IMMUNOMODULATING EFFECTS OF MICROORGANISMS AND THEIR PRODUCTS ON THE IMMUNE RESPONSE MECHANISMS

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INTRODUCTION

The immune defense system of an individual depends on a complex series of interactions among cells and molecules following exposure of lymphoid cells to specific antigen. Much is now known about the major mechanisms of antibody responses and cell mediated immunity at both the humoral and cellular levels. The magnitude and range of the immune response to a specific antigen are regulated by a wide variety of factors, including soluble mediators derived from various cell types which serve as additional signals to the immune response mechanisms. In this regard, microorganisms and their products, including those derived from Gram-negative and Gram-positive bacteria, are known to exert marked influences on the immune response system of animals and man, both in vivo and in vitro[2,8,11]. Microbial products have been shown to either enhance or suppress the immune response as well as to modify the nature of the response. In addition, many microbial agents, especially viruses, are now known to have the ability to markedly influence the immune response mechanisms, both at the cellular and humoral levels[1,3,4,7,9,10]. In addition, all other microbial classes, including fungi and yeasts, rickettsiae, and single or multiple cellular parasites, are also known to affect immune competence. Besides stimulating specific immune responses to the microorganism itself, antigens derived from many of these microbes are now known to affect in a negative or positive manner a wide range of immune responses.

Polyclonal adjuvantic effects of bacteria and viruses, as well as the immunoderegulation occurring in many microbial infections, are important characteristics of the interaction of microorganisms with a host. In this regard, the effects of a

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given microbial agent or its products may be on the afferent limb of the immune response arc, the sensitization phase or, in contrast, on the efferent or effector phase. It is often difficult to ascertain which phase if any is involved and frequently both may be influenced by a microbial agent. Moreover, the specific mechanism of action on the immune system may be difficult to ascertain. For example, the sensitization stage or disposition of specific antigen to which an individual is responding may be altered or there may be a direct effect on cells participating in the reaction, i.e., macrophages, T or B lymphocytes, etc. On the affector phase of the humoral immune response, qualitative changes in antibody functional activities, alterations in activation of classic and alternative complement pathways, or changes in the release or action of pharmacological mediators may occur. In reactions of cell mediated immunity, the affector cells, i.e., lymphocytes or macrophages, as well as their products, may be affected by microbial agents.

This review will be limited to a general discussion of the effects of selected bacteria and viruses on the immune response system, especially in regards to predisposing immunodeficiency of the host infected with a microorganism, either a bacterium or virus, and in terms of altered immune competence and dysfunction.

GENERAL EFFECTS OF MICROORGANISM ON THE IMMUNE RESPONSE SYSTEM

The immune response system, especially its interaction with microbes, is being increasingly investigated since it is apparent that immune competence of a normal individual depends upon a complex network of interdependent components. A comprehensive knowledge of the immune system depends upon analyses of each of these components as well as the mechanisms of their interactions. Knowledge of the nature of the immune response provides an essential basis for understanding the mechanism of how a microbe interacts with the immune system. The basic mechanisms controlling different types of immune responses resulting from challenge with a microbe are complex. An imbalance of hemostasis and deregulation of lymphoid cell proliferation and maturation often occurs during infection or exposure of an individual to microbial agents. The lymphoid system is highly dynamic and regulated by an intricate network of interactions among different cells, including lymphoid cells and accessory cells, as well as between cells and soluble mediators, antibodies, antibody-antigen complexes and idiotype-antiidiotype networks.

Lymphoid cells capable of recognizing antigens serve a central role in the immune system and may be divided into two major sublines: a) B-cells (bone marrow derived) i.e., lymphocytes that express antibody molecules on their surface

and can be induced to produce and secrete antibodies; and b) T cells, i.e., stem cells "educated" in the thymus to recognize specific antigens in conjunction with cell surface proteins coded for by the major histocompatibility complex.

T cells may be divided into several subsets which carry out different effector cells functions. Some T cells mediate local delayed hypersensitivity reactions, others are cytotoxic and lyse either cells infected with an intracellular microbe or tumor cells. Other regulatory T cells may help or suppress different immune responses affected by other lymphoid cell populations. These T cell populations vary in phenotypic expression of defined surface proteins but the nature of the T cell receptor remains elusive. The B cell population is also heterogeneous and evidence for several functionally separate subsets of B cells has accumulated. B cell subsets are defined by differential responsiveness to a selection of antigens, either directly or by means of T cells. B cells with suppressive activity have been described in a number of systems in the absence of antibody involvement. However, it is evident that antibody can inhibit the generation of effector T cells and exert a feedback control.

Following antigenic challenge, both T and B cells divide and differentiate, resulting in antigen reactive populations of memory cells, and also mature into cells that carry out effector functions, such as antibody secretion or target cell killing. In addition to T and B lymphoid cells, which are responsible for recognizing both self and non-self antigens, certain accessory cells such as macrophages and natural killer cells are now known to play an important role in responding to various antigens including those derived from microbes, interacting with lymphoid cells as well as controlling their function. Among these various cell populations, macrophages and T cells are important in removing invading microorganisms in the presence of antibodies. The function of the system thus depends on continuous developmental stages in the life of different lymphoid cell populations and a highly complex network of interactions among cells and secretory molecules provided by some of the effector and accessory cells regulating the system.

During the normal immune response, the network is finally balanced to permit the induction of different types of immune responses as required, followed by additional responses leaving the host with memory T and B cells. The development of immunological memory occurs rapidly following exposure to a microorganism or other antigens and reflects the ability of the host to respond more rapidly and effectively to a subsequent encounter with the same antigen because more cells, at an advanced level of development, are available to interact specifically with the antigen.

It should be noted that immune balance may be readily perturbed during an infection, potentially leading the host to show altered control of lymphoid cell function. Examples of the presence of persistent virus infection despite immunological responses is well known in infections by viruses such as hepatitis B, herpesviruses, parainfluenza viruses, etc.[1,9]. Similar events may occur with intracellular microbial infections[2,11]. Possible mechanisms enabling the microbe to abrogate the host's immune response involves the localization of the microorganism within sites that are protected from the immune response of the host, but quite often may be due to a direct effect of the microorganism on the immune response, depressing specific or nonspecific reactions. A general discussion of how bacteria and viruses may influence the different pathways of the immune response system is presented below.

EFFECTS OF BACTERIA AND THEIR PRODUCTS ON IMMUNITY

It is widely acknowledged that many bacteria, both Gram-negative or positive, may influence the immune response mechanisms either by directly infecting cells of the immune response system or releasing soluble substances which have immunomodulatory properties. Numerous studies in recent years have been concerned with the adjuvantic activity of bacteria and their products as well as the general or selected immunostimulatory or suppressive properties of such organisms. Considerable work has been concerned with the action of immunomodulatory components of bacteria. A common mechanism so far has not been elucidated and it is probable that different microorganisms affect the immune response system in different ways. However, certain mechanisms of action appear to be common in regards to immunostimulation. Many bacteria and their antigens act directly on cells involved in the immune response system. They also may modify the configuration and presentation of antigens, alter the metabolism of antigens by lymphoid cells and, when acting directly on the response system, may interact directly with cells resulting in activation of macrophages, B cells or T cells. Bacteria and their products may affect the immune response by specifically acting on certain cell membrane enzymes causing their activation or inhibition.

In terms of immune suppression, it is quite apparent that most pathogenic bacteria, as well as opportunistic microorganisms in general, not only must first establish themselves within a host, but must also avoid destruction by the immune response system. Various interactions of bacteria with the host defense system are therefore central to the nature of bacterial virulence. A non-immune host depends upon non-specific defenses such as complement, phagocytosis and nutrient limitation.

Even when specific protective immunity is present, it often functions merely by refining nonspecific mechanisms. It is apparent that defenses against bacterial infections include not only nonspecific humoral defenses based on phagocytosis, complement and other cellular and soluble humoral factors, but also on specific immunity. A brief review of some of the components associated with microorganisms which are now known to be involved in the resistance of a microorganisms against the host defense system is discussed below.

Gram-positive bacteria, including cocci, have long been known to have mechanisms whereby they can elude the host defense system. Among the Gram-positive organisms the staphylococci and streptococci have been studied in some detail in terms of immunomodulatory factors. As indicated in Table 1, staphylococcal extracellular or surface components such as capsules or clumping factors, protein A and protein B, as well as many extracellular enzymes including enzymes specific for host serum proteins, blood cell membranes, leukocytes, etc., may influence the immune response in a variety of ways. More recently, it has been shown that the cell wall components of cocci, including peptidogylcan and lipotechoic acids, are strongly immunomodulatory. The host responds to these factors by formation of antibody and specifically-sensitized T lymphocytes. Nevertheless, rapid growth of these bacteria in a susceptible host often results in the release of toxins and cellular components which may depress in a specific or nonspecific manner the host immune system.

Gram negative bacilli, in particular, have been studied in great depth in terms of immunomodulatory activities (Table 1). It is now widely acknowledged that Gram-negative bacilli influence in both a negative as well as positive manner, nonspecific as well as specific host defenses[2,11]. Most of these activities have been associated with the lipopolysaccharide (LPS) structure of the cell walls of these bacteria. Such LPS may contribute to resistance of most Gram-negative bacteria to complement associated lysis[8]. This may be due to superficial branched chain sugar residues of LPS, which may interfere with access of complement to target antigens on the cell envelope. The presence of LPS may also be involved in resistance of some organisms to natural killing by phagocytes. LPS has been studied in much detail immunochemically and is known to be the structural component of cell walls of all Gram-negative bacteria. LPS may serve as a powerful adjuvant for antibody formation in vivo as well as in vitro. It may also abrogate immunologic tolerance and convert a tolerogenic dose of an antigen into an immunogenic one. LPS may also induce nonspecific differentiation of B cells into antibody forming cells, i.e., polyclonal activation. It also may stimulate lymphocytes to produce soluble mediators, as well as macrophages, stimulating their differentiation and inducing them to produce a wide variety of soluble immunostimulatory molecules.

Table 1. Bacterial Factors Affecting Immune Responses

BACTERIA	FACTOR
Gram-Positive Cocci	
Staphylococci	Capsule, clumping factor, Protein A and B, teichoic acid
Streptococci	Lipoteichoic acid, membrane enzymes, pyrogenic exotoxin, peptidoglycans
Pneumococci	Capsule, cell wall
Gram-Negative Cocci	
Neisseria	Cell walls, cord factor, exotoxins
Other Bacteria	
Mycobacteria Cornebacteria	Cell walls, cord factor, peptidoglycans, MDP
Gram Negative Bacilli	
Enterobacteriaceae, Vibrios, Pertussis	Lipopolysaccharide, cell wall components, exotoxins

In vitro treatment of macrophages with LPS activates these cells to produce essentially all of their currently recognized products, including lymphocyte activating factors, i.e., interleukin 1, which acts on T lymphocytes, interferons, colony stimulating factors, prostaglandins, and cellular metabolism factors, as well as other factors.

Although the effects of LPS on B lymphocytes and macrophages are now well established, until recently it was not generally appreciated that LPS may act on T lymphocytes as well. It is now known that the lipid A moiety of LPS enhances the differentiation of thymus populations in vitro. In terms of LPS induced adjuvanticity, it has been found that in vitro stimulation may be mediated by effects on T lymphocytes and macrophages. This does not necessarily depend on direct effects on these cells. LPS stimulation of macrophages may result in release of factors such

as lymphocyte activating factor, and may also result in stimulation of T cells to produce immunostimulatory proteins such as T cell replacing factor or interleukin 2.

Mycobacteria have been studied in great detail in terms of their effects on immune responses (Table 1). Mycobacterial antigens in particular have been incorporated into oils and such preparations have been considered among the most potent stimulants in increasing antibody levels and also potentiating production of delayed hypersenstivity reactions. Recently the chemical structure responsible for the adjuvantic activity of mycobacteria has been elucidated and is similar to the active material involved in the adjuvantic activity and immunoregulatory properties of many other microorganisms. The peptidoglycan lipid material associated with the wax D of these bacteria was utilized to obtain a water soluble nitrogenous material with adjuvantic activity[6]. This nitrogen-containing fraction was characterized by Lederer and associates in France and by Kotani and collaborators in Japan, as the minimal adjuvantic component of bacterial cell walls. This material has been identified as N-acetylmuramyl-L-alanyl-D-isoglutamine (MDP) and can replace mycobacteria in oil adjuvants and has as its primary target macrophages which release monokines which, in turn, activate B and T cells[6].

It is widely recognized that other bacteria have marked immunoregulatory activities. For example, soluble Bordetella pertussis extracts affect both specific and nonspecific immune responses. Soluble extracts are rich in both endotoxins and exotoxins. The exotoxins in particular preferentially augment IgG as well as IgE antibody formation. This may result from direct stimulatory effects on T and B cells. Macrophage activating activity has also been found in pertussis extracts. Many immunostimulatory properties of pertussis appear to reside in the same components responsible for pharmacological effects.

INFLUENCE OF VIRUSES ON IMMUNITY

It is widely acknowledged that many viruses may affect the immune responses either in a negative or positive manner[1,3,4,7,9,10]. Many viral infections suppress one or more components of the host defense mechanism. Which components are impaired and to what extent they are impaired, depends on the many variables among which are virus type and strain. The mechanisms, however, which cause such immunosuppression are still poorly defined and probably are highly diverse. Nevertheless, studies with many different viral infectious agents indicate that some generalizations are possible. In most, if not all instances, some insights into mechanisms have shown that immunologic impairment is due to functional alterations of immunocompetent cells (Tables 2-4). These, in turn, may be caused by direct interactions of

a virus with lymphoid cells and less frequently by substances produced by other cells as a consequence of viral infection.

Many viruses appear to be endowed with direct immunosuppressive properties. However, different cells may be affected by different viruses. Numerous alterations of immunocompetent cell function have been observed in the course of different viral infections. Such functional alterations do not necessarily presuppose extensive damage of lymphoid tissue. In fact, hyperplastic changes may occur but as a rule, substantially few, if any, histological alterations of lymphoid tissue become evident in viral infection. Nevertheless, in some viral infection, lymphatic tissues show lesions usually limited in scope, which may resemble the cytopathic effects characteristic of the infecting virus in vitro. For instance, during measles infections, typical giant cells may develop in various lymphoid organs beginning at the very early stages of infection. Furthermore, in general, viral infection such as dengue hemorrhagic fever, results in various degrees of cellular depletion which affect specific and distinct areas of the lymphoid tissue.

Table 2. Viruses Known to Replicate in Immunocompetent Cells

VIRUS	CELL TYPES
Poliomyelitis	Mo; L*
Coxsackie B	L+
Echo	Mo; L*
Influenza	Mo; LT (abortive infection)
Parainfluenza	Mo; LT; LB
Measles	Mo; LT*; LB
Mumps	L+
Rubella	Mo; LT
Yellow fever	Mo; LT
Dengue	Mo; LB; LT*
Lymphocytic choriomeningitis	Mo
Adenovirus	L
Herpes simplex	Mo; Lt*; LB*
Varicella zoster	Mo
Cytomegalovirus	Mo; LB
Epstein-Barr	LB
Vaccinia	Mo L*

Mo = macrophages; L = lymphocytes not characterized; LB = B lymphocytes; LT = T lymphocytes; * = viral replication is possible or is substantially potentiated, if cells have been specifically or unspecifically stimulated).

The structural integrity of lymphoid tissue does not prevent immunocompetent cells from exhibiting profound manifestations of functional deficiency. A typical example is the reduced in vitro blastogenic reponses of lymphocytes to specific antigens, mitogens, or alloantigens in many viral infections which are readily reproduced in experimentally infected animals. Among the various other modifications of immunocompetent cell behavior are those of lymphoid cell migration, both in vivo and in vitro. Modifications in lymphocyte traffic are well documented and have contributed to cell surface changes which subsequently reduce the ability of affected cells to interact with either endothelial cells of vessels or other reticuloendothelial cells. Altered cell traffic patterns may account for the fluctuations of peripheral blood leukocyte counts which occur in many viral diseases and which remain unexplained. It is widely recognized that lymphopenia occurs in various virus infections such as those induced by measles, rubella, varicella, poliomyelitis and influenza, as well as those caused by coxsackievirus, adenovirus and arbovirus infections. Transient lymphopenia may be present in early stages of viral infections and may become pronounced, affecting all or only selected cell populations.

It seems likely that the major mechanisms whereby immunocompetent cell alterations occur in virus infections may be associated with either direct activity of the virus or an indirect one mediated by soluble factors (Table 4). Direct action of the virus may occur, expecially in acute phases of infection where virus sometimes is isolated from peripheral blood leukocytes. Many viruses are capable of replicating within immunocompetent cells (Table 2). Various studies have permitted recognition of the cellular types and specific subtypes of lymphoid cells susceptible to virus infections. Experiments in vitro in which various immunocompetent cell classes have been infected have proven fruitful in providing new information concerning virus-cell interactions and the possible regulatory factors involved.

It has been established that the outcome of the interaction between a virus and an immunocompetent cell markedly depends upon the metabolic state of the target cell itself, possible more so than with the virus type (1). Thus, macrophages, often restricted for many viruses, may undergo changes in susceptibility to virus infection once specifically activated through signals emitted by lymphocytes. In turn, the latter cells, if placed in contact with a virus while in the quiescent state, very often result in abortive infection followed by incomplete synthesis of virus

immunocompetent cells have been observed repeatedly. Soluble substances toxic for lymphocytes have been found in various patients in the acute phase of different viral infections (Table 3). Furthermore, it has been found that serum factors nonspecific-

Table 3. Parameters of Immunological Responsiveness Suppressed During Viral Infections

IMMUNE PARAMETER	VIRUS
Ig levels in serum	Congenital rubella
Antibody response	Many
Antibody-dependent hypersensitivity	Junin
Circulating autoantibody	Reovirus, selected retroviruses
Spontanteous autoimmune lesions	Lactic dehydrogenase virus
Cell-mediated hypersensitivity	Many
Contact sensitivity	Polio, Coxsackie B, mumps, measles, Epstein-Barr
T-cell-mediated cytotoxicity	Selected retroviruses
Skin allograft rejection	Cytomegalovirus (murine), Marek
Graft-versus-host induction	Dengue
Immunological maturation	Lymphocytic choriomeningitis
Tolerance induction	Venzuelan equine encephalitis, lymphocytic choriomeningitis
Lymphocyte and antigen trapping by spleen	Lactic dehydrogenase virus
Resistance to superinfection	Cytomegalovirus, influenza, measles, parainfluenza
Resistance to tumor induction or growth	Cytomegalovirus (murine), lactic dehydrogenase virus

ally inhibiting cell mediated responses may occur in patients with infectious mononucleosis or hepatitis. Although such factors appear not to be viral components, their exact chemical nature and role have yet to be defined. In addition, tissues outside the immune system may release substances during virus infection which affect the immune responsiveness. This is exemplified by fibroblast interferon which is endowed with distinct immunomodulatory properties. Similarly, the gamma-interferon released by certain activated lymphocytes also has immunoregulatory properties that may be induced by virus infections. It should be noted, finally, that some of the pathogenesis associated with virus-induced immunomodulation may be

due to autoimmune "phenomena" in which viral antigens are expressed on lymphoid cell surfaces. These antigens may then be recognized by other immunocompetent host cells, which then react against lymphoid cells bearing the virus antigen. Such cells, even though functionally normal despite their virus infection or expression of viral antigen, are then destroyed or inactivated, resulting in net loss of immunocompetent cells and/or immunologic determination.

Table 4. Some Stratagems, Other than Immunosuppression and Immunocompetent Cell Invasion, that Allow Viruses to Elude Host Immune Defenses

Integration in unexpressed form into host cell DNA	Papovaviruses, retroviruses
Intracytoplasmic latency with occasional reactivation concomitant with declines in host resistance	Herpes simplex, varicella - zoster
Direct cell-to-cell spread	Herpes simplex, cytomegalovirus
Budding on intracellular membranes	Coronaviruses
Antigenic drift	Influenza, visna
Deletion of virion envelope genes	Defective retroviruses
Propagation as naked genomes	Putative viroids (rheumatoid arthritis)
Incorporation of host antigens in virion envelope	Retroviruses
Lack of stimulation of immune responses	Unconventional viruses (spongiform encephalopathies)
Partial tolerance	Lymphocytic choriomeningitis, rubella
Induction of non-neutralizing antibodies that hinder neutralization or facilitate viropexis	Lactic dehydrogenase virus, dengue, reoviruses
Production of excess soluble antigens that compete with virions for immune effectors	Hepatitis B
Depression of response to interferon induction	Cytomegalovirus, lymphocytic choriomeningitis, selected retroviruses
Low sensitivity to interferon	Adenoviruses
Induction of anticomplementary factors	Junin virus
Invasion of body districts in which immune effectors are weak (skin, exocrine glands, kidney, CNS)	Papilloma, mumps, Creutzfeld-Jakob, KB, measles

DISCUSSION AND CONCLUSIONS

It has now become widely appreciated that the interaction of microorganism and a host is a two-way reaction in that the host attempts to respond to the microbe by preventing attachment, colonization and eventually infection and, in turn, the microbe attempts to subvert the defense mechanism of the host in order to establish a foothold. Over the millions of years of natural selection of a host and its parasites, a symbiotic relationship has developed in which most microorganisms, after establishment within a certain species, do not cause harmful effects. In turn, much of the responsiveness of the host to microorganisms may actually be of benefit to the host in that the immune system develops, matures, and becomes competent only after constant exposure to normal flora from birth onwards. In terms of possible detrimental effects, it is now apparent that microorganisms interact with nonspecific host defenses by developing methods to avoid complement and antibody-associated lysis and utilizing nutritional and environmental factors from the host for their own benefit. The host, in turn, may resist invasion by a microorganism, even after colonization has occurred, by mobilization of bone marrow-derived cells necessary for nonspecific immune defenses as well as by inflammatory and chemotactic reactions to the invading microorganism, opsonization of the microbe by humoral antibody and complement, phagocytosis, and finally, intracellular killing of those organisms which penetrate into the host proper and intracellular millieu. As a consequence, many microorganisms, especially pathogenic ones, have evolved "virulence" factors and they are often capable of overcoming some or all portions of the host defense system. These include genetically and phenotypically programmed microbial factors such as capsules, cell wall components and extracellular products which may either prevent the microorganism from being recognized and opsonized by the host and/or actively subvert the immune response system.

Many factors associated with different pathogenic microorganisms as well as opportunistic pathogens and normal flora are now known to be immunomodulatory. It is now widely recognized that relatively small amounts of many bacterial products, as well as virus components, may serve as potent stimulators of specific components of the host defense responses, including phagocytic reactions, B and T lymphocyte activities and macrophage function. It is important to note, however, that there are relatively large amounts of the same components which have also been found in many cases to be immunosuppressive and to block various host immune defenses. Thus, there is a crucial balance between the responses of the host to a relatively small quantity of microorganisms or their products vs. the inability of the host and its defense mechanism to be activated or respond in a productive manner to

larger amounts of the same products. A further understanding of the complex interactions between microorganisms, including bacteria and viruses, with the host defense system is necessary to develop a more rational basis for successful treatment of infectious agents, especially those which are associated with immune deficiency. With the advent of many immunorestorative substances and development of new knowledge in the area of immunopharmacology and immunobiology in general, a better understanding of basic interactions between microbes and the host immune system is evolving so that the appropriate strategy may be developed to tip the balance of the host-parasite relationship in favor of the host during infectious diseases.

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