Lymphology 21 (1988) 66-69

IMMUNE DEFECTS AND THERAPEUTIC APPROACHES TO IMMUNE RECONSTRUCTION IN AIDS/ARC

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A great deal is known about the virus that causes AIDS, but very little about the full set of pathogenic processes which follows, particularly in regard to the immune system. In this respect, the scientific effort to deal with this serious public health problem, should encompass a three pronged approach; (1) the development of antiviral agents, (2) the development of vaccines, and (3) the pursuit of drugs that modify the immune deficiency. More needs to be done on the latter. Ultimate therapy for acquired immune deficiency/AIDS-related complex (AIDS/ARC) is likely to be in the form of combination therapy, possibly utilizing antiviral medication in the short term and immunomodulators in the long term.

A primary pathogenic defect resulting from AIDS virus (HIV) infection is in the T helper $CD4^+$ cell *(Fig. 1)*. While the pathogenesis of the resultant defects are poorly understood, a prime manifestation is the loss of the patient's ability to mount an immune response against specific foreign challenges (antigens), including the causative virus itself. It is of note that the antibody which is produced after infection (and is the basis for the AIDS antibody test) is apparently not protective. Immunosupportive agents should have, as one objective, the ability to restore the patient's ability to generate normal specific responses to antigen(s). Most immunologists agree that getting these patients' immune systems to respond in a more normal fashion would make them less susceptible to opportunistic infections. That point of clinical efficacy will have to be proved in suitable clinical trials.

Loss of critical T helper function is fundamentally responsible for the difficulties of these patients. It is true that HIV is present in the brain and that neurologic symptoms develop, but it is not clear how much of the clinical dementia is directly attributable to HIV. Many serious neurologic deficits result from opportunistic infections in the brain such as toxoplasmosis, or the development of lymphomas. We still do not know how much neurologic damage is attributable to the decline in immune function and opportunistic infection, rather than to a direct effect of HIV itself. Moreover, there is no clear understanding of why Kaposi's sarcoma is such a predominant malignancy in this disease, and why only selected AIDS patients develop Kaposi's sarcoma.

It is well to note that effects of HIV on cells and tissues may require a defect in immune function as a prerequisite. We also need to know much more about cofactors that contribute to HIV infection, and viral pathogenesis.

Additional questions that require investigation are (1) the basis of the striking overproduction of non-specific immunoglobulins and (2) the cause of the follicular hyperplasia seen in the germinal

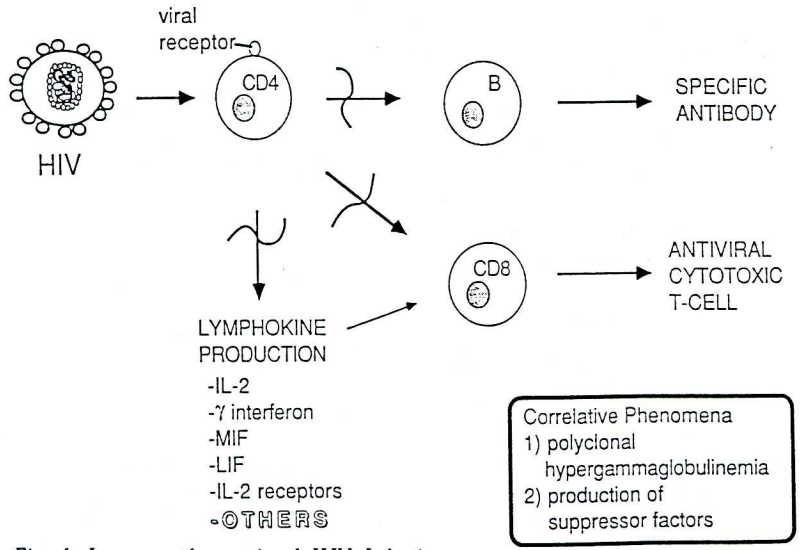

Fig. 1. Immunopathogenesis of HIV Infection.

centers. It is also unclear why infection with HIV induces antibody production against the virus. Much has yet to be learned about how to induce the formation of antiviral cytotoxic cells against HIV. There is likely to be a major defense mechanism against HIV, and we need to learn much more about how to induce these cytotoxic cells. Clearly, such information would be very useful in developing vaccines against HIV.

We don't fully understand the effects of HIV on $CD4^+$ cells--for example, some are killed, while others are persistently infective or persist as cells bearing viral determinants on their surface, which in turn interact with $CD4^+$ determinants on other cells, damaging those cells. But what about latency--what is the effect of latent HIV on $CD4^+$ cell progenitors within the bone marrow? Will immune function "come back" automatically after treatment of a patient with a suitable antiviral drug? What determines whether a cell is killed, becomes persistent or enters into a latent state? How does one explain the occasional HIV infected patient with nearly normal cell numbers and little immune function?

Table 1 presents the criteria for an effective antiviral drug against AIDS/ARC. Such an agent would have to satisfy criterion 4 to be administered widely, i.e., to all HIV-infected persons. It is important to recognize that "cure", i.e., removal of all viral material from the body is beyond our technological capabilities at the present time. Antivirals will, therefore, have as their primary objective the suppression of HIV production, and reduction of infection of other $CD4^+$ lymphocytes. Azidothymidine (AZT) is an early step in this direction, but its application is likely to be limited by bone marrow toxicity and anemia. It is clearly not the total answer to the problem of AIDS/ARC.

Table 1
Criteria for Effective Antiviral Therapy in AIDS/ARC

(1)	Suppress production of new virus so that additional $CD4^+$ cells are not infected
(2)	Prevent infection of $CD4^+$ cells by virus
(3)	Eliminate virus from genome (unlikely to be achieved)
(4)	Accomplish (1) and/or (2) without adverse effects on production of lymphocyte progenitors in bone marrow, or on $CD4^+$ effector functions, or other toxicities

It is also worthwhile to recognize that HIV infection produces a spectrum or range of immune deficiency--all the way from minimal effect on immunoreactivity to complete loss of immunity. Those patients in whom immune function is critically impaired have the highest incidence of serious and often fatal complications such as opportunistic infections and/or Kaposi's sarcoma.

It is useful to introduce the concept of immunologic compensation, analogous to that of cardiac compensation. When a patient sustains a myocardial infarct with damage to cardiac muscle, the residual muscle fibers must "pick up the slack." Such compensation is not infinite and if the damage is too great, heart failure ensues. Similarly, as the number of $CD4^+$ cells falls, the residual cells compensate so that in the early stages, functional tests of cell mediated immunity are still normal. Some possible mechanisms of immunologic compensation are shown in *Table 2*. As the disease progresses,

Table 2
Possible Mechanisms of Immunologic Compensation in AIDS/ARC

(1)	Increase in functional performance and/or relative numbers of functional
	(a) $4B4^+$ helper-inducer cells
	(b) $CD8^+$ antiviral-cytotoxic cells
(2)	Participation of $2H4^+$ "suppressor-inducer" cells
(3)	Shift in relative numbers of Leu $2a^+15^+$ and Leu $2a^+15^-$ (effector cytotoxic cells)
(4)	Participation of NK cells

the immune defect deepens, the residual $CD4^+$ cells (which are continuing to drop in numbers) fail to compensate and the system fails. One goal of immunosupportive therapy is to prevent the system from decompensating by supporting the patient's functional immune capabilities.

The rationale for development of immunosupportive drugs as biologics in HIV disease is shown in *Table 3*.

Table 3
Rationale for Immunosupportive Therapy in HIV Disease

(1)	The primary defect in the disease is an immune deficiency.
(2)	An effective antiviral drug for widespread application is not available. The anticipated timetable for such a drug is 5-15 years.
(3)	The ability and/or period of time required for the $CD4^+$ cell population to be reconstituted in numbers and function, once viral production is suppressed, is unknown.
(4)	Improving immune function in AIDS/ARC patients may reduce the incidence of opportunistic infections and/or malignancies.
(5)	There is a possibility of enhancing cytotoxic cell activity against the HIV strains with which the patient is infected.

I should like now to describe one approach to development of an immunosupportive agent for treatment of patients with AIDS/ARC. Some years ago, I discovered that fractions of leukocyte dialysates were capable of augmenting and accelerating reactions of delayed hypersensitivity to recall antigens (1). Isolation techniques were developed and refined so as to permit the recovery of a single immunomodulatory fraction from the dialysates which we have designated as $IMREG^R$-1. We have been able to show that antigen is required for the effects of $IMREG^R$-1 on delayed-type hypersensitivity (DTH) reactions. Moreover, in the presence of an antigen or mitogen, $IMREG^R$-1 was able to enhance the production of other biological response modifiers and lymphokines, including the migration inhibitory factors, MIF and LIF, by $CD4^+$ cells (2). More recently, we have demonstrated the ability of $IMREG^R$-1 to enhance the antigen-induced expression of receptors for interleukin-2 on $CD4^+$ cells, an important *in vitro* correlate of specific immunity to antigen.

These *in vitro* results led us to carry out an open Phase II trial of IMREG^{R}-1 in patients with AIDS/ARC. This trial, which was intended to assess effects on the patients' immune status, produced important findings including: (a) restoration of delayed hypersensitivity reactions to recall antigens in patients who had been anergic prior to treatment, (b) weight gain, (c) clearing of candidal infections, (d) a decreased rate of destruction of $CD4^{+}$ cells, as compared with untreated historical controls (3). In turn, these observations have led us to design and implement a Phase III double-blind, randomized, placebo-controlled trial in patients with AIDS/ARC at eight medical centers nationwide. This trial is scheduled for completion in 1988.

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