An idiotypic network model of AIDS immunopathogenesis

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Communicated by Niels K. Jerne, December 19, 1990 (received for review July 6, 1990)

ABSTRACT Considerations from a network theory of the immune system suggest that human immunodeficiency virus and allogeneic stimuli may act synergistically to cause AIDS. The immune responses to these stimuli include two components that are directed against each other. In some AIDS risk groups other antigens that mimic major histocompatibility complex antigens may substitute for allogeneic stimuli. Implications for the prevention of AIDS are discussed.

The idea that human immunodeficiency virus (HIV) is the sole cause of AIDS (without any cofactors) and is directly responsible for the depletion of CD4-bearing T cells is currently being questioned by many researchers for several reasons. A surprisingly low number of T cells are infected with HIV in AIDS (1), and immunosuppression occurs prior to depletion of CD4 cells (2). Furthermore, immunity against HIV does not protect against AIDS; AIDS patients have high quantities of anti-HIV antibodies in their sera (3) and generate a strong anti-HIV cytotoxic T-cell response (4) but are not protected. In fact, people tend to become seriously ill only after they make anti-HIV antibodies. In spite of intensive research, a detailed mechanism explaining T-cell depletion in vivo, only on the basis of HIV infection, has not been characterized.

An alternative possibility being considered by several groups of researchers is that HIV induces a deleterious immune response that attacks the immune system itself (5–15). In this paper, we describe an immunological process that could lead to AIDS.

Network Regulation

The recognition of variable (V) regions by lymphocytes and vice versa is widely believed to be a central aspect of the specific regulation of the immune system (16). The relative levels of populations of lymphocytes and the topology of their interactions are then key aspects of a description of the system. Some lymphocyte populations recognize an invading antigen, and some have V regions that functionally resemble the antigen in that they have complementarity to the V regions of antigen-specific clones. Specific interactions between these populations are believed to regulate the immune response. An explicit network model accounts for a considerable range of phenomena, including memory, separate roles for IgM and IgG, helper T cells, suppressor T cells, and specific T-cell factors (10, 11, 17–21).

The theory we describe here emerges from that model. An important component of the theory is the concept of network focusing, which refers to the ability of the network to select clones that are images of particular antigens, including self antigens. A second component is the idea that there is a major axis of specificities in the immune system, bounded by self class I and class II major histocompatibility complex (MHC) antigens. We suggest AIDS is a consequence of a destabilization of the system after excessive stimulation along its major axis.

T cells with receptors that have weak complementarity to MHC molecules are known to be positively selected in the thymus and become the mature helper and cytotoxic T-cell populations. Helper T cells are selected that have receptors with complementarity to class II MHC molecules. Much suppressor T-cell phenomenology can be understood in the context of the network model mentioned above if it assumed that at least some suppressors are positively selected to recognize helper T-cell idiotypes (10). Such T cells would then have epitopes on their receptors that resemble epitopes on class II MHC molecules from the point of view of the helper T cells. Their V regions are complementary to helper T-cell V regions, which are in turn complementary to class II MHC, so they are an internal image of class II MHC. Bidirectional stimulatory interactions between helper T cells (anti-class II) and the image-of-class-II-MHC T cells would be mutually stabilizing. These considerations lead to a "network focusing" topology (Fig. 1). Each suppressor T cell is idiotypically connected to a large number of helper T cells and the suppressor T cells are said to have a high network connectivity. The idea that suppressor T cells have higher network connectivity than helper T cells is a basic aspect of the theory (10, 11). The two sets of cells shown in Fig. 1 can be thought of as being like a tent, consisting of a center pole and a canvas. The helper cells correspond to the canvas, and the internal image of class II corresponds to the center pole. The canvas stabilizes the center pole and the center pole stabilizes the canvas.

Similarities Between Class II MHC and HIV Proteins

Autoimmunity models of AIDS are based on similarities between HIV proteins and class II MHC. Ziegler and Stites (5) and Andrieu et al. (7) suggested that since the envelope glycoprotein gp120 is complementary to CD4 (22) and CD4 is complementary to class II MHC (23), gp120 could resemble class II MHC and the immune response to gp120 could cross-react with class II MHC. This concept is supported by evidence that the binding sites for gp120 and class II MHC overlap in the first immunoglobin-like domain of CD4. Recombinant gp120 can block the interaction of CD4 with class II MHC (24–26) as can antibodies that recognize the gp120 binding site of CD4 (27). Analysis of the effects of mutations in CD4 shows that there is some overlap in the sites for interaction with gp120 and class II MHC. While the sites are separable in the sense that some mutations affect the gp120 binding site but not the class II binding site and vice versa, there are also mutations that affect both interactions (28, 29), consistent with there being some overlap. A serological similarity between class II MHC and gp41 of HIV has also been reported (30, 31). Sequence homologies have been

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Abbreviations: HIV, human immunodeficiency virus; V region, variable region; MHC, major histocompatibility complex; SIV, simian immunodeficiency virus.

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Fig. 1. A model for idiothetic relationships between helper T cells and T cells with class II MHC-image idiotypes. Indirect evidence suggests that clonal selection among T cells interacting with self class II MHC antigens and with each other leads to this network focusing topology (10, 21). Helper T cells have a low affinity for class II MHC antigens. We can expect T cells whose V regions have determinants that are complementary to many helper T-cell idiotypes to be positively selected in preference to T cells with idiotypes that recognize only a few helper T-cell idiotypes. The diverse helper T cells would then interact with T cells that express MHC class II-image epitopes. Mutually stimulatory interactions between the anti-class II helper T cells and the class II image T cells are thought to stabilize both populations. This mutual stabilization suggests a simple metaphor for this part of the T-cell repertoire: a tent consisting of a canvas (the helper T-cell idiotypes) holding up a center pole (the class II image idiotypes), and the center pole holding up the canvas. A similar topology has been suggested by Grossman (50), based on asymmetric “network” interactions, but it is not clear that his model refers to interactions between idiotypes and antiidiotypes.

reported between a conserved region of gp120 and MHC class II (32) and also between Nef of HIV and MHC class II (33). If, however, the breaking of tolerance to self class II MHC is the primary pathogenetic event, we would expect B cells, macrophages, and monocytes (cells that express high levels of class II MHC) to be preferentially killed rather than T cells. On the other hand, if the above center pole model is correct, rather than class II MHC itself being an accidental second target of the immune response to gp120, MHC class II image on suppressor T-cell idiotypes could be a target. An attack on this center pole could be a step toward destabilizing the system.

**Foreign Lymphocytes and Synergy Between Two Immune Responses**

People in some high risk groups are also typically exposed to foreign lymphocytes that are present in blood or ejaculates. A possible connection between alloimmunity and AIDS was first suggested by Shearer on the basis of similar pathologies in AIDS and graft-versus-host disease (34). The immune response to foreign lymphocytes includes responses both to conventional histocompatibility antigens and to receptors on the foreign lymphocytes that recognize the host (35–37). The latter receptors have mainly anti-host MHC specificity, and the response to them is an “anti-anti-self MHC” or “self MHC-image” response.

The relationships between the various components that we need to consider are shown in Fig. 2. The components include class II MHC, anti-class II (idiotypes of helper T cells and of foreign lymphocytes that recognize host MHC), CD4 (also complementary to class II), class II MHC image, gp120, anti-gp120, and anti-(MHC class II image). In people exposed to HIV and allogeneic cells, there is the possibility of two immune responses that are directed against each other. As explained above, parts of the anti-HIV response may be anti-(MHC image), while the response to foreign lymphocytes includes an MHC-image response. Each of these two responses sees the other as the “enemy,” even though the original responses were provoked by something else. The two responses can therefore be expected to synergize, and they confuse the other responding cells with the provoking antigens. That is, they attack not only HIV and the foreign anti-self idiotypes, but also the endogenous center pole (MHC image) and canvas (anti-class II helper-cell idiotypes), destabilizing this central T-cell idiotypic structure.

In summary, AIDS may be an autoimmune disease that can be triggered by a combination of HIV and allogeneic stimuli rather than by HIV alone. Synergy between the MHC-image and anti-MHC-image immune responses is envisaged as destabilizing the system and producing characteristic symptoms of HIV disease (increased immunoglobulin levels, immune complexes, and a failure of normal regulation leading to the production of autoantibodies) during the so-called latency period.

This mechanism of AIDS pathogenesis is consistent with the observation that AIDS develops after a prolonged period of immune system activation. The typical delay in the onset of AIDS may result from the immune system being a self-stabilizing network with a large number of different clones stabilizing the center pole. The destabilization of a complex self-stabilized network could take a long time.

Homosexuals typically receive allogeneic lymphocytes in ejaculates. Intravenous drug users are exposed to only small amounts of allogeneic cells, and the reader might well ask whether such small stimuli could trigger a catastrophic process. However, the proposed synergy means an allogeneic stimulus may be primarily important for getting the MHC-image clones started. Clones responding to HIV could then become the stimulus for the MHC-image clones and vice versa, and the process could become self-propagating. AIDS in risk groups that are not exposed to allogeneic cells is discussed below.
It is noteworthy that the idea of two complementary antigens being important in autoimmunity has also been discussed by Westall and Root-Bernstein in the contexts of experimental allergic encephalitis, postinfectious neuropathy, and postvaccinal neuropathy (51, 52). They suggest that the second antigen is an adjuvant component. Their model does not include MHC image or anti-MHC image responses.

Polymorphic and Monomorphic MHC Determinants

gp120 of HIV is complementary to CD4, which in turn is assumed to be complementary to a monomorphic part of class II MHC. The anti-MHC-image response may then be against a monomorphic part of the center pole. On the other hand, alloimmune responses are usually thought to be against polymorphic determinants, but the center pole model leads to the idea that foreign T-cell receptor idiotypes specific for monomorphic epitopes of class II MHC may nevertheless play a role. According to the model, allogeneic helper cell idiotypes are selected in their original environment to be weakly anti-class II and anti-class II image, and during that selection (leading to MHC restriction within a single individual) no distinction can possibly be made (by the individual's T cells) between monomorphic and polymorphic class II determinants. The T cells of each individual attain a state of equilibrium in which the helper cells' idiotypes are attuned to the endogenous center pole idiotypes. Different MHC molecules select different sets of helper-cell idiotypes together with corresponding center poles. The helper-cell idiotypes of a particular individual that are anti-(monomorphic class II determinants) are then specific for (and regulated by) center pole idiotypes of that particular individual. Allogeneic helper cell idiotypes, including those that recognize monomorphic determinants, are under the regulatory control of the center pole idiotypes of a different host. When helper T cells are transferred into an allogeneic environment, there is a mismatch in between the idiotypes of the helpers and the idiotypes of the endogenous center pole. Each of these sets of idiotypes regards the other as foreign, and mutual stimulation seems likely to ensue. It follows that both MHC-image and anti-MHC-image responses may include monomorphic determinants.

We now turn to considering some of the various AIDS risk groups. We see some interesting serological differences between homosexuals and hemophiliacs.

Anti-collagen Antibodies in Homosexuals

Anti-collagen antibodies are not predicted by the above model, but their occurrence in AIDS patients and elsewhere provides circumstantial support for it. We found anti-collagen antibodies in the sera of many homosexuals, both HIV negative (32%) and HIV positive (66%), and in the sera of 100% of homosexual AIDS patients (38). The anti-collagen antibodies react preferentially with denatured collagens and are rarely seen in rheumatoid arthritis or other arthritides. Such antibodies are also found in graft-versus-host disease (39), a form of alloimmunity with similarities to AIDS in its pathology (34). It is possible that anti-collagen is a marker of alloimmunity, such that many homosexuals express anti-collagen antibodies as a consequence of alloimmunity and independently of HIV infection. Since only those that make anti-collagen antibodies appear to develop AIDS, the findings are consistent with alloimmunity and HIV being cofactors that cause autoimmunity and AIDS in homosexuals.

Anti-anti-CD4, Anti-anti-CD8, and Anti-anti-gpl20 in Hemophiliacs

The immune system of hemophiliacs seems to have been perturbed along the major axis by MHC-like antigens, because many HIV-negative hemophiliacs make anti-anti-CD4, anti-anti-CD8, and anti-anti-gpl20 antibodies (M.D.G., unpublished data). The fraction of hemophiliacs expressing these antibodies increases after HIV infection. Since CD4 and CD8 are complementary to class II and class I MHC, respectively, anti-anti-CD4 may resemble anti-class II or anti-class II image, and anti-anti-CD8 may resemble anti-class I or anti-class I image.

These results can be considered in light of another idea about the T-cell repertoire. Suppressor T cells and cytotoxic T cells are often viewed as belonging to the same broad class of T cells, since they both express CD8. Cytotoxic T cells are selected to be weakly anti-class I MHC, and CD8 itself has complementarity to class I MHC. Together with the idea that at least some suppressor T-cell idiotypes are selected to recognize and be recognized by anti-class II MHC helper T-cell idiotypes, this suggests the existence of a "major axis" of specificities in the selected T-cell repertoire, consisting of the sequence class II MHC-CD4 T-cell idiotypes-CD8 T-cell idiotypes-class I MHC. Class I and class II MHC molecules are then viewed as boundary conditions of the T-cell repertoire.

What MHC or MHC-like antigens could be responsible for the production of the anti-anti-CD4-image, anti-anti-CD8, and anti-anti-gpl20 antibodies in hemophiliacs? Hemophiliacs are exposed to factor VIII that is obtained from blood. One possibility is that factor VIII preparations contain HLA antigens. An alternative speculative possibility is that antibodies in factor VIII play a role. Factor VIII preparations can have an immunoglobulin content up to 10% of total protein (P. Spith, personal communication). It is conceivable that the V regions of the antibodies are selected to be (weakly) MHC mimicking. MHC molecules belong to the immunoglobulin supergene family, so there is an a priori similarity between immunoglobulin and MHC. If B-cell idiotypes are positively selected to recognize helper T-cell idiotypes (which are weakly anti-class II MHC as a class), the antibodies would have V regions that tend to be class II MHC image-like. Rossi et al. (40) have reported that not 7% of B-cell precursors are anti-class II MHC as detected in an ELISA, indicating that a minority of antibodies may be fairly strongly MHC image. In view of the fact that intravenous immunoglobulin is widely used in therapy of autoimmunity (41), a possible implication of foreign immunoglobulin in autoimmune pathogenesis is a counterintuitive twist. It does not, however, disqualify the idea, for cellular immunologists are familiar with immunological reagents having opposite effects in different circumstances.

Hemophilic AIDS and homosexual AIDS seem to differ in several respects. For example, Kaposi sarcoma is common in homosexual AIDS, but it is rarely seen in hemophilic AIDS. We detect anti-collagen antibodies with high prevalence in homosexuals (see above) but not in any HIV-negative hemophiliacs (0/44), and in only 13% of HIV-positive hemophiliacs (3/24). Another difference is that we see elevated levels of anti-anti-CD4, anti-anti-CD8, and anti-anti-gpl20 antibodies in very few homosexuals, in contrast with the high prevalence in hemophiliacs (M.D.G., unpublished data). Different cofactors that are MHC mimicking or anti-self MHC image can be expected to cause different modes of response of the system, albeit the perturbations are eventually fatal in both cases.
AIDS in Africa

In Africa and some parts of the Carribbean, AIDS is equally prevalent among males and females. Ordinary heterosexual practices do not typically result in alloanimmunity, and in this case other factors may play the role of an allogeneic stimulus. The association between mycobacterial infections, which are widespread in developing countries, and autoimmune has been recently reviewed (42), and the fact that there is a cross-reaction between Mycobacterium leprae (the causative agent of leprosy) and HLA-DR (43) may be an important link with the model described above. There is also a cross-reaction between M. leprae and HIV5 that could play a role. Anti-collagen antibodies occur in lepromatous leprosy (39), and this serological similarity with homosexuals may be significant.

The longer history of HIV infection in Africa may alternatively have led to the emergence of a virus that more accurately mimics a common center pole shape. The three-dimensional shapes of proteins are related to nucleic acid and protein sequences in a nontrivial way, so unfortunately this idea is unlikely to be either supported or refuted by sequence data. If selective processes have resulted in HIV in Africa having more cross-reactivity with endogenous center poles than is the case elsewhere, synergy may be less important in evoking disease. From the standpoint of the above model, simian immunodeficiency virus (SIV) in the macaque monkey could be analogous to heterosexual AIDS in Africa. The SIV envelope protein binds to simian CD4, so SIV may have the essential antigenic feature needed to induce an AIDS-like disease in the context of the above model. Natural infection with SIV is widespread in the wild and does not cause disease. On the other hand, a laboratory-isolated SIV strain causes rapidly fatal disease with a pathology similar to AIDS and without any need for an allogeneic cofactor.

AIDS in Babies

HIV-infected babies often develop AIDS very quickly—namely, a few months after birth. They are exposed to maternal cells at birth and to maternal immunoglobulin in utero. The maternal cells are typically semiallogeneic, and the maternal immunoglobulin is typically selected in a semi-allogeneic MHC environment. The postulated center pole structure presumably forms early in development, when the immune system is sensitive to even very small perturbations. The development of the center pole could easily be disrupted by the presence of HIV and allogeneic stimuli.

Anti-HIV and MHC-Image Antibodies in Alloimmune Mice

We also see anti-p24 antibodies in murine alloanimmune sera (44). In view of evidence of similarities between class II MHC and each of gp120, gp41, and Nef, it is possible that the anti-p24 activity is also due to crossreactivity between p24 and class II MHC image. The possibility of at least four different HIV components being involved in the postulated mechanism of pathogenesis suggests that there has been evolutionary pressure for HIV components to be MHC mimicking.

As discussed above, in addition to the putative anti-MHC-image antibodies, alloimmune mice contain MHC-image antibodies. Alloimmune mice thus contain both forms of immunity postulated in the above model, but their MHC-image-anti-MHC-image activation evidently does not normally reach a level such that the postulated synergy leads to disease.

Anti-HIV, MHC-Image, and Anti-collagen Antibodies in Alloimmune Mice

The MRL lpr/lpr and MRL +/+ strains are models of the autoimmune disease, systemic lupus erythematosus. We found that anti-gp120 can also be detected in the sera of both strains of mice (44). This is of particular interest because systemic lupus erythematosus and AIDS have at least 31 features in common (45). We also see MHC-image antibodies, including class I image and class II image, in MRL mice but not in normal mice (44). These mice have no way of “knowing” the difference between monomorphic and polymorphic MHC determinants, and in this case polymorphic determinants may play a role, since we see MHC-image reactivity against anti-I-A5 and anti-H-2Kd but not against anti-I-A5 or anti-H-2Kd monoclonal antibodies.

Thus, both kinds of immunity that are postulated in our AIDS model (MHC image and anti-MHC image) occur in this murine model of autoimmune disease. There is a slow onset of disease in MRL mice, with death at ~6 months in the MRL lpr/lpr strain and at ~18 months in MRL +/+ . Hence, even in the absence of extrinsic stimuli there is an inherent instability in the immune systems of MRL mice that leads to autoimmunity, and it occurs together with MHC-image and presumptive anti-MHC-image antibodies. Thus, the evidence supports a network model of pathogenesis for autoimmune mice, and allogeneic lymphocytes and gp120 provoke the production of antibodies with similar specificities. The similarity between systemic lupus erythematosus and AIDS is further emphasized by the fact that anti-collagen antibodies are also seen in MRL mice (46).

Conclusions

The idea that AIDS is an autoimmune disease induced by two agents—namely, HIV and allogeneic or other MHC-mimicking stimuli—seems to provide explanations for some puzzling aspects of the disease. It is noteworthy that the basic model emerges from postulates about the immune system that were made without reference to AIDS. The postulates had been made anyway; they were not tailor-made to solve this problem. Elsewhere (47), we discuss how the model may account for 11 paradoxes formulated by Duesberg (48). A dynamic model of HIV-mediated killing, designed to account for some of the puzzling features of AIDS, such as the low frequency of virus particles and the long latency period, has been formulated by Perelson (49). That model does not involve the immune system actively in the pathogenic process, so it cannot provide explanations for the serological phenomena we have discussed.

The most satisfying evidence for a particular model of pathogenesis would be the discovery of successful disease prevention strategies that are formulated on the basis of the

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model. Autoimmunity models suggest we should be trying to induce specific tolerance to HIV proteins rather than immunity. An important experiment will be to determine whether induction of tolerance to SIV proteins prevents the development of disease upon subsequent infection with SIV in the macaque model of AIDS.

Anti-collagen antibodies were found in the serum of all of 17 homosexual AIDS patients studied. If we can specifically suppress the production of these antibodies, it is conceivable that we may also affect the network in a way that helps to suppress the development of the disease. This scenario would be of interest at least for HIV-positive, anti-collagen negative homosexuals.

The induction of tolerance to HIV is precisely the opposite approach from that currently pursued by most researchers involved in vaccine development. A possible AIDS prevention strategy would be to induce tolerance in individuals at risk of HIV infection and allow benign HIV infection to become widespread. Such a strategy would necessitate a significant psychological adjustment on the part of the public. A less radical approach would be to attempt to induce tolerance to MHC-mimicking parts of HIV, while inducing immunity to other parts. The extensive experience that immunologists have accumulated in methods for generating specific immunological tolerance can be brought to bear on these problems.

We suggest that this MHC-image–anti-MHC-image theory of AIDS pathogenesis be called the "MIAMI model" for short. It will be disproven (or at least shown to be less helpful than anticipated) if the disease is not prevented by inducing tolerance to HIV components that cross-react with MHC images on T cells.

We thank Drs. Jerry Nepom, John Schrader, and Patricia Fultz for helpful comments on an earlier version of this manuscript. Also, our thanks go to the National Health Research and Development Program, the Natural Sciences and Engineering Research Council, and the Medical Research Council of Canada for funding.