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MINIREVIEW

Use of Immune Modulators in Nonspecific Therapy of Bacterial Infections

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INTRODUCTION

Despite the availability of a wide variety of potent antimicrobial agents, severe bacterial and fungal infections represent a continuing threat to patients. This is due not only to the antimicrobial resistance of the involved microorganisms but also to the increasing number of patients with severely hampered host defense mechanisms. This failure of antimicrobial therapy has led to attempts to enhance the nonspecific resistance of the host. Since the beginning of this century, many studies have demonstrated nonspecific resistance to infection that can be enhanced by the administration of killed microorganisms like mycobacteria (*Mycobacterium bovis* bacillus Calmette-Guerin [BCG]) (21), *Corynebacterium parvum* (now called *Propionibacterium acnes*) (1), and *Listeria monocytogenes* and *Candida albicans* (68). Several preparations derived from microorganisms are capable of duplicating these effects; bacterial endotoxin (lipopolysaccharide [LPS]), muramylpeptides, glucan, and protodyne increase the survival of gram-positive and gram-negative bacteria, some viruses, fungi, and protozoans (4, 14, 74). However, most of these substances are too toxic for clinical use. The exact mechanisms by which these immunomodulators enhance nonspecific resistance are unknown. Since most of these immunostimulants are potent inducers of cytokines like interleukin-1 (IL-1), tumor necrosis factor (TNF), and IL-6 (10, 28, 52, 54), it is logical to ask whether these cytokines are able to induce nonspecific resistance. This minireview examines the effects of these cytokines on nonspecific resistance to infection. In addition, a brief review is given on the effects of interferons, colony stimulating factors, and IL-2. The use of cytokines like IL-1, gamma interferon (IFN-γ), and IL-2 as adjuvants for vaccines are beyond the scope of this review.

INTERLEUKIN-1

IL-1 is an inflammatory glycopeptide that is produced by many types of cells (Table 1) after stimulation with various physical, chemical, or microbial agents (19). There are two structurally different IL-1 molecules, IL-1α and IL-1β, coded for by separate genes. Although these 17-kDa proteins have only limited amino acid homology (26%), they bind to the same receptor, and their pleiotropic biological effects are similar (19). Administration of IL-1 has been shown to prevent death in a variety of experimental infections in both normal and granulocytopenic animals (Table 1). If IL-1 were the endogenous mediator responsible for enhanced nonspecific resistance induced by the immunomodulators mentioned above, very low dosages of IL-1 should provide protection, since the IL-1 concentrations produced by injection of an immunomodulator like LPS are low and short-lived (10). Indeed, a single low dose of IL-1 (0.3 μg/kg) was found to be protective. IL-1 needs some time to generate its protective effect; the agent works only if it is given an appreciable time (e.g., 24 h) before the production of an infection with a rapidly fatal course (63, 64). In infections with a relative slow course, IL-1 administration can be delayed until shortly after the infectious challenge (15, 43, 67).

Despite many investigations, the mechanism of the protective effect of IL-1 has not been elucidated. The possible mechanisms are summarized in Table 2. Since a direct antimicrobial effect of IL-1 has been excluded, indirect mechanisms can be considered; these indirect mechanisms should be in agreement with the short half-life of IL-1 in vivo (5 min in the circulation) and with the above-mentioned necessity of a time lag between pretreatment with IL-1 and infectious challenge.

Since phagocytic cells (monocytes-macrophages and neutrophils) are of major importance in the defense against bacterial and fungal pathogens, they could represent the major effector mechanism. However, IL-1 did not seem to produce macrophage activation (64). It is controversial whether the clearance of microorganisms, which is effectuated by phagocytic cells, is enhanced (15, 43, 47, 56, 64, 67) (Table 2). Although several investigators do report lower numbers of microorganisms in IL-1-treated animals (43, 47, 56), it has not been shown whether this is the explanation for increased survival. At least in murine malaria, the effect of IL-1 on parasitemia does not seem to be linked to the actual cause of death, i.e., cerebral malaria (15). Also, the reports on neutrophil counts in IL-1 treated mice and controls are conflicting; while some investigators find no difference (Table 2), others report increased numbers in IL-1-treated normal and granulocytopenic mice (45, 47). Another argument against a role of neutrophils in the IL-1-induced nonspecific resistance is the observation that IL-8, a cytokine which is induced by IL-1 in many cell types (73) and which is considered a major chemoattractant and activator of neutrophils, does not protect against infection under most circumstances (70). Many microorganisms need iron for their growth, and although LPS protects to some extent via induction of hypoferremia (22), no such effect of IL-1 was found (Table 2).

In the lethal phase of infection, circulating endogenous cytokines, such as IL-1 and TNF, contribute to death (10, 71). It may well be that IL-1 preexposure counteracts the

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TABLE 1. Comparison of cytokines with respect to source and effect on nonspecific resistance

	IL-1	TNF	CSFs	IL-2
Principal sources	Monocyte/macrophage (fibroblast endothelial cell smooth muscle cell T- and B-lymphocyte NK cell keratinocyte and other cell types)	Monocyte-macrophage (keratinocyte, T lymphocyte, natural killer cell, mast cell)	T lymphocyte, macrophage, fibroblast, endothelial cell, mast cell	T lymphocyte
Type of infection improved	*Pseudomonas aeruginosa* (47, 53, 64)	*Pseudomonas aeruginosa* (63)	*Pseudomonas aeruginosa* (44)	*Klebsiella pneumoniae* (39)
	Klebsiella pneumoniae (45, 47, 63)	*Klebsiella pneumoniae* (36)	*Escherichia coli* (44)	*Escherichia coli* (11, 26)
	Salmonella typhimurium (46)	*Salmonella typhimurium* (50)	*Serratia marcescens* (44)	*Listeria monocytogenes* (29)
	Escherichia coli (56)	*Streptococcus pneumoniae* (55)	*Salmonella typhimurium* (27)	*Trypanosoma gondii* (60)
	Staphylococcus aureus (45, 46)	*Legionella pneumophila* (8)	*Staphylococcus aureus* (24, 44)	*Trypanosoma cruzi* (12)
	Streptococcus pneumoniae (46)	*Listeria monocytogenes* (17)	*Streptococcus* group B (9)	Herpes simplex virus type 2 (72)
	Listeria monocytogenes (16, 47)	*Candida albicans* (20)	*Streptococcus pneumoniae* (34)	
	Candida albicans (43, 67)	*Plasmodium* spp. (13)	*Listeria monocytogenes* (47)	
	Plasmodium berghei (15)	DNA, RNA viruses (7)	*Mycobacterium avium* (6)	
	Viruses (38)	*Mycobacterium avium* complex (5)	*Candida albicans* (44)	
		Toxoplasma gondii (18)	*Leishmania tropica* (30)	
		Trypanosoma cruzi (18)	*Trypanosoma cruzi* (57)	
			Viruses (38)	
Type of infection not improved	*Streptococcus pneumoniae* (64)	Murine cytomegalovirus (66)		
	Murine cytomegalovirus (66)			

production or effects of these cytokines. This might occur by lower production at the cellular level, by induction of IL-1 inhibitors, such as the IL-1 receptor antagonist and a soluble IL-1 receptor (23, 31) or TNF inhibitor, such as the soluble TNF receptor (59), or by downregulation of receptors for IL-1 and TNF (37, 76). Further studies are needed to evaluate whether these changes take place in vivo.

OTHER ENHANCERS OF ANTIBACTERIAL RESISTANCE

It is likely that the increase of resistance to infection by bacterial products is not mediated by IL-1 alone. Studies have been performed on other cytokines and growth factors that are induced by endotoxin and other aspecific immunos-

TABLE 2. Possible mechanisms of protection by IL-1 against lethal infection

Possible mechanism	Comments	References
Direct antimicrobial effect	No inhibition of in vitro growth of bacteria by IL-1	45, 63
Enhanced clearance of microorganisms	No reduced numbers of microorganisms	15, 64, 67
	Reduced numbers of microorganisms	43, 47, 56
Macrophage activation	No enhanced superoxide production after IL-1	64
Neutrophil accumulation/activation	Protective effect of IL-1 in neutropenic mice	43, 64, 67
	No enhanced granulocyte accumulation after IL-1 at foci of infection	43
Induction of IL-8	No protection after treatment with IL-8	70
Induction of TNF	Limited protection after treatment with TNF	63
Induction of IL-6	Negligible protection after treatment with IL-6	65
Induction of acute-phase proteins	No protection after passive transfer of plasma or serum from IL-1 treated mice	64, 67
	No protection after treatment with IL-6, a major inducer of acute-phase proteins	65
Induction of hypoferremia	No difference in serum iron in mice treated with IL-1 and control mice	56
Induction of cyclooxygenase metabolites	No influence of cyclooxygenase inhibitors on the protective effect of IL-1	63, 64
Interference with cytokinemia	Downregulation of cytokine receptors (in vitro)	37, 76

timulants. One of these is TNF-α (syn-cachectin), a 17-kDa protein that is produced mainly by mononuclear phagocytes (7) (Table 1). Its spectrum of activity is very similar to that of IL-1 (7).

TNF has also been reported to increase host resistance. Endogenously produced TNF plays a role as a mediator in the host defense against infections caused by facultative intracellular bacteria such as *L. monocytogenes*, since early administration of neutralizing antibody to TNF accelerates death (33). Enhancement of macrophage bactericidal capacity has been suggested as a mechanism (32).

A protective effect of exogenous TNF has been demonstrated in vitro and in vivo in infections with a wide range of microorganisms (Table 1).

In our experiments (63), TNF was much less effective than IL-1 in providing protection against lethal *Klebsiella pneumoniae* infections. To some extent these results may be explained by the use of human TNF-α in mice.

The mechanism of the protective effect of exogenous TNF has not been clarified. As in the case of IL-1, early administration (up to 24 h before infection) of low dosages of TNF is optimal in most cases (50, 61). Considering the wide variety of microorganisms against which TNF exerts its protective effect, several mechanisms, both cellular and noncellular, are probably involved. Although conflicting results with regard to the numbers of microorganisms after TNF treatment in vivo have been reported (36, 50), enhanced killing of organisms by macrophages or neutrophils has been found in vitro (5, 8, 20). Several other mechanisms are possible. TNF might directly destroy infected cells (33). Also, TNF is known to induce other cytokines like IL-1, IFN-γ, IL-6, and colony-stimulating factors (CSFs), which in turn could enhance aspecific protective mechanisms in the host (48, 51). TNF might induce reduced sensitivity of target cells to TNF in the phase of "lethal cytokinemia" by downregulation of TNF receptors (37) or might protect cells by inducing shedding of TNF receptors, which then may act as TNF antagonists (59). In view of the above observations, despite the small therapeutic index of TNF, the possibility of treatment of infectious diseases with this potent cytokine should be further explored.

IFNs could also be of use to increase host defense in a nonspecific fashion. Preexposure to IFN-α, -β, or -γ has been shown to protect mice against infections caused by obligate or facultative intracellular pathogens (25; for a review on IFN-γ, see reference 49) and by other microorganisms (13, 36, 77). The protection by the IFNs is thought to be through activation of macrophages and, possibly, neutrophils, resulting in enhanced phagocytosis and killing of pathogens. Also, induction of secondary mediators may play a role (58). The IFNs have already been used as immunomodulators in infections in humans. In acute visceral leishmaniasis in humans, a combination of IFN-γ with pentavalent antimony was efficacious (3). In a multicenter, double-blind, placebo-controlled study, recombinant IFN-γ has recently been shown to be able to prevent infections in chronic granulomatous disease, a group of disorders of the oxidative microbicidal capacity of phagocytes. The mode of action of IFN-γ in these disorders is not fully understood (40).

Some of the biological response modifiers that enhance nonspecific resistance to infection also induce CSFs (2, 68) either directly or via induction of IL-1 and TNF (69). Apart from their effect on hematopoiesis, CSFs are also able to activate macrophages and neutrophils (75). In addition, granulocyte-macrophage CSF has been shown to induce IL-1 and TNF (62). Studies that have been performed on the effects of CSFs in vitro and in animal models are reviewed in Table 1. In vivo, protection was observed in nongranulocytopenic (9, 24, 27, 34) as well as in granulocytopenic (44, 47) animals. Under both conditions, an increase of neutrophil numbers as well as functional activation of macrophages and neutrophils were shown to play a role.

IL-2, a 15-kDa protein, has been shown to possess a broad spectrum of immunoregulatory activities. Although it does not directly activate macrophages, it enhances the activities of natural killer cells and cytotoxic T cells (35, 60). In animal models, a protective effect against several microorganisms has been shown (Table 1). In many instances, relatively high dosages of IL-2 were given. Since it is known that IL-2 stimulates the production of IFN-γ, TNF-α, and IL-1, it is possible that the effects of IL-2 in such models are largely mediated by these cytokines (42).

IL-2 also has negative effects; with systemic administrations of high-dose IL-2 for cancer therapy in humans, an increased incidence of *Staphylococcus aureus* bacteremia has been encountered, most likely because of an impairment of neutrophil chemotaxis induced by IL-2 (41).

PERSPECTIVE

As may have become clear from the above discussion, cytokines seem to have a great potential for reducing the mortality caused by a variety of infections. Whether they are useful as such in clinical medicine will become clear in the next couple of years. Some of the cytokines (such as granulocyte-macrophage CSF, IFN-γ, and, to some extent, IL-2) are beginning to find their way to use as therapy for infections in humans. Their toxicities appear to be acceptable. Whether the proinflammatory cytokines IL-1 and TNF can be used for treatment of infections should be investigated. Their therapeutic index is lower, but perhaps administration of low dosages via the subcutaneous routes is feasible. Also, premedication with cyclooxygenase inhibitors, which do not seem to interfere with the beneficial effects, should be further explored. The use of certain combinations of cytokines should be examined in order to find the greatest degree of protection with the least side effects.

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