VIRUS INTERACTIONS WITH THE IMMUNE DEFENSE SYSTEM

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Viruses, which are obligate intracellular parasites, are not only cytolytic for target cells, but also may affect many physio-pharmacologic and immunologic parameters of the host. In particular, viruses may influence humoral or cellular immune defenses that develop as protective mechanisms against microbial infection (24,31,33,37,38,40). In this context, viruses have developed various strategies to survive in harmony with a host in which they replicate. One such mechanism is the ability to subvert or impair immune responses, especially those, which may be detrimental to the survival of the virus (2,4,10,17-20). The methods whereby viruses may affect immunity, either in a positive or a negative manner, are still not clear. In general, modification of host immune responses may be manifested by altered humoral or cellular immunity, or both, as well as altered susceptibility to infection by the same or other microorganisms.

GENERAL CHARACTERISTICS OF VIRUS INTERACTION WITH THE IMMUNE SYSTEM

The type as well as strain of a virus, the genetic and phenotypic character of the host, are important determinants in establishment of a virus infection, either overt or subclinical (2,12,15,17,37,40). Viruses have a strong affinity for certain cell types. Although specific receptors on various cell populations are important for initiating the process resulting in virus replication (14), various nonspecific factors may also influence resistance vs. susceptibility. For example, factors as divergent as the temperature of the host, pH of the body fluids, general environmental niche of both the host and virus, etc., serve an important role in delineating the host/parasite relationship in virus infections. There are also a series of effectors, both specific and nonspecific, which are specialized in nature and probably evolved to counteract viruses and other invading agents. For example, phagocytosis is considered an important aspect of host defenses to viruses (2,21,24,33,40) together with nonspecific antiviral serum factors, including enzymes such as lysozyme, the complement system, etc. As far as specific immunity is concerned, it is widely accepted that antibody responses to specific viral antigens are important in limiting viral invasion. Thus, lymphocytes sensitized with specific antibody as well as T lymphocyte responses during cell mediated immunity are considered essential components

A. Szentivanyi et al. (eds.), *Viruses, Immunity, and Immunodeficiency*

of resistance to most viruses (2,39,40). Humoral mediators, that is lymphokines, monokines, and cytokines, including interferons and interleukins, have important roles in antiviral immunity. Many of these agents are produced not only by lymphocytes and macrophages but also by other cell types which may serve as a target for virus infection.

VIRUS INDUCED IMMUNOMODULATION

Viral infections may suppress or enhance one or more components of the immune system (3,5,8-11,17-23) while under certain circumstances no detectable effect may occur. The virus infection may induce specific immune paralysis, especially when infectious to a newborn or fetus as well as nonspecific immune suppression, either finite or permanent (17-20). It is the latter type of suppression which has attracted much attention in recent years, especially with recognition that certain retroviruses may suppress immunity not only in experimental animals but also in man.

Conversely, viruses may stimulate specific as well as nonspecific cellular and humoral immune responses to the virus itself or to its components. Enhancement of cellular and humor immunity mostly occurs through direct stimulation of lymphoid elements or through altering the secretion or formation of immunoactive substances by these cells.

Table 1. Major Effects of Viruses on Humoral vs. Cellular Immune Responses and Cells of the Immune System.

Virus	Immune System Affected		Cell Type Affected		
	Cell-Mediated	Humoral	Macrophages	T cells	B cells
Adenovirus	+	+		+	+
Coxsackievirus	+	+			+
Cytomegalovirus	+	+	+		+
Dengue	+	+	+	+(±)	+
Echovirus	+	+	+	+(±)	
Epstein-Barr	+			+	
Hepatitis A	+		+	?	?
Hepatitis B	+		+	+	
Herpex Simplex	+	+	+	+(±)	+(±)
Influenza	+	+	+	+(±)	
Lymphocytic choriomeningitis			+	+	
Measles	+	+	+	+	+
Mumps	+			+	+
Poliovirus	+		+	+(±)	
Retrovirus	+	+	+	+	+
Rabies	+		+	+	
Rubella	+	+	+	+	
Smallpox	+		+	+(±)	
Vaccinia	+		+		
Varicella-Zoster	+		+	+	
Yellow Fever	+				

Table 1 lists the major effects of viruses on humoral and cellular immune reactivities and the cell types that participate in the organization of these responses. Table 2 presents some of the cell classes or parameters of immunologic responsiveness which have been found suppressed during viral infections. The mechanisms whereby such suppression occurs are still ill-defined and probably highly diversified, but from studies concerning many different viral infections some generalizations are now possible. In most, if not all instances where some insights into mechanisms have been obtained immunological impairment appears due mainly to functional alterations of immunocompetent cells. This may occur because of direct interactions of immunocompetent cells with a virus and/or less frequently by substances produced by cells as a consequence of viral infection (2-5,17-20). As indicated in Table 1, a large number of viruses have been found to replicate in lymphoid cells, including T and B lymphocytes and macrophages. Such replication may affect the functional activity of the lymphoid cells and the general immunocompetence of the individuals (Tables 3, 4, and 5). Alteration of cell mediated immunity may be due to effects of a virus on T lymphocytes or macrophages, or both, as well as related to products produced by B cells. Humoral immunity can be affected not only by the influence of virus on B lymphocytes, but also on helper or regulatory T lymphocytes as well as accessory macrophages necessary for antibody responsiveness.

Because of functional complexities, the immune system can be affected by viruses that influence different levels of the response system. Such functional alterations do not necessarily presuppose extensive damage to lymphoid tissue itself. Indeed, hypoplastic changes may occur but, as a rule, substantially few, if any, histologic alterations of lymphoid tissues become evident during many viral infections (2,17-20). Nevertheless, in some virus infections lymphatic tissues show usually limited lesions which may resemble the cytopathic effects characteristic of the infecting virus in vitro. For instance, in measles infection typically polynucleated giant cells develop in various lymphoid organs beginning at the very early stages of infection. Furthermore, in certain viral infections various degrees of cellular depletion may occur which affect distinct areas within the lymphoid tissue.

Table 2. Parameters of Immunological Responsiveness Suppressed During Viral Infections

Virus	Immune Parameter
Congenital Rubella	Ig levels in serum
Junin	Antibody-dependent hypersensitivity
Reovirus, selected retroviruses	Circulating autoantibody
Lactic dehydrogenase virus	Spontaneous autoimmune lesions
Lactic dehydrogenase virus	Lymphocyte and antigen trapping by spleen
Polio, Coxsackie B, Mumps, Measles, Epstein-Barr	Contact sensitivity, cell-mediated hypersensitivity
Retroviruses	T cell-mediated cytotoxicity
Cytomegalovirus, Marek	Skin allograft rejection
Dengue	Graft-versus-host induction
Lymphocytic choriomeningitis	Immunological maturation
Venezuelan equine encephalitis, lymphocytic choriomeningitis	Tolerance induction
Cytomegalovirus, influenza, measles, parainfluenza	Resistance to superinfection

The structural integrity of lymphoid tissue does not prevent immunocompetent cells from exhibiting profound manifestations of functional deficiency. A typical example is reduced in vitro blastogenic responsiveness of lymphocytes to specific antigens, mitogens, and alloantigens which is readily reproducible in experimentally infected animals (17-22,25,27). Tables 4 and 5 list some of the alterations in lymphoid classes which have been noted during virus infections in vivo or, in experimental situations, in vitro when individuals or cells are infected with a particular virus. For instance, B lymphocyte number and function can be markedly altered by viruses, either in a positive or negative manner both in vivo and in vitro. T cells are also readily affected. In addition, viruses affect other lymphoid cells, including null cells, K cells, NK cells, etc. Traffic of infected lymphocytes may also be affected by virus infection (1,2). This may be due to cell surface changes which reduce the ability of cells to interact with endothelial cells or to "home" to appropriate target organs.

Altered peripheral lymphocytes may also occur in many viral diseases. It is widely known that infections induced by measles, rubella, varicella, poliomyelitis, adenovirus or arbor viruses markedly alter lymphocyte number and function. Such changes are often transient. For example, lymphopenia may be present in early stages of certain infections or may become pronounced later, affecting all or only selected cells or subpopulations of lymphocytes.

Major effects of virus infection may be associated either directly or indirectly with mediators of immunological mechanisms (5-7,16). A direct

Table 3. Possible Mechanisms of Virus Induced Immunosuppression

Inactivates or modifies (binds) Ig, including antibody and antibody forming cells.
Inactivates complement or complement producing cells.
Directly infects antibody producing B cells.
Directly affects effector and/or helper/suppressor T cells or their functions.
Affects precursor T or B cells or stem cells.
Affects macrophages and their function.
Induces suppressor T cells or macrophages.
Indirect effects on B or T cells or macrophages by products induced by other cells, either lymphoid or non-lymphoid.
Induces immunomodulatory soluble substances such as lymphokines, monokines, prostaglandins, leukotriens, specific kinins, the amine mediators (histamine, serotonin, acetylcholine, the catecholamines) etc.
Suppressor Ag (virus)/antibody complexes.
Direct or suppressive effects by virus components.
Direct or indirect suppressive effects by products of virus infected cells (suppressor molecules).

Table 4. Alterations in Lymphocyte Function or Activity by Viruses

B Lymphocytes:	
Peripheral blood number	Increase or decrease
Surface Ig expression	Decrease mainly
Surface Ig capping	Decrease mainly
Proliferation, spontaneous	Increase mainly
Mitogen induced blastogenesis	Decrease mainly
Polyclonal Ig synthesis	Decrease or increase
Specific antibody formation	Decrease mainly
T Lymphocytes:	
Peripheral blood number	Increase or decrease
E-rosette formation	Decrease mainly
Thy-antigen expression	Increase or decrease
Proliferation - spontaneous	Decrease or increase
Mitogen induced blastogenesis	Decrease mainly
Antigen-induced blastogenesis	Increase mainly
Lymphokine production	Decrease mainly
Cytotoxicity	Decrease mainly
Antibody dependent cytolysis	Decrease mainly
B-cell helper activity	Decrease mainly
Suppressor cell activity	Increase or decrease
Uncharacterized Lymphocytes:	
Peripheral blood number	Increase or decrease
Leukocyte circulation and migration	Increase or decrease
Proliferation - spontaneous	Increase mainly
K and NK Activity:	
Natural cytolysis of target cells	Increase or decrease
Antibody dependent cytolysis	Decrease mainly
Interferon production	Decrease mainly
Response to cytokines	Decrease mainly

action of a virus may affect mediator formation or storage, especially during cytolytic infection of leukocytes, although it is to be noted that certain viruses do not replicate within leukocytes. Nevertheless, various studies have permitted recognition of cellular classes and sometimes specific subclasses of lymphoid cells capable of replicating viruses. Experiments in vitro have shown that many lymphoid cells may be targets of virus infections, in general, and macrophages in particular (3-5,13,17-22). While the latter are often restricted in susceptibility to infection by viruses, these cells may undergo changes in their susceptibility once nonspecifically activated through signals emitted by lymphocytes. As is apparent in Table 5, macrophages and monocytes in general may show functional alterations following viral infections.

It is interesting to note that despite the repeated observations that certain cells of the lymphoid system may have innate susceptibility to virus infection, activation of lymphocytes by nonspecific means, such as

mitogenic or antigenic stimulation, may alter their susceptibility (2-5). It is important to note that in vitro a variety of viruses may cause unsensitized lymphocytes to undergo polyclonal activation and/or blastogenesis. This does not appear to be experimental artifacts because lymphocytes from subjects in the acute phases of measles or rubella infection, when cultured in vitro, often show a high degree of spontaneous proliferation. Furthermore, during mononucleosis caused by EB virus extremely large numbers of activated lymphocytes appear in the patient's circulation. It is not clear whether such effects of viruses on lymphocytes are related to functional alterations. However, it should be noted that as a result of direct contact of viruses with lymphocytes in vitro immunocompetent cells may develop similar defects as those observed following in vivo experimental or clinical infections. Nevertheless, virus induced changes do not necessarily require that the virus replicates in the infected cells since in some instances inactivated viruses or purified viral components also produce in similar alterations (Table 6).

Many observations suggest that in a large proportion of cases where immune depression occurs during viral infection the mechanism may be related to the ability of a virus to interact directly with cells of the immune system and/or replicate selectively in those cell populations actively engaged in immunologic reactions (10,13,17,29,30). As seen in Table 6, indirect effects of viruses on immunocompetent cells have been observed repeatedly. Soluble substances toxic for lymphocytes have been found in patients during acute phases of viral infections. Furthermore, it has been found that serum factors that nonspecifically inhibit cell-mediated immune responses or humoral antibody formation may occur in patients with infections such as hepatitis, mononucleosis, etc. These factors include antigen-antibody complexes and a large variety of substances potentially released during viral infections such as lymphokines, monokines, specific kinins, prostaglandins, leukotrienes, the so-called amine-mediators (catecholamines, acetylcholine, histamine, serotonin) etc.

LEUKEMIA VIRUS INDUCED IMMUNOSUPPRESSION

There is much current interest concerning immunodepression induced by retroviruses. The explosive interest revolving around human T cell leukemia viruses have focused attention on the nature and mechanism whereby leukemia viruses may affect the immune response in general. There are numerous studies concerning feline, murine, and human leukemia viruses, as well as

Table 5. Effects of Viruses on Macrophage/Monocyte Function or Activity

Number in peripheral blood	Increase mainly
Attachment/spreading on surfaces	Increase or decrease
Motility/chemotaxis	Decrease mainly
Phagocytosis	Increase or decrease
Phagosome-lysosome fusion	Decrease mainly
Microbe or particle ingestion	Decrease
Cytolysis/cytostasis	Increase or decrease
Antigen/presentation	Increase
Ia antigen expression	Decrease
Suppressor cell activity	Increase
Soluble mediator formation	Increase or decrease
Interferon production	Decrease

Table 6. Some Mechanisms, Other than Immunosuppression, that Allow Viruses to Elude Host Immune Defenses

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

the avian leukemia and leukosis viruses (2-4,17,20-22,35). The murine leukemia viruses in particular have been studied in great depth in regard to biochemistry, epidemiology and pathogenesis and there is an expanding literature on the nature and mechanism whereby leukemia viruses suppress immune function. The latter may directly affect the function of immunocompetent cells, and they also induce altered lymphoid cell surfaces resulting in auto-immune type responses of the host to the altered cells. The systemic antitumor virus immunity may result in the release of relatively high levels of immunosuppressive factors. Tumor virus antigen/antibody complexes may also serve as nonspecific immunosuppressants.

Viral antigens or inactivated virus may affect antigen processing cells such as macrophages, and the virus itself, or its antigens, may affect antibody precursor cells as antigen reactive cells, etc. Many of these mechanisms have been studied in great detail in recent years. Among these studies

have been those concerning immunosuppression induced by the Friend leukemia virus (FLV) complex. During the early 1960's it was observed that Swiss mice infected by FLV showed depressed immune responses to an antigen such as sheep red cells (2-4,17-20). Stemming from this observation are the extensive investigations concerning the mechanisms involved. A complex series of interactions occur following infections of a susceptible mouse with this virus, resulting in marked splenomegaly, hepatomegaly, and blood cell dyscrasia, culminating in erythroleukemia and death of the animal (28,32,36). Besides direct immunosuppression, heightened susceptibility to infection with other viruses, bacteria, and fungi also occurs (34).

Studies on immunosuppression induced by FLV have dealt with the effects of the virus on both antibody formation and cell mediated immunity, especially to nonmicrobial antigens. As is evident in Table 7, following infection of susceptible BALB/c mice with FLV a marked increase in spleen weight occurs, concomitant with a marked decrease in antibody formation, both primary and secondary, to a T-dependent antigen like sheep red cells or a T-independent gram negative bacterium. The level of immunosuppression is related to the dose of virus used for infection as well as the type and form of antigen used for challenge. Suppression of antibody response also occurs for protein antigens, bacteria and other viruses (2-4,17,20-22). Mice infected with FLV also show decreased delayed hypersensitivity reactions and allograft immunity. Examination of the antibody responsiveness of FLV infected mice has provided information concerning the possible mechanisms involved. Although it was felt initially that the virus may compete with antigen for a

Table 7. Effects of Friend Leukemia Virus (FLV) Infection on Antibody Responses in Vivo to Sheep RBC's and E. coli LPS

Day After Infection[B]	Spleen Weight (mg)	Antibody response (PFC[A]/Spleen)* AntiSRBC[C] Primary (IgM)	Secondary IGM	Secondary IgG	Anti E. Coli[D]
None (control)	122± 13	42,500	38,750	97,500	65,300
- 1	129± 11	46,300	30,300	66,300	70,100
- 3	136± 22	31,400	15,500	44,400	51,300
- 5	158± 30	12,900	10,300	21,500	32,100
- 8	197± 43	5,310	6,500	12,300	19,400
-15	1640±380	1,500	2,100	3,100	2,400

*Individual Spleens for 3-5 mice per group.

[A]Plaque Forming Cells (PFC)

[B]Groups of BALB/c mice injected i.p. with ID_{850} FLV on day indicated relative to day of immunization with 4 x 10^8 SRBC or 10^9 heat killed E. coli.

[C]Average number of hemolytic PFC to SRBC per spleen for 3-5 mice per group four days after primary or secondary immunization of mice with SRBC; IgG PFC's detected by antiglobulin facilitation procedure using mice primed four weeks earlier with same dose of erythrocytes.

[D]Number of bacteriolytic PFC to E. coli in spleen of 3-5 mice four days after primary immunization with E. coli.

finite number of precursor cells, deviating them into the pathway of leukemogenesis, it appears likely that the mechanism of immunosuppression is much more complex. Electron micrographic studies revealed that lymphoid cells from FLV infected mice exhibited both replicating virus and antibody formation at the individual cell level (29,30). Thus it did not appear that virus infection per se inhibited antibody synthesis. B lymphocytes involved in antibody production seemed most suppressed at the single cell level. T lymphocytes also showed some defect but usually later in the infection. Budding viruses could also be seen on the surface of both B and T lymphocytes (29,30). Functional assays showed that although B lymphocytes were markedly markedly suppressed early after viral infection, helper T cell function was also inhibited within a short time after infection.

It is apparent in Table 8 that bone marrow cells derived from FLV infected animals are markedly depressed in their ability to reconstitute the immune response of irradiated animals receiving thymocytes from normal mice. In contrast, thymocytes from early infected (i.e., seven days) animals reconstituted the immune response of irradiated animals given optimal numbers of marrow cells from normal mice. However, the competency of thymocytes after infection was quite finite; within 10 days to two weeks after FLV infection

Table 8. Effect of FLV* Infection on the Capability of Bone Marrow or Thymus Cells to Collaborate in Anti-SRBC Response When Used to Reconstitute PFC** Responsiveness of Irradiated Recipient

Cells Transferred[a]	PFC per Recipient Spleen[b] Day +5	Day +10
None (control)	100	180± 62
Spleen cells - normal	3580±560	4900±730
Spleen cells - FLV infected	290± 40	386± 90
Thymus cells - normal plus normal marrow cells	3500±800	3950±765
Thymus cells - normal plus FLV marrow cells	176± 38	250± 69
Thymus cells - FLV infected plus normal marrow cells	2950±640	3250±178

* Friend Leukemia Virus

** Plaque Forming Cells

[a] Indicated suspension of cells ($5x10^6$) from normal or FLV infected donor BALB/c mice injected i.p. into groups of x-irradiated (750R) recipient mice five or ten days before i.p. immunization with 4 x 10^8 SRBC; infected donor injected with 100 ID_{50} FLV ten days before cell transfer.

[b] Average number of anti-SRBC PFC ± SE for individual spleen of 3-5 mice five or ten days after challenge immunization with SRBC.

the thymocytes lost their ability to serve as helper cells for antibody formation in irradiated animals.

Thus selected cell populations are involved in immunosuppression induced by FLV. Further analysis showed that suppressor activity was evident when cells from infected animals were co-cultured with normal spleen cells (Table 9). The major suppressor cell population appeared to be FLV transformed cells (13,29,30,35). However, cell free supernatants from these leukemic cells also had marked immunosuppressive activities, both in vivo and in vitro (Table 10). In addition, suppressor macrophages as well as an occasional suppressor T cell were also evident late after FLV infection (26,30, 35). Restoration of immune responsiveness in FLV infected mice could be accomplished with syngeneic macrophages (Table 11). Furthermore, soluble factors released from normal macrophages stimulated in vitro with bacterial lipopolysaccharide had marked immunorestorative activities for FLV suppressed spleen cell cultures in vitro (2,6,16,23,35).

DISCUSSION AND CONCLUSIONS

Many unanswered questions remain as to the role of virus induced immunosuppression in the development of the primary infection and how it contrib-

Table 9. Effect of Spleen Cells from FLV*-infected Mice on the Antibody Responsiveness of Normal Spleen Cells in Vitro

Spleen Cell Source[a]		Antibody Response[b] PFC/10^6 Spleen Cells	Percent of Control
Normal (control)		865±76	--
FLV-infected	0 day	730±32	84%
	+3 days	510±45	59%
	+7 days	320±30	37%
	+12 days	235±65	27%
	+20 days	140±38	16%

*Friend Leukemia Virus

[a]Spleen cells ($2x10^5$) from indicated donor mice added to cultures of $5x10^7$ normal spleen cells immunized in vitro with $2x10^6$ SRBC; infected mice injected with 100 ID_{50} FLV on day indicated.

[b]Average direct PFC response ± S.E., for 3-6 cultures per group five days after in vitro immunization.

utes to subsequent pathology. Although generalizations are not possible, the contribution of immunopathology to virus induced damages is quite consistent. In some infections, both the experimental and naturally acquired pathologic lesions appear to be due solely to an immune response against antigens of the infecting virus and/or against host structure(s) modified by the virus. The classic example of such disorders is the disease caused by lymphocytic choriomeningitis virus in mice (2,4). Similarly, immunopathology may contribute to the liver damage caused by hepatitis B and yellow fever viruses. Moreover, immune complexes are also found in many viral infections (4,17,18, 37-40). These may contribute to the development of skin lesions in measles, and other viral exanthemata, and represent a pathogenic basis for some of the related complications or sequellae such as polyarthritis nodosa, urticaria, and vasculitis.

Immunopathologic mechanisms triggered by virus infections have been implicated in the genesis of chronic gloumerulonephritis and other autoimmune diseases. This may suggest that at least in some circumstances immunologic impairment caused by a virus, even if it facilitates the spreading of the virus and causes a delay in recovery, nevertheless may be beneficial to the individual by containing the immunologically mediated damage caused by the virus infection. On the other hand, immunosuppression associated

Table 10. Effect of FLV-containing Cell-free Extracts on Antibody Response of Normal Spleen Cell Cultures

Addition to Source[a]	Antibody Response[b] PFC/10^6 Spleen Cells	Percent of Control
Normal (control)	955±73	--
Spleen extracts - normal	1030±80	108%
- FLV + 5 days	438±72	46%
+15 days	310±50	33%
+25 days	180±32	19%
Ascites fluid - FLV + 5 days	573±68	60%
+10 days	210±42	22%

[a] Indicated extract, in 0.1 ml quantities, added to cultures of 5×10^7 normal mouse spleen cells immunized in vitro with 2×10^6 SRBC; infected donor mice injected with 100 ID_{50} FLV on day indicated prior to testing.

[b] Average direct PFC response, ± S.E., for 3-6 cultures per group five days after in vitro immunization.

Table 11. Effect of Normal Peritoneal Exudate (PE) Cells or LPS Stimulated PE Cell Supernatants on Antibody Responsiveness of Normal or FLV-infected Spleen Cell Cultures.

Addition to Spleen Cell Cultures[a]		Antibody Response (PFC/10^6 Spleen Cells)[c]	
		Normal Cultures	FLV-infected Cultures
None (control)		738± 65	285±36
PE cells	10^3	782± 95	398±76
	10^4	810±140	435±69
	10^5	720± 78	630±88
	10^6	630± 53	686±73
PE cell supernatant[b]			
	0.1 ml	790± 48	435±60
	0.2 ml	890± 76	595±38

[a]Indicated material added to cultures of $5x10^7$ spleen cells from normal or 10-day infected mice.

[b]Supernatant obtained 48 hours after in vitro incubation of 10^6

with retroviruses, such as leukemia viruses in experimental animals, and now apparently acquired immunodeficiency in man may be important in reducing the immune competence of an individual, at least at the initial site of virus infection (2-4,17).

Replication of the virus and transformation of target lymphoid cells may occur despite the concomitant appearance in the cells of virus associated antigens that are either unrecognized or undisturbed by the host immune response. This may enable the initial virus transformation of cells to result in a rapidly replicating mass of tumor cells. Furthermore, the virus may specifically delete certain important cells necessary for normal immunocompetence, such as helper T lymphocytes as in the case of HTLV. B lymphocytes or their precursors are affected very early after infection with murine leukemia virus, whereas helper T cells at a somewhat later time (17-20). Macrophages may also be suppressed during virus infections, including leukemia virus infections (2-4).

There have been many attempts to reverse virus induced immunosuppression by various immunomodulating agents (2-4,35). In this regard it must be taken into account that some of these agents may enhance the number of target lymphoid cells, resulting in greater rather than less virus replication. Many believe that immune responses can be restored in virus suppressed individuals. This could contribute to control of the infection, but is is also possible that this may actually augment the infection. Knowledge concerning the mechanism of the immune response to viruses, including the role of different cell classes and the importance of antibody vs. other humoral factors, such as interferons and interleukins, are necessary to develop

useful strategies for treating not only the virus infection itself but the immunoderegulation caused by the infection. It seems difficult at the present time to develop rational approaches to potentiate natural defenses to viral infection and limit the damage done to or by the immune response.

SUMMARY

Many viruses interact with cells of the immune response system. Both enhancement and suppression of immunity may occur during virus infection and such effects may be related to the time of virus infection relative to the time of assay, the dose of virus, etc. Suppression in general may be due to direct effects of a virus on end stage effector lymphocytes or their precursors. Viruses may also affect stem cells or selected cell populations such as antibody producing plasma cells or B lymphocyte precursors, T lymphocytes involved in cellular immunity as effector cells and regulatory T cells such as helper or suppressor cells. Equally important, however, may be the effect of virus infections on macrophages. Both the number and functions of these cells, as well as their secretory and/or regulatory function, may be affected, usually by suppression but sometimes by enhancement. Viruses may also stimulate nonspecific suppressor activity by macrophages or T cells and thus influence the control of immune responsiveness of the host. Recent studies concerning humoral factors involved in immunity have shown that some viruses, especially the retroviruses, may induce various lymphoid and non-lymphoid cells to produce soluble substances, probably immunoregulatory lymphokines, prostaglandins, etc. Furthermore, interferon production by virus affected cells may also have marked immunoregulatory activity. Thus it is apparent that virus infections markedly influence a wide variety of immune parameters. The complexity of the interaction of viruses with the immune system indicates that further studies are necessary to dissect and understand the mechanisms involved.

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