches to the generation and clinical development of ''second-generation,'' small-molecular-weight, orally bioavailable cytokine inhibitors. In the future we can expect to see more and more examples of these inhibitors and eventually to find them on the shelves of pharmacies as novel and more potent anti-inflammatory, anticancer, and antiviral agents.

The editors wish to express their gratitude to Sara Razzicchia. Without her invaluable editorial assistance on this project the book might not have been born.

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Rocco Savino

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