The pathogenesis of AIDS: classical and alternative views

ABSTRACT—As HIV readily kills CD4 cells *in vitro* it has been widely assumed that this would account for the declining CD4 counts *in vivo*. A growing number of reports suggest that the pathogenesis of AIDS is considerably more complex than had been thought. A number of indirect mechanisms for CD4 cell death have been proposed. In this review of alternative theories which could explain the features of AIDS, autoreacivitiy and genetic restriction to the development of disease are considered the most important. In addition it is suggested that if HIV is able to mimic MHC antigens on the surface of antigen presenting cells then this could stimulate 'allo reactive' T lymphocytes, which would explain the marked similarity of HIV infection to chronic graft versus host disease.

Two recent reports have suggested that the pathogenesis of AIDS is not as simple as previously assumed [1,2]. The conventional view is that, since HIV infects CD4 cells *in vitro*, the cytopathic properties of HIV adequately account for the slow decline of CD4 cells *in vivo*. However, this theory does not adequately explain why the decline in CD4 cells takes so long (the mean time from HIV infection to AIDS is approximately 10 years), why so few CD4 cells are infected *in vivo*, and why some people never appear to suffer any symptoms even after 10 or 15 years [3–5]. The easiest way to answer these questions, from a classical cytopathic virus standpoint, is that the virus becomes persistent, infecting a variety of CD4 bearing cells including antigen presenting cells in the lymph nodes, and that it evades an initial effective immune response by nature of its highly variable envelope. Thus the virus could escape neutralising antibodies for instance by mutating into an 'escape mutant' which would then continue killing CD4 cells [6].

The results of two recent studies suggest that it may not be so simple: the demonstration that uninfected 'allogeneic' human lymphocytes were able to protect rhesus macaque monkeys from infection following an SIV challenge [1], and that allogeneic cells were able to induce a humoral response in certain breeds of mice which cross reacted with the gp120 (envelope) and p24 (core) proteins of HIV [2].

Although neither of these studies is conclusive, it appears from both that the virus may mimic a normal cellular ligand. In 1988, whilst reviewing the interaction of gp120 And the CD4 molecule, John Habeshaw and I were impressed with the amount of literature that reported clinical and immunological data consistent with an autoreactive or autoimmune disease process [7]. We postulated that the most likely explanation for the pathogeneis of AIDS would be if HIV induced an autoreactive process in susceptible individuals by nature of its ability to mimic MHC (major histocompatibility complex) class II and stimulate allo reactive lymphocytes—a process that results in 'graft versus host disease' (GVHD) in mice injected with allogeneic lymphocytes from a haplotypically different mouse. The similarity between AIDS and GVHD had been noted before the discovery of HIV when it was suggested that allo lymphocytes transmitted in blood and semen may induce the disease, a theory quickly buried when cell-free HIV was shown to cause AIDS [8]. Our suggestion is that HIV converts a 'self' cell into a foreign or 'allo' cell by nature of its ability to mimic MHC class II directly. Although we reviewed the immunological and stuctural knowledge of gp120 nearly three years after our first review [9] and found the data even more supportive of the contention that gp120 could functionally mimic MHC class II, there was little enthusiasm for alternative views until the 'SIV' and 'mouse' reports appeared. However, there has been an abundance of alternative views on pathogenesis, most of which have not been taken too seriously by the majority of AIDS researchers. Although AIDS is probably an immunological and not primarily a virological disease, less than 3% of all AIDS literature is primarily immunological. This review will deal with the most pertinent observations and interpretations.

Methods of CD4 cell killing

HIV will kill CD4+ cells *in vitro*. Certain cells are more susceptible than others to the cytopathic effects of HIV, and the susceptibility of peripheral blood cells is probably restricted by additional molecules other than CD4 such as MHC class II. [10]. Nevertheless, the primary importance of CD4 is reflected in the fact that monoclonal antibodies to the gp120 binding site on CD4 will prevent the cytopathic effects of HIV [11]. In the past few years it has become apparent that the most readily observed cytopathic effect—syncytial formation, which is the phenomenon whereby cell membranes fuse together in the presence of virus to form a multinucleate cell—is not a prerequisite for infection. The ability to fuse or 'balloon' is a phenomenon which

A. G. DALGLEISH, MD, MRCP(UK), FRACP
Professor of Oncology, St George's Hospital Medical School, London

depends on the binding of the HIV envelope gp120 to the CD4 receptor [10,12,13]. After that has taken place it is likely that conformational change of both gp120 And CD4 is required in order to allow the virus to fuse with the cell membrane, and then enter the cell [14]. Mouse cells transfected with human CD4 cannot be infected with HIV although the virus will bind to the CD4 molecule [15]. Other ligands are therefore involved; several have been suggested but none appears to be a singular absolute requirement [16]. It may be that a cellular protease present on human cells is require with or without another ligand [17,18]. In this regard it is interesting that some cellular protease inhibitors will inhibit syncytial formation without affecting virus replication *per se* [19] (and J. Moore, personal communucation). In our experiments the most important molecule after CD4 appears to be HLA class I as this will allow HIV entry into mouse cells already transfected with CD4 (Newell A, Bountiff L, Dalgleish AG, unpublished observations). Moreover, HLA class I is involved in the functional operation of several receptors such as the insulin receptor [20]. In spite of detailed knowledge of gp120/CD4 interactions and some of the subsequent events, it is still not known whether syncytial formation is important *in vivo*. Most researchers would probably argue that it is not, as there is little evidence for it *in vivo*.

Recent work has suggested that gp120 is readily shed or discarded from the virion and that this might be a prerequisite for virus induced fusion [21,22]. Free gp120 *in vitro* is able dramatically to inhibit antigen specific recognistion events [23,24]. The mechanisms whereby this is achieved appear to be mainly due to its ability to bind CD4, as the effect can be mimicked by anti-CD4 monoclonal antibodies and restored with interleukin–2 [24]. However, when antigen presenting cells (APC) are pulsed with antigen in the presence of HIV and antigen specific T cells, not only is there no response from the T cells but they remain anergic even after stimulating with 1L-2 [24]. However, contrary to what we initially believed, the cells are not killed by HIV; they can be detected by specific markers many weeks later, but they will no longer proliferate in response to specific signals and thus are anergic. This antigen specific dysfunction is due entirely to signalling of the CD4 memory lymphocyte and is not a result of APC dysfunction [24,25]. This is particularly important as APCs can readily be infected *in vitro* and have been shown to be infected *in vivo* [26].

Gp120 has not been detected 'free' in the serum. Thus it has been argued that it plays no role in HIV pathogenesis. However, it has a high affinity for CD4 and therefore should readily attach to the numerous molecules sported on a wide variety of cells. Siliciano and colleauges [27] have demonstrated that gp120 could render uninfected CD4 cells a ready target for gp120 specific CTL cells. This could be an effective way of killing uninfected CD4 cells *in vivo*.

CD4 infection *in vivo*

There was considerable surprise when Harper *et al* [28] showed that only 1 in 10^5 susceptiible CD4+ cells were infected with HIV in seropositive patients, with up to 1 in 10^3 in people with cells infected with AIDS. A recent study using the supersensitive polymerase chain reaction [29] has led to similar conclusions. Most of the infected cells are CD4 lymphocytes although a virus reservoir exists in lymph nodes where APCs may provide good reservoir for HIV antigen since they may be less susceptible than lymphocytes to the cytopathic effects of HIV [30].

Autoimmunity

Much as been written of the autoimmune features of HIV infection but until recently it has been widely ignored as having a significant role in the pathogenesis of HIV [31–33]; instead, the various manifestations have been considered merely as 'side effects' of HIV infection.

Clinical autoimmune features are well recognised, especially the eczema-psoriaform skin lesions and the less frequent thrombocytopaenia. However, careful documentation of any HIV infected cohort will reveal that most, if not all, patients progressing to disease will have at least one clinical feature of autoimmune disease. In addition, these patients will have evidence of enhanced immunoreactivity as judged by increased cellular expression of IL-2 receptors and HLA molecules, increased markers of immune activation such as B_2 microglobulin, neopterin and hypergammaglobulinaemia [34,35]. More detailed analysis of T cell subsets reveals that B cells, CD4 and CD8 cells gradually become permanently activated as disease progresses [36–39].

Virus versus autoimmunity

The classical viewpoint is that virus replication prefers activated cells for both infection and production, and that virus replication activates cells [40.41]. This argument would suggest that the markers of activation are secondary to virus replication. However, the opposite is more likely to be true. Significant immune defects can be found within a few weeks of seroconversion, with marked signs of immune activation occurring in the absence of HIV antigenia or viraemia [42,43]. Indeed the level of this activation appears to correlate directly with rapid progression to AIDS, in addition to being closely associated with certain MHC haplotypes [34] (Table 1).

MHC restriction

The fact that there are such major differences in the rate at which people progress (or fail to progress) to HIV infection clearly necessitates a 'co-factor' or other

explanation. It has been popular to look for other micro-organisms, and different cohorts of patients in various parts of the world have been linked with mycoplasma, the new herpes virus HHV-6 and cytomegalovirus. None of these is particularly convincing. Another possibility is that the most important co-factor is the host itself. The initial observation that patients with the haplotype HLA-1 B8 DR3 were more susceptible to AIDS has been confirmed in a number of studies [44] (Table 1). It is interesting that this haplotype is also associated with several autoimmune diseases. Other haplotypes have also been associated with progression or resistance to disease (Table 1). That genetic influences could be the strongest co-factor should come as no surprise since the same HIV virus that causes AIDS in humans causes no disease in chimpanzees even though its lymphocytes and monocytes are readily infectable *in vitro* and *in vivo* [45].

Superantigens

There has been a lot of interest in the role of 'superantigens' in disease over the past year. Superantigens are antigens that can stimulate specific T cell receptor pathways without being processed through the classical pathways, and which are not MHC type restricted [46]. A well elucidated example is the staphylococcal enterotoxin which is the causative agent of the tampon toxic shock syndrome and the scalded baby syndrome. The pathology of skin inflitration, inflammation, gut disturbance (including diarrhoea) and lymphadenopathy is due to the inappropriate activation of a large percentage of the T cell repertoire. It was a surprise to many to discover that some retroviruses also encode superantigens [47]. Indeed, the mouse mammary tumour virus encodes the M1s antigen, which was discovered by Professor Festenstein at the London Hospital, the causative ligand of graft versus host disease in MHC class I and II matched mice. M1s appear to be able to bind and stimulate T cells with the appropriate responding variable gene product. This is almost certainly important for the survival of the virus as it needs to induce lymphoproliferation in order to replicate and ensure its survival. In the world of viruses it is not alone: both HIV and HTLV-1 induce marked proliferation of lymphocytes in some individuals [48]. It therefore was reasonable to search for a superantigen in HIV. None has been discovered but indirect evidence has been claimed by the discovery that the T cell repertoire in AIDS patients contains deletions of certain Vß genes [49]. It is also possible that superantigens other than HIV can cause certain subsets of T cells to proliferate and then die in HIV infected patients only—in other words that HIV has somehow put a signal on uninfected CD4 cells so that they will respond abnormally to a second signal. This abnormal response may result in either proliferation or death.

Programmed cell death or apoptosis offers another explanation for uninfected CD4+ cell death [50]. This can occur when the second 'signal' is not received. Some workers have claimed that this is the real cause of cell death and disease in HIV infection, and that it could all be explained by the ability of gp120 to bind to CD4 cells when the second signal is either absent or inappropriate.

Immunopathogenesis

Whereas escape mutants, whether neutralisation or CTL mutants, are claimed to be the reason why the virus persists in spite of an apparently initially effective immune system, it still remains likely that the immune response to a changing virus may contribute more to the pathology than the control of the virus. Indeed, imbalance between the virus and the immune system is the deciding factor in pathogenesis in other virus disease systems [51].

It was noticed soon after AIDS was recognised as a

Table 1. Determinants of HIV disease progression

HLA associations withHIV disease progression	
HLA1 B8 DR3 (progression)	Simmonds et al. *Lancet* 1991;**338:**1159
HLA DR5 (progression)	Cruse et al. *Pathobiology* 1991;**595:**324.
HLA DRBI × 0702 DQA1 * 0201 (with absence of disease)	Louie et al. *J Aids* 1991;**4:**814.
HLA B8 DR3 (progression)	Kaplan et al. *Heredity* 1990;**40:**290.
HLA-DP (decreased in AIDS)	Odum et al. *Dis Markers* 1990;**8:**113–6.
B35 CW5 (progression)	Jeannett et al. *J Aids* 1989;**2:**26.
B35 (ancestral haplotypes and progression)	Cameron et al. *Hum Immunol* 1990;**29:**282.
Initial immune response and progression	
Non-specific activation	Simmonds et al. *Lancet* 1991;**338:**1159. Sheppard et al. *J. Aids* 1991;**4:**704. Fuchs et al. *Immunol Lett* 1990;**26:**75. Schechter et al. *Aids* 1990;**4:**185.

distinct entity that the clinical and immunological features were similar to those of experimentally induced graft versus host disease in mice [7–9], specifically in mice in which MHC class II but not MHC class I or lpr was mismatched. The common features are shown in Table 2.

Graft versus host disease (GVHD) is the classic 'autoreactive' disorder. Here, foreign or 'allo' cells replicate in the host and stimulate 'dormant' T cells into non-specific or allo reactivity. GVHD is not one disease but, rather like cancer, a generalised description of several acute and chronic conditions, as well as a host of mismatches and combinations thereof, alluded to previously. The important point about GVHD is that it probably occurs only if the host contains a T cell receptor variable gene that recognises MHC as foreign and is non-specifically activated. In addition, a degree of immunosuppression enhances induction of GVHD in some systems. Of interest to HIV and the chimpanzee is that GVHD does not cross species.

Clearly HIV can induce AIDS without foreign or allo cells. However, could it induce a GVHD-like response by causing syngeneic GVHD, ie altering self cells so that they appear as non-self to certain self T cells. Moreover, AIDS fits MHC class II mismatched GVHD better than other models, and HIV has been noted to contain MHC class I homology, in addition to the fact that both MHC class II and gp120 specifically bind CD4. Two areas of MHC class II homology have been known for some time but dismissed by many as not being of significant size [52,53]. We and others have been impressed by the fact that there are further structural homologies with MHC class II (and I) and gp120. We therefore suggested that since this area is close to the CD4 binding loop on the carboxy terminal it may be seen by the T cell receptor (TCR) after CD4/gp120 binding has taken place as the CD4 molecule is crosslinked to the TCR during antigen presentation.

Armed with this suggestion, Elizabeth Hounsell and colleagues at the Clinical Research Centre set out to model the carboxy terminus of the gp120 by comparing it with the known structures of molecules that have been successfully crystalised. Computer analysis

Table 2. Major features of GVHD shared with HIV disease

- Activation of T lymphocytes
- Antigen specific dysfunction
- B cell hyperreactivity leading to hypergammaglobulinaemia and autoreactive antibodies
- Change in CD8 total and relative number
- Suppressor cells selective for CD4 cells
- Cytotoxicity for autologous cells
- Skin lesions, scaly (eczema/psoriasis like)
- Gastrointestinal symptoms/disease
- Lymphadenopathy
- Opportunistic infections
- High grade lymphomas
- Angiodysplasia-like lesions
- Hypercytokinaemia, including TNF and IL-6

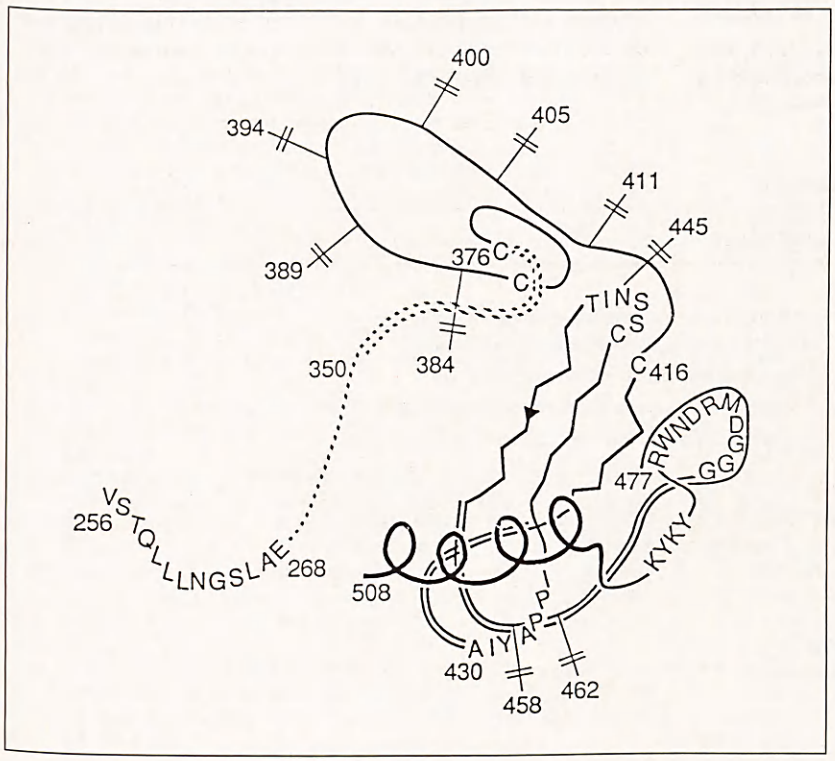

Fig. 1. *Modelling of the carboxy terminus of gp120 (ELI isolate).* Note the alpha helix beginning at amino acid 508, the minor alpha helix at 477, and the ß pleated sheets marked with an arrow. The CD4 binding site is the loop behind the alpha helix (=). The AIYAPP1 segment is probably also involved in CD4 binding activity. The 256 to 268 site contains MHC class I and class II sequences.

showed that a large alpha helix is conserved through all known HIV isolates, and that this has structural identity with the alpha helix of MHC class I and, by extrapolation, with (the uncrystallised) MHC class II [54]. As MHC class II and gp120 both bind CD4, the MHC class II 'mimicry' may be more relevant. Furthermore, allo recognition can occur because of changes in the alpha helix of MHC molecules. We have now made a helical peptide of this stucture and shown that it behaves an an allo epitope in antigen recognition assays performed by M. Clerici and G. Shearer (manuscript in preparation).

Computer modelling has been used to describe the relationship between the virus and the immune system, and has been used to support the 'mutant escape; scenario [55]. However, when basic immune parameters are considered, it is just as easy to model a longitudinal autoreactive interaction of the virus and immune system which would produce the features of HIV infection.

Is AIDS 'GVHD' induced by HIV?

The fact that micro-organisms can induce autoreactivity is beyond contention. Indeed, a major problem is that nearly all the common viruses are associated with the induction of autoantibodies, many of which are not associated with disease [51]. However, certain viruses induce autoreactivity which comprises nearly all of the pathology associated with infection [51]. In particular, all the lentiviruses are associated with autoreactive pathology (see Table 3).

Several recent reports have added further evidence to the GVHD scenario [56–58]. The CD8 subset, defined by the CD38 and CD57 markers, increases as HIV disease progresses until there are no CD38 or CD57 negative cells in the terminal stages of the disease. In short, the cells move from a specific functional group of cells, which can readily exhibit cytotoxic T cell activity on virus infected lymphocytes, to a pool of broadly reactive cells which probably inhibit helper cell activity. Stimulatory CD4 subsets change as disease progresses as does the cytokine profile [58]. Although there are no specific markers to define the human equivalent of the T helper type 1(Th1) and type 2 (Th2) cells, the cytokine profile associated with HIV infection is similar to that seen in chronic GVHD. Recent reports claim that certain preparations of gp120 can actively induce monokines/cytokines especially in cells from HIV seropositive donors [59,60].

It is the broad clinical and immunological features, especially the time span, that make the comparison of AIDS to GVHD so compelling. The major prerequisites for this cell activation, such as a readily expressed envelope protein on the surface of antigen presenting cells in the lymph nodes, can readily be demonstrated. The fact that immune activation appears to be necessary for progression to AIDS is also consistent with the hypothesis, as is the MHC genetic restriction, which would explain why some people do not develop disease. Although associated with certain MHC types, it may be due to the presence of variable genes in the TCR, so that only people who express the particular gene product progress to AIDS (and those with a higher level would progress more quickly).

This can all be tested but has had to wait until new tools have become available to dissect the human TCR. With the monocloncal antibodies now available we have looked for and found a significant Vβ selection in people with early HIV infection who had some evidence of early activation such as skin lesions or hypergammaglobulinaemia [61].

Table 3. Viruses associated with autoreactive pathology

Virus	Host	Pathology
Lentiviruses		
Equine infectious anaemia	Horse	Autoimmune reactions against antigens on surface of erythrocytes causes anaemia
Caprine arthritis encephalitis virus	Goat	Synovitis and multi-system disease
Visna maedi	Sheep	? Immune response against neural antigen
HIV	Man	? Aids as an autoreactive disease
Human viruses which induce autoreactive antibodies		
The following viruses induce a broad range of autoantibodies to DNA, lymphocytes, neutrophils, erythrocytes, IgG, etc. However, antibody response does not correlate with disease except for the antibodies against the heart in the viruses marked †		
Epstein-Barr	Measles †	
Cytomegalovirus	Chickenpox †	
Hepatitis A, B. C, D	Coxsackievirus †	
Influenza †	HIV †	
Mumps †		

Treatment and vaccines

If the major part of the pathogenesis of HIV infection is GVHD-like or TCR-restricted, then it should be possible to identify and immunise against the responding TCR gene or genes (or the corresponding epitope on the virus). Of note is the fact that monocloncal antibodies against specific Vß gene products in the TCR can abort GVHD in mice [62,63]. Until this has been identified, early anti-retroviral agents (to reduce antigen load) plus an immunosuppressant should be tried (on a proper trial basis) in patients who are activating their immune system. Although cyclosporin A is an obvious candidate, and has been used in terminal AIDS patients with symptomatic relief; other agents such as FK506 and rapamicin might be worth considering; so also is thalidomide which has a good record as an anti-GVHD agent and is already used in HIV infected patients [64]. Other approaches include specific tolerisation to the MHC-like components of HIV and the development of drugs or peptides that interfere with 'allo' recognition of HIV.

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Address for correspondence: Professor A. G. Dalgleish, Department of Cellular and Molecular Sciences, St. George's Hospital Medical School, Division of Oncology, Cranmer Terrace, London SW17 0RE.