

EDITORIAL

Cytokines – An Overview

T. Pang, PhD

Institute for Advanced Studies, University of Malaya, 59100 Kuala Lumpur

Cytokines describe a large group of protein regulatory factors, released by a wide variety of cell types, and capable of affecting a wide range of biological functions. The most important cytokines are the interferons, interleukins, hematopoietic factors (e.g. G-CSF, GM-CSF) and tumour necrosis factor (TNF). They are released by various cells in the body, including macrophages, monocytes, lymphocytes, fibroblasts and endothelial cells. The cytokines are multifunctional signalling molecules which play a central role in regulating cell growth and differentiation with a wide array of biological effects on developmental, physiological and immunological processes. They form a complex network of interactions *in vivo* and exert their effects by binding to specific receptors on target cells. They are able to elicit beneficial as well as pathogenic effects.

Due to its central role in numerous homeostatic processes, the therapeutic potential of cytokines is obvious. The clinical use of cytokines was further boosted by advances in genetic engineering and biotechnology which has made highly purified, recombinant forms of these factors available in significant quantities. Numerous studies have shown the beneficial effects of administration of cytokines in a variety of conditions, including infections, autoimmune diseases, hematological disorders, allergic diseases and malignancies, and many trials are currently in progress. Cytokines have been used singly, in combination, or to pre-activate lymphocytes prior to injection into patients. For example, impressive results have been obtained with hematopoietic growth factors in the treatment of anemia and hematological malignancies and with interleukin-2 (IL-2) in the treatment of patients with various tumours, for example renal carcinoma and melanomas. Trials are under way to assess the usefulness of cytokines in AIDS, wound infection and healing, and in autoimmune and inflammatory diseases.

Despite its clear therapeutic potential, the clinical use of cytokines has to be approached with a certain amount of caution. Toxicity following systemic administration of cytokines has proven to be a serious problem. This can include fever, malaise, nausea, diarrhea, hypotension, anemia, thrombocytopenia, and also amnesia and neuropsychiatric complications. The systemic toxicity problem often precludes the use of sufficient doses to induce tumour regression. It was also realized recently that certain cytokines can actually *potentiate* infections by acting as a growth factor for a variety of microorganisms. On reflection, the many problems associated with therapeutic use of cytokines is a predictable result of their complex, multiple, and overlapping cell regulatory actions and the complexity of the interactions between cytokines and target cells in the *in vivo* situation. Under physiological conditions, cytokines are highly potent factors which are produced transiently and locally from diverse sources, acting in a paracrine or autocrine, rather than an endocrine manner. It is thus extremely difficult to attribute a given biological effect to the direct action of a particular cytokine as there exists, in the *in vivo* milieu, a dynamic interplay of cytokines that act in a co-ordinated and

temporal manner to produce various biological responses. Taking all of the above into consideration, the liberal, systemic administration of these potent factors in human patients would, not surprisingly, produce homeostatic imbalances with immediate toxic effects and largely unknown, longer term consequences. In a related vein, the molecular processes by which cytokines affect cellular behaviour remains unknown although the molecular characteristics of many cytokine receptors have recently been elucidated. In relation to the regulation of cytokine production and effects, the role of cytokine inhibitors and autoantibodies to cytokines also requires further study. These regulatory mechanisms may be vital in determining whether a given cytokine has beneficial or pathogenic effects.

In conclusion, although the potential therapeutic benefits of cytokines are clear, a certain amount of caution seems warranted. The same approaches of molecular biology and recombinant DNA technology, which has made therapeutic applications a reality, must now be used to obtain a better understanding of the mode of action of cytokines at the cellular and molecular level. This knowledge should be combined with *in vivo* assessment of interactions and carefully controlled clinical trials in humans. To address the problem of systemic toxicity, alternative modes of delivery should be evaluated which maximise local responses whilst causing minimal systemic toxicity. Ultimately, a better understanding of the temporal interactions in the cytokine network and the ability to rationally utilize these cytokines, and perhaps alter the expression of their receptors on relevant target cells, may result in them fulfilling their promise as therapeutic agents in human disease. The challenge of the future revolves around optimizing the therapeutic benefits of cytokines.