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Mechanisms of autoimmunity and AIDS: prospects for therapeutic intervention

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SUMMARY

The network theory of autoimmunity is presented with recent experimental data relevant to the understanding of the pathogenesis of AIDS. Schematically, effector T cells specific for self-antigens exist normally, but their activity is modulated and prevented by networks of regulatory T cells. As a result of mimicry between molecular components of microorganisms and self-antigens, autoimmune disease can be triggered by specific foreign pathogens which alter the state of activity of the network from suppression to activation. Conversely, by a procedure known as T-cell vaccination, autologous effector T cells re-injected after *in vitro* stimulation and attenuation may alter the state of the network from an activation to a suppression.

Numerous observations are reviewed that support the concept of autoimmune activity in the destruction of non-infected T4 cells. Such activity is presumed to be triggered by an antigen of viral origin, the most likely, but not the only one, being the envelope protein gp120. Based on this hypothesis, a T-cell vaccination procedure against effector T cells responsible for autoimmunopathic activity in HIV-seropositive patients is proposed, similar to the one known from experimental study of autoimmunity and presently being tested in human autoimmune diseases. Its purpose would be to prevent T-cell loss and the onset of immunodeficiency disease in HIV-seropositive patients. Apart from its potential therapeutic value, this procedure will have use as a therapeutic test from which insight will be gained about the immunopathogenesis of AIDS.

Key-words: AIDS, Autoimmunity, T lymphocyte, Immunotherapy; Networks, T-cell vaccination, Immunopathogenesis; Review.

Introduction

In previous communications (Atlan, 1992; Atlan *et al.*, 1993), we have suggested that T-cell vaccination may be applied to HIV-seropositive patients in order to prevent the development of AIDS. T-cell vaccination is a well-documented procedure designed as a specific cellular im-

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munotherapy against autoimmunity (Cohen, 1991a). T-cell vaccination has been effective in a number of experimental autoimmune diseases, and is presently being tested in humans affected by multiple sclerosis (Hafler *et al.*, 1992; Zhang *et al.*, 1993) and rheumatoid arthritis (van Laar *et al.*, 1993) with no toxic effects and encouraging preliminary results.

Several lines of evidence suggest that development of the acquired immunodeficiency syndrome (AIDS) in individuals infected with the human immunodeficiency virus (HIV) does not result solely from direct cytopathic effects of the virus (Shearer, 1983; Ziegler and Stites, 1986; Klatzmann and Montagnier, 1986; Klatzmann and Gluckman, 1986; Procaccia *et al.*, 1987; Ascher and Sheppard, 1988; Isaksson *et al.*, 1988; Kaplan *et al.*, 1988; Kopelman and Zolla-Pazner, 1988; Schattner, 1988; Martinez-A. *et al.*, 1988; Bacchetti and Moss, 1989; Duesberg, 1989; Schnittman *et al.*, 1989; Ascher and Sheppard, 1990; Hoffman *et al.*, 1991; Maddox, 1991; Hsia and Spector, 1991; Morrow *et al.*, 1991). It is true that more sensitive PCR techniques have shown that the proportion of $CD4^+$ T lymphocytes latently infected with HIV is much higher than originally thought, even during the clinical latency period (Embretson *et al.*, 1993). However, the presence of viral DNA in the genome of the cells is not lethal in itself in the absence of activation. Therefore, the question remains open concerning the immunopathology of AIDS. The long and variable interval between infection with HIV and development of immunodeficiency disease (Klatzmann and Gluckman, 1986; Isaksson *et al.*, 1988; Kaplan *et al.*, 1988; Bachetti and Moss, 1989), clinical and pathological similarities with known autoimmune disorders (Procaccia *et al.*, 1987; Kopelman and Zolla-Pazner, 1988; Schattner, 1988; Morrow *et al.*, 1991) and the observation of genetic correlations with patterns of HIV disease progression (Steel *et al.*, 1988; Jeannet *et al.*, 1989; Simmonds *et al.*, 1991; Puppo *et al.*, 1991; Louie *et al.*, 1991), all suggest more complex pathological processes involving the immune response of the organism to HIV infection.

A number of immunopathic mechanisms with several features of autoimmunity have been proposed as contributing to the development of AIDS. These include cross-reactive recognition of self-MHC and a secondary antiidiotypic response to CD4, to be found in the first large set of references mentioned above, elimination of infected T4 cells by virus-specific, HLA-restricted cytotoxic lymphocytes (Shearer, 1986; Zinkernagel, 1988), elimination of uninfected T4 cells by immune responses directed against HIV (Klatzmann and Gluckman, 1986; Salk, 1987; Lyerly *et al.*, 1987; Lanzavecchia *et al.*, 1988; Lanzavecchia, 1989; Siliciano *et al.*, 1988; Israel-Biet *et al.*, 1990; Morrow *et al.*, 1991) and/or T4 cell antigens (Stricker *et al.*, 1987; Martinez-A. *et al.*, 1988; Kowalski *et al.*, 1989; Zarling *et al.*, 1990), unrestricted T-cell activation by HIV-infected macrophages with consequent immune dysregulation and T-cell death (Ascher and Sheppard, 1988, 1990), superantigen effects of HIV components leading to widespread deletion of T4 clones (Imberti *et al.*, 1991), other non-specific immunosuppressive effects mediated by HIV components including gp120 (Weinhold *et al.*, 1989) and the *tat* gene product (Viscidi *et al.*, 1989) and inappropriate activation-induced T-cell death (apoptosis) in mature T4 cells (a process which is normally observed only in immature thymocytes) (Ameisen and Capron, 1991; Terai *et al.*, 1991; Montagnier *et al.*, 1991; Groux *et al.*, 1992). Graft-

AA = adjuvant arthritis.
AIDS = acquired immune deficiency syndrome.
CMI = cell-mediated immunity.
CMV = cytomegalovirus.
CTL = cytotoxic T lymphocyte.
DTH = delayed-type hypersensitivity.
EAE = autoimmune encephalomyelitis.
EAT = experimental autoimmune thyroiditis.
EBV = Epstein-Barr virus.
FDC = follicular dendritic cell.
HIV = human immunodeficiency virus.
HSV = herpes simplex virus.
MBP = myelin basic protein.
MHC = major histocompatibility complex.
PCR = polymerase chain reaction.

versus-host and host-versus-graft responses to allogeneic class II MHC antigens, with consequent immune suppression, have also been suggested (Shearer, 1983; Klatzmann and Gluckman, 1986; Moser *et al.*, 1987). On the basis of observed cross-reactivity between MHC and HIV proteins, it has been suggested that HIV envelope antigens induce a chronic autoreactivity similar to graft-*versus*-host disease (Habeshaw *et al.*, 1992).

More recently, a highly plausible hypothesis on the immunopathology of the development of ARC/AIDS has been proposed (Pantaleo *et al.*, 1993). This hypothesis is based on the observation that large numbers of human immunodeficiency viruses and of HIV-infected cells are present in the lymphoid organs during the clinical latency period, associated with a progressive dysruption of the follicular dendritic cell (FDC) network in the lymph nodes. It is suggested that during the progression of the disease, most of the HIV-infected $CD4^+$ T cells are no longer prevented from circulating in the peripheral blood by being destroyed in the lymph nodes, when the FDC network cannot continue to perform its normal functions of trapping and antigen presentation. Then, further activation of large numbers of circulating infected $CD4^+$ T cells would allow for viral replication and cell death responsible for the increased viraemia observed at the late stages of the disease. However, the critical event in this mechanism, namely the destruction of FDC, does not seem to be produced by a direct viral cytopathic effect, but again by an immunopathic response leading to activated $CD8^+$ cytotoxic T lymphocytes (CTL) infiltrating the lymph node follicles.

Thus, on the one hand, immune responses to HIV infection might be immunoprotective through destruction of HIV-infected cells and neutralization of free virus. On the other hand, however, some aspects of the immune response might be autoimmunopathic and contribute to the development of immunodeficiency through destruction of both infected and uninfected T4 cells, and/or of follicular dendritic cells in the lymph nodes. The rate of T4-cell decline and HIV disease progression might thus reflect, in part, the balance between immunoprotective and autoimmunopathic facets of the anti-HIV immune response.

In the present article, the first section will review the relevant experimental and theoretical background on autoimmunity and T-cell vaccination. Recent developments in the network theory of autoimmunity (Cohen, 1986; Cohen and Atlan, 1989; Atlan and Hoffer-Snyder, 1989; Cohen and Young, 1991; Atlan and Cohen, 1992; Cohen, 1992a, 1992b) shed light on the nature of various autoimmunopathic mechanisms that might be operative in HIV disease and suggest ways in which such autoimmunopathic processes might be prevented or controlled. According to that theory, for example, molecular mimicry between a strong foreign epitope and a self-antigen may lead to the breaking of tolerance to the self-antigen through perturbation of a pre-existing regulatory network. Autoimmunopathic destruction of T4 cells might thus result, in this case, from the destabilization of a self-tolerance-maintaining regulatory network by immune responses to HIV components with homologies to antigens normally present on T4 cells. Another alternative would be that HIV antigens presented by $CD4^+$ T cells or follicular dendritic cells would have a similar destabilizing effect by activating helpers and cytotoxic cells against those cells.

In section II, we shall examine existing evidence for autoimmunopathicity in HIV disease and discuss how the concepts developed in section I can be applied to a possible immunotherapy of HIV-seropositive patients. Several models of how regulatory networks might be related to autoimmunopathicity in HIV disease and implications with respect to potential modes of intervention will be discussed.

In section III, we shall propose a detailed protocol for a first therapeutic test to be implemented. A general discussion will serve as a conclusion.

I. — Network theory of autoimmunity

Contrary to the global theories of the idiotypic network, initiated by the pioneering work

of Jerne (1974), the network theory of autoimmunity is a local description of interactions between identified cell populations involved in the occurrence of specific autoimmune diseases (Cohen and Atlan, 1989; Cohen, 1989a). According to its main concept, autoimmunity is "natural" (Horton, 1993) and is present in healthy organisms. It is controlled by a network of regulatory T cells (and possibly lymphokines, B cells, antibodies) which prevents normally existing effector cells reactive to a given self-antigen from being activated. The balance between stimulating and suppressive effects depends on the connection structure of the network, *i.e.* the nature and the strength of the interactions between the network elements. Depending on that structure, the network stabilizes in a normal or pathological state, where the effector cells directly responsible for the disease are activated or inactivated, respectively. However, the connections between the elements can be modified by external antigenic stimuli or internal regulatory signals produced by the network's own temporal evolution (Atlan and Hoffer-Snyder, 1989). Thus, such a network, like neural networks in the central nervous system, is endowed with "cognitive" properties, *i.e.* self-organizing learning and adaptive capacities (Atlan and Cohen, 1992; Cohen, 1992a, 1992b). Relevant examples of those mechanisms will be discussed further (in section II, parts 1b and 2).

The network theory of autoimmunity is based on the evidence that effector cells with specificity for self-antigens normally exist *in vivo* (Guilbert *et al.*, 1982; Burns *et al.*, 1983; Cohen and Young, 1991). Such effector cells are either prevented or not from exerting autoimmune effects. This depends on the state of activity of other, regulatory, cell populations, mainly (but not solely) antigen-specific and idiotypic-specific (Ben-Nun *et al.*, 1981a, Holoshitz *et al.*, 1983; Lider *et al.*, 1987; Lider *et al.*, 1988; Kakimoto *et al.*, 1988; Lohse *et al.*, 1989; Cohen, 1989b; Roubaty *et al.*, 1990). When this finely tuned regulatory system is appropriately perturbed by the introduction of a foreign antigen, cross-reactive with a given self-antigen or interfering with antigen presentation, the ensuing stimuli delivered to the various component cells of the network change the steady state of the network in such a way that expression rather than suppression of autoimmunity occurs.

Conversely, the regulatory network is enhanced or strengthened with respect to its ability to suppress autoimmunity by exposure to a non-pathogenic form of the relevant effector cells. Such enhancement is learned and "memorized" in the structure of the network, so that subsequent exposure either to the pathogenic effector cells or to the potentially immunopathogenic antigen would not produce autoimmunity. This concept is particularly relevant to studies of T-cell vaccination as a prophylactic and therapeutic procedure against autoimmune diseases (Ben-Nun *et al.*, 1981a; Cohen *et al.*, 1985; Cohen, 1986, 1989b,c, 1991a; Atlan and Hoffer-Snyder, 1989; Roubaty *et al.*, 1990; Cohen and Young, 1991; Elias *et al.*, 1991; Beraud, 1991; Atlan and Cohen, 1992; Hafler *et al.*, 1992).

Studies with experimental autoimmune diseases have provided most of the data underlying the network theory of autoimmunity. The best studied model has been experimental autoimmune encephalomyelitis (EAE). This disease, characterized by the acute onset of paralysis in genetically susceptible animals following appropriate inductive stimuli, has been shown to be mediated by T4 effector cells specific for myelin basic protein (MBP) (Ben-Nun *et al.*, 1981b). Spontaneous recovery may occur and is associated with the appearance of suppressor cells which react specifically with idiotypic determinants present on the anti-MBP T4 cells (Ben-Nun and Cohen, 1982; Ellerman *et al.*, 1988) or with antigenic determinants on MBP (Ben-Nun *et al.*, 1981b). These and other observations (Lider *et al.*, 1988; Lohse *et al.*, 1989) have led to the formulation of a model in which the onset, remissions and relapses of EAE and other autoimmune diseases can be explained by changes in the interactions among an effector cell and two pairs of regulatory elements: (i) antigen-specific helper and suppressor cells, and (ii) idiotype-specific helper and suppressor cells (Cohen and Atlan, 1989). According to this model, once a state of autoimmunity has resulted from a change in the normal balance among the various elements of a regulatory network, which

has previously served to suppress an anti-self response, the autoimmune state may be stable and persist even after the agent which precipitated the change is no longer present. Alternatively, if the host response to a foreign antigen induces the *de novo* formation of a regulatory network leading to autoimmunity, then the continued presence of cross-reactive self-epitopes may perpetuate the autoimmunopathic state of the network even after the precipitating antigen has been cleared.

Other experimental models of autoimmune disease suggest the existence of further levels of complexity in the regulation of autoimmunity. For example, adjuvant arthritis (AA) is an autoimmune disease which may be experimentally induced by injection of killed *Mycobacterium tuberculosis,* which contains an antigenic protein cross-reactive with a joint cartilage proteoglycan (van Eden *et al.,* 1985). The disease may also be induced by inoculating cells from an anti-*M. tuberculosis* T4 clone which also recognize the proteoglycan (van Eden *et al.,* 1985, 1988). More recent investigation into the nature and dynamics of the regulatory network in AA suggests that at least one additional component may be involved (Cohen, 1989b; Karin, 1991; Atlan and Cohen, 1992). The onset and severity of the autoimmune disease triggered by *M. tuberculosis* has been correlated with the presence of a population of non-specific $CD8^+$ suppressor cells which downregulate the anti-idiotypic regulatory cells to a greater extent than they do the cytolytic effector cells. According to the proposed network model (Atlan and Cohen, 1992), this results in a net increase in effector activity. This contrasuppressive, pathogenic response is partially non-specific (Cohen, 1989b; Lohse *et al.,* 1989; Karin, 1991), being directed not only against the specific antiidiotypic regulatory cells, but also against other anticlonotypic regulatory cells. The latter includes cells which control responses to different epitopes of the self-antigen and others which are involved in the regulation of unrelated autoimmune diseases, such as EAE. It is thus conceivable that partially non-specific suppressor cells might exert contrasuppressive effects and facilitate the expression of autoimmunopathic responses in other diseases. In this regard, it is interesting to note that a subpopulation of $CD8^+$ suppressor cells acting *via* release of a soluble inhibitory factor has been observed in association with HIV infection (Joly *et al.,* 1989; Sadat-Sowti *et al.,* 1991).

The pathogenesis of experimental autoimmune thyroiditis (EAT) provides another example of additional network complexity. This disorder, which can be produced experimentally by inoculation of cells from a thyroglobulin-specific cytotoxic T-cell clone, may entail dysfunction of an immune regulatory network containing humoral as well as cellular components (Roubaty *et al.,* 1990). In this regard, given the homologies that have been described between the HIV envelope glycoprotein (gp120) and immunoglobulins (Bjork, 1991), it is possible that anti-HIV responses, cross-reactive with self-immunoglobulins, might non-specifically perturb the humoral arm of a bipartite cellular/humoral regulatory system and thereby contribute to the immunopathogenesis of AIDS.

Although the detailed mechanisms of network regulation of autoimmunity may be more complicated than presently understood, an appreciation of the dynamic aspect of regulatory networks is useful when considering means to perturb the system intentionally so as to strengthen or to restore the development of a non-immunopathic state. Network models suggest that vaccination with autoimmune effector cells (in a form or under conditions in which the cells are not capable of exerting pathogenic effects) should elicit antiidiotypic and other regulatory cells which might suppress an autoimmune effector cell response, thereby preventing or ameliorating autoimmune disease. An example of such a model is shown in figure 1, where a network of effector cells and five populations of regulatory cells account for complicated and paradoxical data on AA (Atlan and Cohen, 1992). This example is particularly relevant since it involves the participation of a foreign pathogen *(M. tuberculosis)* working as an adjuvant in the triggering of autoimmunity. In the framework of the proposed hypothesis on AIDS, the role of HIV could be similar — as will be detailed below.

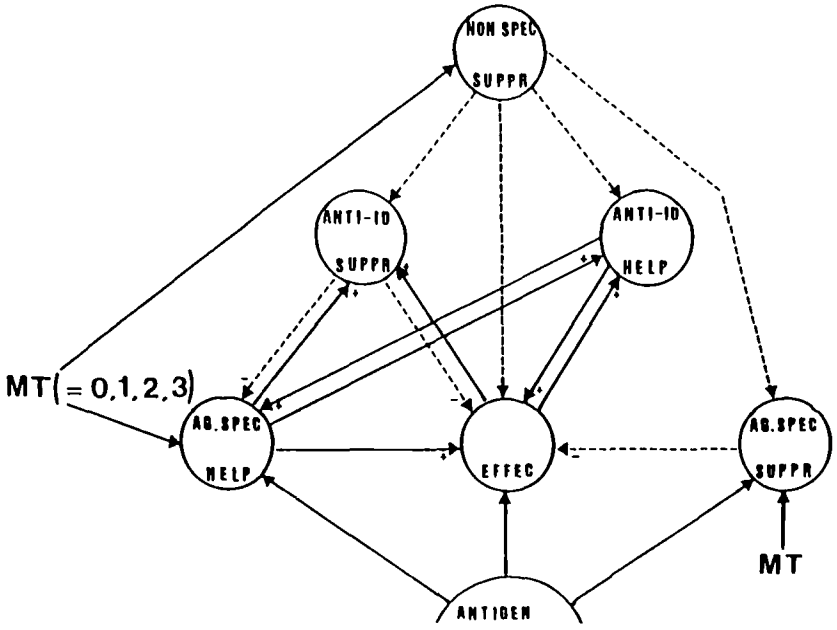

Fig. 1. Network of 6 T-cell populations (effector cells, 4 specific regulatory cells and partly non-specific contra-suppressor cells) identified in various states of AA (Atlan and Cohen, 1992).

Full and dotted arrows represent activating and suppressive connections, respectively. Higher doses of *M. tuberculosis* (MT) — a foreign pathogen working as an adjuvant in the onset of AA, probably because of mimicry with the self-antigen — produce more severe forms of the disease. T-cell vaccination with attenuated effector cells prevents the onset of the disease. Experimental observations on the state of activity of the different cell populations under different conditions (healthy, diseased, vaccinated) are accounted for by the steady states of the network computed as functions of the connections. T-cell vaccination works as a learning process of the network, following given laws which modify the connections in such a way that further exposure to pathogenic doses of MT do not produce a diseased state (Cohen and Atlan, 1989; Atlan and Hoffer-Snyder, 1989; Atlan and Cohen, 1992).

This concept is consistent with the results of studies using T-cell vaccination in a number of experimental autoimmune diseases. Vaccination with subpathogenic doses of effector T cells, or with large numbers of effectors attenuated by irradiation or treatment with glutaraldehyde, mitomycin C, hydrostatic pressure or other agents (Cohen, 1986, 1991a; Lider *et al.*, 1987), has been shown to elicit antiidiotypic (Lider *et al.*, 1987, 1988; Roubaty *et al.*, 1990; Elias *et al.*, 1991) and/or antiergotypic (Lohse *et al.*, 1989; Beraud, 1991) suppressor cells and to be effective in preventing and/or treating EAE (Ben-Nun *et al.*, 1981a; Lider *et al.*, 1988; Lohse *et al.*, 1989), AA (Holoshitz *et al.*, 1983; Lider *et al.*, 1987; Cohen, 1989b), EAT (Roubaty *et al.*, 1990), collagen-II-induced arthritis (Kakimoto *et al.*, 1988), spontaneous autoimmune diabetes (Elias *et al.*, 1991) and experimental autoimmune uveitis (Beraud, 1991).

In humans, clinical trials have been initiated to explore the use of T-cell vaccination for the treatment of some autoimmune diseases with no evidence of toxicity (Hafler *et al.*, 1992; Zhang *et al.*, 1993; van Laar *et al.*, 1993). In patients treated for multiple sclerosis, it is still too early to make any assessment on possible clinical improvement, because of the slow evolution of the disease. However, as expected from above-mentioned previous animal studies on EAE (Lider *et al.*, 1988; Lohse *et al.*, 1989), an antiidiotypic response has been observed after

T-cell vaccination with myelin basic protein-specific T-cell clones (Zhang *et al.*, 1993). A similar procedure was achieved by a different group (van Laar *et al.*, 1993) on patients suffering from rheumatoid arthritis with variable disease duration. On average, a slight decrease in disease activity was observed, with an indication of a clearer improvement in patients with recent onset of the disease.

II. — Autoimmunopathicity in HIV disease

In view of the foregoing, the first question to be asked concerning a given autoimmunopathic mechanism is the nature of the self-antigen involved. A given self-antigen must be identified as the target for autologous CTL and/or autoantibodies. Then, the vaccination procedure will be aimed at strengthening deficient regulatory responses capable of suppressing the activity of those CTL, or antibodies.

It has previously been suggested that the immunosuppression observed in AIDS might be in part attributed to an HIV-triggered immunopathic response directed against uninfected as well as infected T4 cells (Klatzmann and Montagnier, 1986; Klatzmann and Gluckman, 1986; Salk, 1987; Lyerly *et al.*, 1987; Lanzavecchia *et al.*, 1988; Siliciano *et al.*, 1988; Lanzavecchia, 1989; Israel-Biet *et al.*, 1990). In that case, the antigen must be looked for in the membrane of $CD4^+$ T cells themselves. However, as mentioned above, another alternative would be to consider the lymph node FDC as the target for $CD8^+$ CTL activated by the HIV infection. In view of existing experimental evidence, we shall consider the implications of the two possible targets for autoimmunopathic responses — $CD4^+$ T cells and FDC — as far as the identification of the antigen and regulatory network is concerned.

1) $CD4^+$ T cells as targets

From an autoimmunity viewpoint, the simplest assumption would be that the CD4 molecule itself is the self-antigen. However, viral molecules interacting with CD4 must be involved to trigger the immunopathicity against $CD4^+$ T cells. Therefore, the hypothesis of $CD4^+$ T cells being the targets of immunopathic responses must be divided into two possible models, for which supporting data from the literature will be reviewed. In the first model, a viral antigen — the most likely being the envelope glycoprotein gp120 — is directly involved and plays the role of a "self"-antigen after it has been incorporated into the $CD4^+$ T-cell membrane. In the second model, a true self-antigen, pre-existing in that membrane, is activated by HIV infection.

a) *The gp120 antigen model*

According to this view, autoimmunopathic destruction may occur as a result of anti-gp120 effectors killing both infected T4 cells expressing gp120 among other viral antigens on their membrane, and uninfected T4 cells which have bound free gp120 (fig. 2A). That such gp120 binding is likely to occur is supported by the high degree of gp120 shedding after infectious viruses are released (Gelderblom *et al.*, 1985; Schneider *et al.*, 1986) and by the detection of gp120 in sera of HIV-seropositive individuals (Oh *et al.*, 1992). Free gp120 bound by the CD4 molecule might well be internalized and, depending upon the route of metabolism, reexpressed in association with class I (making it a target for classical $CD8^+$ cytotoxic T cells) or class II MHC molecules. Hoffenbach *et al.* (1989) detected MHC-restricted anti-*env* $CD8^+$ cytotoxic lymphocytes in both seropositive and seronegative donors. Since the frequency of these cells declined in seropositives with clinical deterioration, the authors hypothesized that this response was primarily immunoprotective. However, they also noted that these *env*-specific cytotoxic cells might be capable of causing autoimmunopathic T4-cell destruction through the mediation of bound *env* or molecular mimicry. Siliciano *et al.* (1988) were able to precisely demonstrate such a potentially autoimmunopathic effect. They detected anti-gp120 cytotoxic $CD4^+$ lymphocytes

in normal seronegative individuals which could kill, in an antigen-specific, MHC-restricted manner, uninfected activated autologous T4 cells pulsed with gp120.

The presence of anti-gp120 cytotoxic cells in sufficient frequency would be expected, according to the network theory, to induce the formation of a network which would regulate the activity of these effector cells. Given the persistence of HIV infection, and therefore the continued presence of HIV antigen, we postulate that the regulatory network established would be configured so as to favour stimulation of the anti-gp120 response. From the viewpoint of autoimmunity, however, such a network would be ineffective, insofar as it would fail to restrain the effectors of autoimmunopathic destruction. Thus, in this model, autoimmunopathicity in AIDS would result from (i) gp120 bound to uninfected T4 cells coupled with (ii) a regulatory network configured to stimulate, rather than suppress, the anti-gp120 autoimmune effectors. The significance of the autoimmunopathicity would depend upon the relative balance between the protective aspect of the response (destruction of infected T4 cells and consequent reduction in viral proliferation) and the immunopathic aspect of the response (destruction of normal T4 cells and consequent reduction of residual immunological potential).

b) *The T4-cell membrane self-antigen model*

The second model is more closely analogous to classical experimental autoimmune disorders. Several findings suggest that one (or more) self-antigen might be normally present on the $CD4^+$ cell membrane and that pre-existing suppressed CTL against that antigen would be activated by HIV infection. For example, Zarling *et al.* (1990) have found such CTL in the blood of HIV-seropositive patients (and not of HIV-infected chimpanzees), capable of killing uninfected $CD4^+$ cells from both HIV-seropositive patients and seronegative controls. Israel-Biet *et al.* (1990) have found $CD3^+$ cells in HIV-infected patients able to kill allogeneic EBV-transformed B cells and $CD4^+$ cell blasts from seropositive and from seronegative subjects. Hoffenbach *et al.* (1989) and Plata (1989) have observed an unusually high frequency of CTL precursors primed to HIV antigens — and not to other viruses — in the repertoire of normal humans in the absence of HIV infection.

As in other instances of autoimmunity triggered by foreign pathogens (van Eden *et al.*, 1985, 1988; Morrow *et al.*, 1991; Karin, 1991; Cohen and Young, 1991; Horton, 1993), the triggering of a true autoimmune response by an HIV antigen could imply some mimicry between that antigen and the pre-existing self-antigen. Class II MHC antigen has been suggested as being the postulated self-antigen (Hoffman *et al.*, 1991). However, in that case, one might expect AIDS to be characterized by a significant depletion of B cells and antigen-presenting cells, the primary expressors of MHC class II antigen, rather than, or in addition to, T4-cell depletion. Rather, one might hypothesize that T4 cells carry an additional unique marker which is cross-reactive with gp120 (perhaps structurally or physiologically associated with CD4 on the T4 cell membrane), either directly or by complexing with MHC molecules. The detection by both Hoffenbach *et al.* (1989) and Siliciano *et al.* (1988) of anti-*env* specificities in cytotoxic lymphocytes of seronegative individuals might be postulated to be due to the existence of such a cross-reactive self-antigen. The inability of Siliciano *et al.* (1988) to detect killing by such cells of uninfected autologous T4 cells *not* pulsed with gp120 might be related to a subthreshold level of surface expression of the self-antigen (marker) under the ambient conditions of the assay.

In summary, according to the T4-cell membrane self-antigen model (fig. 2B), effectors specific for this putative cross-reactive self-antigen exist prior to HIV infection; but they are inactive, owing to a dominant suppressive effect exerted by a pre-existing regulatory network. This phenomenon would be similar *e.g.* to what is observed in experimental AA (van Eden *et al.*, 1985, 1988; Atlan and Cohen, 1992), where a foreign bacterial antigen in the adjuvant (from *M. tuberculosis*) is cross-reactive with a joint cartilage self-antigen. The bacterial antigen serves as a strong antigenic stimulus to a pre-

existing regulatory network, quantitatively related to the amount injected. In the absence of adjuvant stimulation, the network is normally in a suppressive state, preventing the activity of cytotoxic effector cells against the joint cartilage.

Similarly, in our T4-cell self-antigen model, the pre-existing regulatory network would be destabilized by the strong antigenic stimulation produced by the introduction of (foreign) gp120. As a result, the network would be driven to a new steady state characterized by activated effector cells able to destroy *(in vivo)* uninfected marker-bearing T4 cells, independent of the presence of bound and reexpressed gp120. Early in the course of HIV infection, these activated cytotoxic cells are still subject to some network regulation by the suppressor cells. Therefore, only a mild form of autoimmune disease, typified by a moderate degree of killing of T4 cells, occurs. With time, however, the network moves into a more pathological state in which the suppressor cell activity is itself suppressed or insufficient.

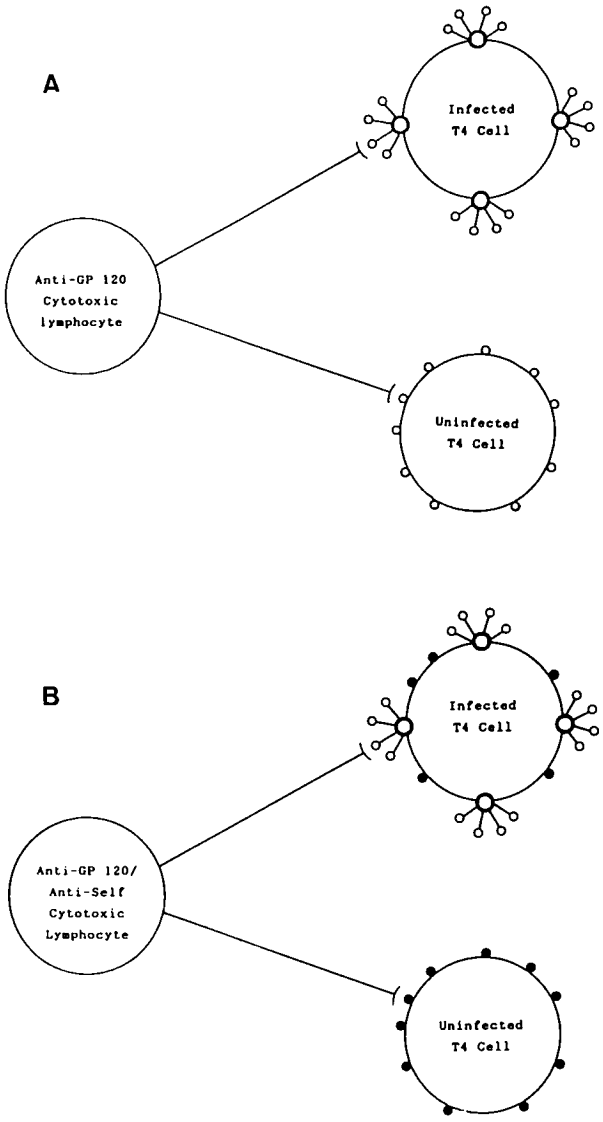

Fig. 2A. Model 1: gp120 is expressed by infected cells; uninfected $CD4^+$ T cells are coated with circulating gp120.

Fig. 2B. Model 2: uninfected $CD4^+$ T cells present a self-antigen interacting with anti-gp120 cytotoxic lymphocytes.

As in other instances of pathological autoimmunity, the progression of the disease may be explained by several mechanisms. For example, after the onset of an active state against the antigen, a progressive increase in the efficiency and diversification of antigen presentation may produce a reinforcement of the antigenic stimulus. Such processes of alterations in self-antigen presentation, leading *e.g.* to the display of previously cryptic self-determinants (Lehmann *et al.*, 1993), may explain the time course of autoimmune diseases, including virus-induced progressive states of autoimmunity, such as chronic active hepatitis (Ohtani *et al.*, 1987) and EAE-like lesions induced with coronavirus (Watanabe *et al.*, 1983). A "vicious circle of cytokine-driven upregulation of autoantigen presentation" (Lehmann *et al.*, 1993) may be produced by cross-reactivity with viral antigens, but may also occur in the absence of cross-reactivity, leading to "ongoing T-cell stimulation, further T-cell recruitment and determinant spreading, greater cytokine production, and so forth".

This process can be accelerated as intercurrent infectious and non-infectious stresses contribute to an increase in virus and viral antigen production, leading to a heightened activation of the effector and helper regulatory cells. Particular intercurrent infections could also precipitate an increase in contrasuppression, as in AA, where the level of contrasuppressor activity varied directly with the dose of adjuvant *Mycobacterium* administered (Karin, 1991; Atlan and Cohen, 1992). Such a mechanism could

contribute to the observation that certain opportunistic infections appear to accelerate the clinical progression of HIV/AIDS.

In any case, as mentioned above, as far as the connection structure of the regulatory network is concerned, this kind of vicious circle would amount to a reinforcement mechanism of learning and distributed memory, well-known in neural network modeling (Weisbuch, 1986; Atlan and Hoffer-Snyder, 1989; Atlan and Cohen, 1992). As a result, the earlier disease-free state of the network is destabilized and the network evolves towards more and more activating pathogenic states.

c) *Common features of the two models; T-cell vaccination against anti-gp120 CTL as a therapeutic test*

In both models (sections 1a and 1b), humoral participation in the onset of HIV-triggered autoimmunopathic response is possible, as in EAT. This might be mediated, for example, through the reported homology between a gp120 epitope and immunoglobulins (Bjork, 1991), as well as cell surface proteins with a role in CD4 binding (Beretta *et al.*, 1987; Golding *et al.*, 1988; Young, 1988), which might result in the perturbation of a possible T-cell/B-cell regulatory network. In any case, the search for anticlonotypic cell populations being activated, and for increased concentrations of different antibodies and cytokines in response to the cell clone or line being used in the vaccination procedure, will in itself provide useful information on the nature of the antigen and the regulatory network.

The different reinforcement mechanisms discussed in 1b may also be operative in the model of section 1a since, as mentioned above, they can be triggered after the first immunopathic response has been induced even in the absence of cross-reactivity between pre-existing self-determinants and viral antigens. Increased efficiency in gp120 antigen presentation by specific binding to CD4 and direct processing by $CD4^+$ T cells has been reported by Lanzavecchia *et al.* (1988, 1989). These authors have found that $CD4^+$ cells can capture soluble gp120 and present it to gp120-specific MHC class-II-restricted clones.

As in other well-established autoimmune disorders, an association between HLA haplotype and disease incidence has been reported for development of ARC/AIDS (Steel *et al.*, 1988; Jeannet *et al.*, 1989; Simmonds *et al.*, 1991; Puppo *et al.*, 1991; Louie *et al.*, 1991). Such an association would be consistent with either model for the development of autoimmunopathic disease consequent to HIV infection. However, as in other instances of autoimmunity triggered or facilitated by foreign pathogens, the observation of similar syndromes and cellular lesions occurring in the absence of viral infection — idiopathic $CD4^+$ T-lymphocytopenia or "immunodeficiency without virus" (Fauci, 1993; Smith *et al.*, 1993; Ho *et al.*, 1993) — on a small number of patients with genetic predisposition would be more strongly in favour of the second model.

In theory, the two models, although not mutually exclusive, differ significantly in the prospects for "cure" through the therapeutic elimination of virus. In the first case, complete elimination of virus would also remove the source of the "simulated self-antigen", *i.e.* gp120 bound to T4 cells, and autoimmune destruction of T4 cells would be abrogated. In the second case, however, removal of the inciting cross-reactive foreign antigen, gp120, would not necessarily result in a return of the immunoregulatory network to a predominantly suppressive mode. The new steady state of autoimmunity might be a stable state, sustained by the continued presence of *bona fide* T4-specific self-antigen.

In practical terms, however, the possibility of completely eradicating an established HIV infection is unlikely, at least in the forseeable future. Therefore, *regardless of which model may prove to be correct,* it would be useful to explore adjunctive interventions aimed specifically at controlling the autoimmunopathic destruction of T4 cells. *In either case,* T-cell vaccination using autologous cloned anti-gp120 cytotoxic cells would be expected to enhance (or induce) the antiidiotypic and other regulatory cells of the network, which would act to downregulate the activity of

the anti-gp120/anti-self cytotoxic cells. This should occur whether or not the viral infection is concurrently controlled or eliminated, because the focus of intervention is the autoimmunopathic destruction which occurs as a result of the host response to infection, rather than the virocytopathic destruction which occurs as a result of infection *per se*. An associated reduction in viral burden by independent means, however, would be expected to synergize in limiting autoimmunopathic destruction by reducing antigenic stimulation to the autoimmunopathic effector cell.

To the extent that the autoimmunopathic destruction of T4 cells is a major factor in the development of HIV-associated disease, such T-cell vaccination should serve to enable the HIV-infected host to live with, integrate and compensate for the perturbations induced by a persistent viral infection. Under these conditions, HIV infection might be expected to come to resemble infection with other persistent viruses, such as EBV, CMV and HSV, which are relatively innocuous in most cases. In addition, from the response to the proposed intervention, it will be possible to test the validity of the hypothesis and to expand it, for example, by looking for *in vivo* activation of anti-anti-gp120 suppressor cells and for their TCR specificities.

2. Lymph node FDC as targets

Considering the above-mentioned observations on the progressive destruction of FDC (follicular dendritic cells) by $CT8^+$ cytotoxic cells during the latency period (Pantaleo *et al.*, 1993), we are still facing a tissular anti-self immune response. Again, the question is raised as to the nature of the antigen which transforms FDC into targets for $CD8^+$ CTL. In view of the observed concomitant accumulation of viruses in the lymph nodes, it is reasonable to assume that $CD8^+$ CTL might be activated by the large numbers of viral antigens presented by FDC. In addition, the antigen presentation function of FDC in the microenvironment of lymphoid organs may be favorable to the onset of a vicious circle or reinforcement of antigen presentation (Atlan and Hoffer-Snyder, 1989; Atlan and Cohen, 1992; Lehmann *et al.*, 1993), whereby the strength of activation against various antigenic determinants increases continuously, as discussed above.

However, contrary to the T4-cell target models, there is no direct documented experimental indication of possible specific mechanisms responsible for the activation of $CD8^+$ CTL against FDC. Therefore, since we do not want to produce an overall suppression of antiviral cellular response, these $CD8^+$ anti-FDC cytotoxic cells should be first characterized by some antigen specificity before a T-cell vaccination procedure against those cells can be tested. In the meantime, the proposed procedure described in the following section might also turn out to be effective in the context of the FDC target model. That would be the case to the extent that anti-gp120 CTL might participate in immunopathic responses involving FDC, as well as in the direct destruction of $CD4^+$ T cells discussed above (sections I and II/1).

III. — Proposed intervention

In view of the foregoing considerations, we propose that T-cell vaccination be explored first as a strategy for reducing direct autoimmunopathic T4-cell destruction in HIV infection. The T-cell vaccination technique (Cohen, 1991a) would consist of reinjecting cloned autologous effector cytotoxic cells after *in vitro* activation and either irradiation or treatment with a cross-linking agent (such as glutaraldehyde) to prevent proliferation. Thus, although the effector cells are presented to the regulatory network in an immunologically active form, they are both autologous and non-proliferative, hence not pathogenic. Reinjection of these cells is intended to launch the network into a new stable state where the regulatory suppressor cells are strongly activated. The resulting change in connectivity of the network would suppress the development of active, pathogenic, effector or helper cells, and thereby suppress autoimmunopathicity. The key to the success of such an approach is identification of the responsible effector cell. As dis-

cussed earlier, the working hypothesis is that cytotoxic effectors with specificity for gp120 are responsible for the immunopathic destruction of uninfected T4 cells that culminates in AIDS. However, it is still possible that autoimmunopathic destruction of T4 cells could be mediated by cytotoxic effectors with specificities directed against HIV antigens other than gp120, against cellular antigens which are cross-reactive with HIV antigens other than gp120, or against cellular antigens which are not cross-reactive with HIV (*e.g.* new CD4 epitopes exposed as a result of binding with gp120 (Stricker *et al.*, 1987; Kowalski *et al.*, 1989)).

The effects of T-cell vaccination with anti-gp120 cytotoxic effectors will be assessed by looking for desired induced modifications of the regulatory network, in the form of *in vivo* activation of anti-anti-gp120 suppressor cells and antibodies. Qualitative and quantitative assessment of such responses will determine whether or not it is useful to pursue studies using effectors with other specificities.

In the flow chart presented in table I, we outline a first protocol currently under development.

We propose that studies be initiated in a small group of HIV seropositives with comparable viral burdens who have recently begun to manifest a decline in T4 cells. To facilitate the subsequent analysis, it will be preferable to study subjects who have been followed with serial T4 counts for at least 18 months, whose T4 level is above 500, and who, at study entry, demonstrate a significantly negative T4-cell slope. Thus, a possible therapeutic effect could be subsequently assessed by looking for a slowdown of that slope.

Cell-mediated immune responsiveness will be assessed by standard skin test for delayed-type hypersensitivity (DTH), since a correlation has been observed between favourable clinical history of HIV-seropositive patients and high DTH response (Salk *et al.*, 1993). The post-vaccination follow-up might indicate that DTH response could be used as a criterion for future patient selection.

Peripheral blood T lymphocytes will be plated in limiting dilution with irradiated autologous antigen-presenting cells and gp120. Cloning will be performed at the outset to permit calculation

Table I. Proposed protocol for T-cell vaccination in HIV/AIDS.

1) Patient selection: HIV-seropositive subjects;
   T4-cell count above 500;
   significantly negative T4-cell slope
2) Collect peripheral blood T lymphocytes
3) Plate in limiting dilution (*) with irradiated autologous antigen-presenting cells
   + antigen = gp120 + antigen = CD4 (**)
4) Growth in culture (*)
5) Test for: Antigen specificity;
   MHC restriction;
   CD4/8 phenotype;
   cytotoxicity for $CD4^+$ T cells;
   TCR variable gene usage
6) *In vitro* expansion of antigen-specific cytotoxic clones (*)
7) Inoculate donor: with 10^8-10^9 irradiated autologous effector cells
   (include all, or the most frequently used, TCR genes)
8) Assess: T4-cell count;
   effectiveness of vaccination;
   therapeutic efficacy

(*) It is planned to prepare autologous EBV-transformed B cells into which are introduced the gene for gp120 or CD4. This would provide a permanent source of stimulator and target cells for CTL generation and testing, as well as for growth expansion.

(**) CD4 antigenicity should also be tested, since anti-CD4 CTL could also be activated through interactions of CD4 with molecules different from gp120.

of precursor frequencies prior to therapeutic intervention. Responding HIV-uninfected clones will be expanded *in vitro* and then tested for antigen specificity, cytotoxicity, MHC restriction and CD4/8 phenotype.

We suggest that T-cell receptor (TCR) gene usage also be explored, since use of a restricted number of V_β genes might permit the future development of a non-autologous and therefore generally applicable preparation (Cohen, 1991a). This technique has been used successfully in some instances of experimental autoimmunity (Howell *et al.*, 1989; Vandenbark *et al.*, 1989; Offner *et al.*, 1991). In EAE (Owhashi *et al.*, 1988) and EAT (Texier *et al.*, 1992), monoclonal antibodies against TCR of antigen-specific effector T-cells produced a protective effect similar to that induced by vaccination against the effector cells themselves. Moreover, in EAE, TCR specific for the encephalitogenic determinant of MBP use similar V_α and V_β chains in two different species, although the MHC and antigenic determinants are different (Burns *et al.*, 1989). Similarly, in our case, a characterization of conserved TCR structures could dispense the technique with the need for cumbersome autologous preparations on a patient per patient basis.

Initially, however, autologous antigen-specific cytotoxic clones will be expanded and activated *in vitro,* followed by irradiation or treatment with a cross-linking agent, prior to reinoculation into the donor.

It is anticipated that the effectiveness of vaccination may be evaluated by serial measurements of (i) DTH responsiveness, (ii) the AMLR (autologous mixed lymphocyte reaction) against the injected T-cell clone, (iii) levels of circulating T cells with idiotypic specifications identical to injected cells (anti-gp120), and (iv) levels of antiidiotypic and antiergotypic T-cell responses (anti-anti-gp120). On the other hand, measures of therapeutic efficacy would be monitored by following peripheral blood T4 cell counts (both absolute and as a percent of total T cells) and clinical indicators of disease progression. Measures of static virus burden (HIV-DNA PCR) and active virus burden (glycine-dissociated P24 antigen, HIV-RNA PCR) might be included to monitor for secondary effects on virus clearance.

Discussion and Conclusions

The major thrust of AIDS research has been identification of the responsible virus and elucidation of its biology, in the hope of discovering means by which the virus might be successfully controlled or eliminated. The underlying rationale has been that the virus, HIV, directly causes the disease syndrome known as AIDS. Therefore, most strategies for vaccination have been based on the production of neutralizing antiviral antibodies. However, several lines of evidence indicate that antiviral antibody production could be counterproductive in favouring viral infection by preventing efficient cell-mediated immunity. This suspicion is based on (1) the known antagonism between humoral and cellular response and (2) the observed mimicry between HIV protein gp120 and immunoglobulins as well as self-epitopes in other components of the immune system (Beretta *et al.*, 1987; Golding *et al.*, 1988; Young, 1988; Bjork, 1991) which may enable the virus to escape a strong host-immune response (Sastry and Arlinghaus, 1990). That is why an alternative strategy was proposed to develop anti-HIV vaccine that would elicit strong cell-mediated immunity (CMI) by virus-specific CTL in the absence of neutralizing antibody production (Sastry and Arlinghaus, 1990; Shearer and Clerici, 1992; Salk *et al.*, 1993).

However, as discussed earlier, it has become apparent that several aspects of HIV infection are difficult to reconcile with the notion that the virus itself is the sole direct and proximal cause of disease. Moreover, some of the viral stimulation of CTL activity itself, in as much as it does not succeed in completely eradicating viral infection, may be maintained and diverted as a factor of autoimmunity directed against $CD4^+$ T cells, both infected and non-infected, as well as against FDC in lymphoid organs. In other words, an autoimmunopathic disorder precipitated by HIV *infection* may be an important

proximal cause of HIV-related *disease*. Therefore, in parallel with a vaccine strategy aimed at developing early CMI to prevent chronic HIV infection and conversion to seropositivity, a therapeutic-prophylactic strategy against these autoimmunopathic disorders is necessary for HIV-infected seropositive patients.

The thesis presented above is that a major cause of the development of HIV-related disease is the destruction of T4 cells by anti-gp120 cytotoxic lymphocytes. Experimental testing of this thesis is proposed because such cytotoxic lymphocytes have been detected in both seropositive and seronegative individuals. They are postulated to kill *via* gp120 on the surface of uninfected, as well as infected T4 cells, and also perhaps *via* a T4-specific self-antigen which is cross-reactive with gp120. Discussed within the context of network theory, this becomes a testable hypothesis, since T-cell vaccination with autologous anti-gp120 cytotoxic lymphocytes is expected to specifically abrogate the activity of such immunopathic effector cells. The success of such an approach will depend both upon the relative importance of immunoprotective as compared to autoimmunopathic effects of anti-gp120 effector cells and upon the existence of immunoprotective factors with specificities for other HIV antigens such as P24 and P17.

In addition, such direct cytotoxicity of anti-gp120 CTL against $CD4^+$ T cells is certainly not the only possible autoimmunopathic effect which could be triggered by HIV infection. As discussed in the introduction and in section II (2), one might consider that FDC, rather than or in addition to T4 cells, could be the target of autoimmune mechanisms triggered by HIV infection. In other words, cytotoxic $CD8^+$ cell activity against FDC would be triggered by HIV antigens and would be responsible for the observed destruction of the lymph node reticulum, leading to increased viraemia and T4-cell loss. If such putative anti-FDC-specific effector cells could be identified in seropositive patients and expanded *in vitro,* a T-cell vaccination procedure against those cells could be designed and attempted.

In any case, a significant consequence of viewing AIDS in this manner is that it shifts the focus of emphasis from HIV alone to HIV in the context of the particular immune system into which it is introduced. The discovery of new facts and observations has rendered inadequate the classical clonal selection concept of a simple cause-and-effect relationship between exposure to a foreign antigen and the production of specific antibodies against that antigen. Rather than a mere system of defence against foreign invaders, the immune system appears today as a complex dynamic network of interacting elements — effector cells, antigen-presenting cells and various regulatory cells — all modulated by genetic factors, cytokines and mutual recognition units. In particular, recent studies on autoimmunity (see *e.g.,* in addition to the above mentioned, Pereira *et al.,* 1989; Coutinho and Bandeira, 1989; Cohen, 1991b)) have shown that immune responses at the molecular and cellular level are normally triggered by self-constituents (self-antigens, MHC molecules, idiotypes etc.), at least as much as by molecules or cells coming from the outer world. Thus, as discussed elsewhere (Atlan and Cohen, 1989a, 1989b), "problems of complexity, generation of diversity and self-organization have entered the field of immunology" and the immune system has emerged "as an evolving computing network or self-organizing entity — a non-programmed history of encounters with partially random internal and external antigenic stimuli is constantly integrated and serves to modulate and specify the more general initial genetic determinations".

This shift in emphasis means that one must focus on the complex interactions between HIV as an incoming stimulus and the immune system as a pre-existing functional network similar to the nervous and neuro-endocrine systems, in a constant process of self-organization. Whereas reduction of viral burden by an appropriate combination of chemotherapy, active immunization and passive administration of hyperimmune globulin may be useful and should be pursued, such measures may not be sufficient, and an autoimmunopathic component of the disease may need to be addressed independently. To this end, the goal of therapeutic intervention would be to help the immune system reorganize

itself and retain or regain a functional state capable, if need be, of coexisting indefinitely with a persistent viral infection. Such a goal is reminiscent of the use of BCG vaccination against tuberculosis in the pre-antibiotic era.

Drawing on the accumulated insights from other, better understood autoimmune disorders, it has been proposed that T-cell vaccination be investigated in HIV-infected individuals as a means to strengthen the host's immune regulatory network and its consequent control of autoimmunopathicity. Its specific implementation has the advantage of not requiring a detailed understanding of mechanisms in order to be effective, since it emerges from the natural history of HIV/AIDS considered in the light of other autoimmune disorders precipitated by microorganisms. In fact, from the results of its application, it may be possible to learn more about the dynamics of the human immune system exposed to HIV. A more in-depth understanding of these dynamics, coupled with a precise identification of the specificity of the autoimmunopathic effector T-cell clones (by assessment of their TCR variable gene usage), should contribute much to the development of an effective therapeutic and potentially prophylactic vaccine against HIV-related disease. As discussed above, such a T-cell receptor vaccine would be more easily and broadly applicable than the autologous T-cell vaccine implemented on a patient-by-patient basis.

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Mécanismes de l'autoimmunité et SIDA: perspectives pour une intervention thérapeutique

Une revue des fondements d'une théorie en réseaux de l'autoimmunité est d'abord présentée. La pertinence de données expérimentales sur la physiopathologie du SIDA est ensuite analysée dans ce contexte. Schématiquement, suivant cette théorie, des cellules T effectrices spécifiques pour des autoantigènes existent normalement dans l'organisme mais leur activité est modulée et supprimée par des réseaux de cellules régulatrices. Du fait d'homologies entre des structures antigéniques de microorganismes et des autoantigènes, une maladie autoimmune peut être déclenchée par des agents pathogènes étrangers qui modifient l'état du réseau. Celui-ci passe alors d'un état de suppression à un état d'activité. Inversement, par une procédure connue sous le nom de vaccination par cellules T, des cellules T effectrices autologues réinjectées après stimulation et atténuation, peuvent modifier l'état du réseau et l'amener d'un état d'activation à un état de suppression.

De nombreuses observations sont présentées en faveur du rôle d'une activité autoimmune dans la destruction de cellules T4 non infectées suivant l'infection par le VIH. Une telle activité serait déclenchée par un antigène d'origine virale, le plus probable, mais non le seul, étant la protéine d'enveloppe gp120. Sur la base de cette hypothèse, les auteurs proposent d'appliquer une procédure de vaccination par cellules T contre des cellules effectrices responsables d'une activité autoimmune pathologique chez des sujets séropositifs pour le VIH. Cette procédure est semblable à celle mise au point chez l'animal sur des modèles expérimentaux d'autoimmunité, actuellement testée chez l'homme sur des maladies autoimmunes.

Le but recherché est d'empêcher la destruction de cellules T et l'installation de déficience immunitaire chez des sujets séropositifs pour le VIH. Mais en dehors de son efficacité éventuelle, cette procédure présente l'avantage d'un test thérapeutique d'où l'on est en droit d'attendre de nouvelles informations sur la pathologie immunitaire du SIDA.

Mots-clés: SIDA, Autoimmunité, Lymphocyte T, Immunothérapie; Réseaux, Vaccination par cellules T, Immunopathogenèse; Revue.

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