REVIEW ARTICLE

Cytokines in Infection

T. Pang, PhD
Institute of Advanced Studies, University of Malaya, Kuala Lumpur

Summary

Cytokines are central to the development of effective immunity against microbial pathogens and their beneficial effects in the control of a variety of infections of man and animals are well-documented. However, it appears that cytokines may also have detrimental effects in infections by actually enhancing microbial growth. These observations emphasise the fact that many successful pathogens possess mechanisms enabling them to evade the immune response and that caution needs to be exercised in using cytokines as therapeutic agents to control infections in various human diseases.

Key words: Cytokines, infection.

Introduction

The cytokines are a large group of protein factors which play a central role in development processes, homeostasis and the pathophysiology of disease. They interact in a complex network, have overlapping actions and are produced by a wide variety of cell types, including macrophages, monocytes, lymphocytes, fibroblasts and endothelial cells[1]. The most important cytokines are the interferons (e.g., IFN-γ), interleukins (e.g., IL-1, IL-2, IL-4, IL-6), haemotopoietic growth factors (granulocyte colony-stimulating factor, G-CSF; macrophage colony-stimulating factor, M-CSF; granulocyte-macrophage colony-stimulating factor, GM-CSF) and tumour necrosis factor (TNF).

The cytokines function as 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[1].

Protective Effects of Cytokines in Infections

Taking into account the central role of cytokines in the functioning of the immune system, it is clear that these factors may be of importance in infectious diseases. In fact, the first definition of a cytokine function could be attributed to the discovery of the antiviral activity of interferons by Isaacs more than 30 years ago. In particular, due to its critical role in the differentiation and proliferation of T lymphocytes[1], many cytokines, especially IFN-γ and the various interleukins, are closely associated with the development of effective immunity against a variety of infectious agents, including bacteria, protozoa, metazoa and viruses[2]. It is clear that the cytokines are critical factors in the differentiation and proliferation of T cell subsets, such as CD4+ and CD8+ T cells. Definition of the role of cytokines in infection, as well as their use in therapeutic regimes, was given a boost with the advent of recombinant DNA technology which enabled the production of highly pure cytokines in large quantities. In animal models, different cytokines have been shown to produce strong protection against

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microbial pathogens *in vitro* and *in vivo*, including IL-1[3], IL-4[4], IL-2[5], IFN-γ[6], TNF[7] and IL-6[8]. Similarly impressive results have been obtained, for example, in using GM-CSF to control infections in patients with non-myeloid malignancies treated with high-dose chemotherapy and autologous bone marrow transplantation[9]. In this situation, GM-CSF accelerated neutrophil recovery reduced the number of febrile days, the number of days required for isolation in reverse-barrier nursing and the number of days of parenteral antibiotic therapy[9]. GM-CSF has also been used to successfully reduce infection in other conditions such as aplastic anaemia, myelodysplastic syndrome and AIDS[10]. Numerous clinical trials are ongoing for a variety of other diseases. In conclusion, the importance of cytokines and their role in protective immunity against a variety of microbial pathogens is now well-established.

Microbial Strategies in Response to Cytokines

However, in contrast to the beneficial effects of cytokines described above, recent evidence would suggest that cytokines may also play a detrimental role in infectious diseases. It has been shown, for example, that IL-2 and GM-CSF actually enhances the growth of *E. coli in vitro*[11]. IL-6 was also shown to enhance the growth of *M. avium* in human macrophages[11] and, recently, it was shown that sera from patients with AIDS could significantly increase the susceptibility of human macrophages to *M. avium*[12]. This enhancement ability may be due to IL-6, the levels of which have been shown to be elevated in AIDS patients[13]. In another study, IL-1 stimulated the growth of virulent strains of *E. coli* but had essentially no effect on avirulent strains[14]. Binding studies showed that IL-1 was binding to a protein-like receptor molecule present on the cell surfaces of virulent, but not on avirulent bacteria, and that the addition of a factor which blocked the IL-1 receptor abrogated the growth-enhancing effect of IL-1[14]. In contrast to using cytokines to enhance its own growth, the protozoan *Trypanosoma cruzi* releases an immunosuppressive factor which inhibits the expression of IL-2 receptors on lymphocytes[15]. The reduced expression of IL-2 receptors would, in turn, mean that these lymphocytes are unable to respond to antigenic activation and mount an effective immune response.

Implications and Conclusions

It is clear that there are 2 sides to the use of cytokines in modulating infectious diseases. In the true spirit of microbial evolution, many microbes have devised strategies to evade the 'onslaught' from the cytokines, which in some ways can be considered as a form of selective pressure to develop more 'resistant' strains. In the most direct strategy, some microbes appear to have succeeded in acquiring cytokine receptors, thus enabling them to actually use the cytokines as growth factors to enhance their own multiplication. This, of course, implies that certain microbes have succeeded in acquiring mammalian DNA and then expressing the appropriate receptors on their surfaces. It also implies that the appropriate biochemical machinery is present to convert the binding signal to a biological effect. In this sense, the receptor for the cytokine could be considered a virulence factor important in conferring pathogenicity to a particular pathogen. The movement of DNA across species barriers by a variety of means, such as mobile genetic elements (e.g., transposons) and viruses, is now acknowledged to be a distinct possibility and may constitute an important evolutionary strategy for a wide variety of living organisms. In yet another strategy, the pathogen releases a suppressive factor which inhibits the expression of cytokine receptors on cells of the immune system. In either case, the strategy amounts to microbial evasion of hostile mechanisms and the overall effect would be to enhance growth of the pathogen and exacerbate infection.

Another important implication of the above is that caution needs to be exercised in using cytokines as therapeutic agents in man. It would suggest that the beneficial use of cytokines to modulate infections may require careful documentation and monitoring of their effects on the targeted pathogens. In addition, the more general effects of liberal, systemic cytokine therapy on homeostasis of the immune system must also be kept in mind. Imbalances created as a result of such therapy could possibly lead to immunoregulatory disturbances manifesting as autoimmune diseases, immune complex disorders or other pathological effects. Related to this is the fact that little is known about the biochemical basis of cytokine action. Recent advances in knowledge relating to the molecular biology of cytokines and their receptors promises to yield important clues. However,

the central issue is the nature of the link between the basic molecular biology and biochemical pathways being defined and the resulting biological effects. A better understanding of cytokine action, more rational therapeutic regimes and alternative modes of delivery should eventually realise the potential of these factors as therapeutic agents in man.

References

1. Balkwill FR, Burke F. The cytokine network. Immunol Today 1989;10 : 299-301.
2. Scott P, Kaufmann SHE. The role of T-cell subsets and cytokines in the regulation of infection. Immunol Today 1991;12 : 346-8.
3. Pecyk RA, Fraser-Smith EB, Matthews TR. Efficacy of interleukin-1B against systemic *Candida albicans* infection in normal and immunosuppressed mice. Infect Immun 1989;57 : 3257-9.
4. Carter KC, Gallagher G, Baillie AJ, Alexander J. The induction of protective immunity to *Leishmania major* in the BALB/c mouse by interleukin-4 treatment. Europ J Immunol 1989;19 : 779-82.
5. Chong KT. Prophylactic administration of interleukin-2 protects mice from lethal challenge with gram-negative bacteria. Infect Immun 1987;55 : 668-73.
6. Reed SG. *In vivo* administration of recombinant IFN-γ induces macrophage activation and prevents acute disease, immune suppression and death in experimental *Trypanosoma cruzi* infections. J Immunol 1988;140 : 4342-50.
7. Desiderio JV, Kiener PA, Lin PF, Wan GA. Protection of mice against *Listeria monocytogenes* infection by recombinant tumour necrosis factor alpha. Infect Immun 1989;57 : 1615-7.
8. Flesch IEA, Kaufmann SHE. Stimulation of antibacterial macrophage activities by B-cell stimulatory factor 2 (interleukin-6). Infect Immun 1990;58 : 269-71.
9. Sheridan WP, Wolf M, Lusk J, Layton JE, Souza L, Morstyn G, Dodds A, Maher D, Green MD, Fox RM. GM-CSF and neutrophil recovery after high dose chemotherapy and autologous bone marrow transplantation. Lancet 1989;2 : 891-8.
10. Stern AC, Jones TC. Use of human recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) in infectious diseases. In: Breakthrough in Cytokine Therapy—An Overview of GM-CSF. Scarffe JH (ed). Royal Society of Medicine 1991;101-6.
11. Denis M, Campbell D, Gregg EO. Cytokine stimulation of parasitic and microbial growth. Res Microbial 1991;142 : 979-83.
12. Crowle AJ, Cohn DL, Poche P. Defects in sera from AIDS patients and from non-AIDS patients with *Mycobacterium avium* infection which decreases macrophage resistance to *M. avium*. Infect Immun 1989;57 : 1445-51.
13. Breen EC, Rezai AR, Nakajima K, Beall GN, Mitsuyasu RT, Hirano T, Kishimoto T, Martinez-Maza O. Infection with HIV is associated with elevated IL-6 levels and production. J Immunol 1990;144 : 480-91.
14. Porat R, Clark BD, Wolff SM, Dinarello CA. Enhancement of growth of virulent strains of *Escherichia coli* by interleukin-1. Science 1991;254 : 430-2.
15. Kierszenbaum F, Sztein M, Beltz L. Decreased human IL-2 receptor expression due to a protozoan pathogen. Immunol Today 1989;10 : 129-31.