Review

Molecular immunopathogenesis of HIV infection

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Introduction

Studies of HIV infection in the past decade have revealed a great deal about the organisation of our immune system and basic cell biology, as well as about the pathogenesis of HIV disease. The integration of the retroviral genome into that of T-cells results in a major disruption of host-cell gene expression and protein synthesis.¹ HIV results in the destruction and dysfunction of CD4⁺ T-cells, and many other cells of the immune system. Recent studies have emphasised not only the tremendous scale and rate of viral replication, but also an unexpectedly high rate of destruction and compensatory regeneration of CD4⁺ T-cells.^{2,3} Some functional abnormalities, including decreased (antigen-specific) T-cell proliferation and cytokine synthesis (such as interferon- γ),⁴ appear in the early stages of infection before there has been any significant depletion of CD4⁺ lymphocytes. Despite the widespread cellular functional defects observed in individuals with HIV disease, the number of viable cells infected with the virus is relatively low. Estimates of the number of peripheral blood mononuclear cells (PBMC) infected with HIV range from 0.1% to 13.5%; most of these cells contain integrated provirus, usually in a latent or defective form.⁵ Recent studies have shown that fundamental cell processes such as cell cycle regulation are similarly affected among uninfected cells, resulting in premature programmed cell death, or apoptosis.^{6,7} The precise mechanisms by which the virus affects the survival or function of uninfected cells are at present unclear. In this review, we explore some of the key cellular and molecular mechanisms of the host-virus interaction which ultimately lead to such profound damage to the immune system. While some of these are interlinked and some appear to proceed in parallel, it is not yet possible to state precisely what their relative contribution is. Rather we attempt to outline some of the mechanisms that appear to contribute and weave them into a tentative model.

Perturbations of cytokine profiles

Following HIV infection, abnormalities can be observed in cytokine production and the intracellular mechanisms that lead to cytokine gene expression in lymphocytes. Cytokine-producing T-helper (Th, CD4⁺) cells can broadly be classified into three groups according to the cytokines they produce on stimulation: Th1 cells, which are responsible for delayed-type hypersensitivity and macrophage activation,

produce interferon [IFN]- γ , interleukin [IL]-2, tumour necrosis factor [TNF]- β and IL-12; Th2 cells (associated primarily with humoral responses) which produce IL-4, IL-5, IL-6, IL-10 and IL-13; and intermediate Th0 cells which co-express both Th1 and Th2 cytokines in various combinations. Lymphocytes from HIV-infected subjects who progress to develop AIDS have been found to express predominantly Th2-type cytokines.^{8,9} It has been suggested that Th1-type cells may be protective against disease progression, whereas Th2/Th0 CD4⁺ T-cell clones tend to support HIV replication.¹⁰ In a recent study, the cytokine secretion pattern was assessed in T-cell clones from HIV-infected individuals before and after seroconversion.¹¹ There was a decrease in the proportion of Th1 cytokine-secreting clones following seroconversion, while Th2 clones increased. Moreover, antigen-specific CD4⁺ T-cell clones from HIV-infected individuals have a predominantly Th0 cytokine profile, with a reduced proportion of Th1 cytokine-producing clones, compared with uninfected controls.¹⁰

The changing cytokine profiles have recently been linked to changes in other cell surface markers and their soluble counterparts. Thus, a Th2 cytokine secretion profile is associated with increased CD30 expression¹² (and the release of CD30 in its soluble form, sCD30, into circulation) and a lack of CD7 expression on CD4 cells.^{13,14} Rapid progression to AIDS is correlated with higher circulating sCD30 levels.¹²

The induction of Th1/Th2 cytokine gene expression requires the interactions of specific DNA-binding factors with the promoter/enhancer regions of cytokine genes. The nuclear factor of activated T-cells (NF-AT) complex, in response to extrinsic signals such as T-cell receptor (TcR) stimulation, binds to the IL-2 gene promoter element to enhance its expression.¹⁵ The NF-AT complex involved in the induction of the Th2-specific IL-4 gene differs from the Th1-specific IL-2 NF-AT complex in lacking a component called activating protein (AP-1).¹⁶ AP-1 is a protein which, following cell activation, moves into the nucleus from cell cytoplasm and binds to a specific gene sequence (present in, for instance, the IL-2 gene promoter and the HIV-1 Long Terminal Repeat {LTR} region), and may therefore lead to increased host gene/HIV-1 expression.¹⁷ Several key enzymes, including protein kinase C (PKC) and the mitogen activated protein (MAP) kinases, involved in the biochemical signalling path-

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Accepted for publication
19 August 1996

ways responsible for AP-1 induction, are affected by various HIV gene products, in particular gp41¹⁸⁻²⁰ and Nef^{21,22} (see also the section below on "HIV gene products"). Interactions between viral gene products and these signalling proteins may in part explain the HIV-related defects that predominantly affect Th1 cell survival and cytokine synthesis.

The correlation between disease progression and changes in cytokine secretion may be accounted for by considering the specific roles of Th1 cytokines in the immune system. One of the functions of IFN- γ is to prime macrophages for the intracellular killing of organisms such as *Toxoplasma gondii* which cause infections in AIDS. Th1 (but not Th2) cytokine secretion by lymphocytes from patients co-infected with HIV and *T. gondii*, when challenged ex vivo with *T. gondii*-specific tachyzoite antigens, was shown to be greatly impaired.²³ Decreased secretion of macrophage-activating cytokines, coupled with a reduced capacity of HIV-infected macrophages to phagocytose *T. gondii*,²⁴ helps to explain the reactivation of such organisms in AIDS. Strategies which restore the balance of Th1/Th2 cytokine synthesis could provide a useful approach to prevent or treat opportunistic infections.

Activation-induced T-cell apoptosis

Apoptosis is a normal regulatory process by which cells self-destruct and may be increased or decreased in specific cells in various disease states. It is characterised by chromatin condensation, fragmentation of genomic DNA and blebbing of the surface membrane.²⁵ It is involved in the selection process that occurs during the development of lymphocyte precursors in the thymus.²⁶ In contrast to immature thymocytes, mature T-cells are more resistant to the "suicide signal" induced by T-cell receptor (TcR) triggering. Infection with HIV-1,²⁷ interaction of CD4 with HIV gp120-antigen-antibody complexes²⁸ or simply gp120^{29,30} can lower the threshold for TcR-induced apoptosis. This increased susceptibility to activation-induced cell death will interfere with T-cell functions such as antigen recall and immune surveillance. Memory T-cells, which respond to a lower level of antigen than naive T-cells,³¹ are particularly prone to this effect of HIV. For instance, exposure of lymphocytes from HIV-infected asymptomatic individuals to recall antigens results in the deletion of the corresponding specific memory T-cells.³² This may partly explain the decreased responses to vaccination with tetanus toxoid and influenza in HIV-infected individuals.³³ However, while increased CD4⁺ lymphocyte apoptosis appears to be an important feature, several studies^{34,35} (and Johnson *et al*, manuscript in preparation) have shown conflicting results regarding the relationship between the intensity of lymphocyte apoptosis and disease progression.

Recent work³⁶ points towards a possible interplay between HIV-induced susceptibility to activation-induced apoptosis and other T-

cell defects. Th1 cytokines suppress apoptosis in T-cells from HIV-infected individuals.^{36,37} Following in vitro infection with HIV-1 and TcR stimulation, the percentage of apoptosis was 10-fold higher in Th1 T-cell clones than in Th0/Th2 clones.³⁸ Using T lymphocytes from HIV-seropositive donors at various stages of infection, we have shown an inverse relationship between TcR-induced apoptosis and cellular proliferation in response to TcR/integrin costimulation³⁹ (Ng, *et al*, manuscript submitted). These functional defects are probably linked at the subcellular level and may be related to disruption of expression and/or function of key intracellular enzymes involved in proliferation and cytokine synthesis.

Unlike cell necrosis, programmed cell death may be prevented by modifying the biochemical signals generated by cell activation.^{40,41} Accessory, or antigen-presenting cells such as macrophages and dendritic cells (DC) supply the "regulatory" signal that enhances or prevents T-cell apoptosis⁴² through surface adhesion molecules (such as B7, vascular cell adhesion molecule {VCAM}, etc.) that interact with corresponding molecules on T-cells (such as CD28, integrins, etc.). Anti-CD28 stimulation prevents apoptosis of lymphocytes derived from HIV-infected individuals³² as well as prevents HIV-1 infection of CD4⁺ T-cells.⁴³ Anti-CD2 stimulation has also been shown to abrogate gp120-induced T-cell apoptosis.⁴⁴ Our own data suggest that stimulation via CD29 (the β subunit of β 1-integrins) may also provide a "rescue" signal which prevents TcR-induced cell death in lymphocytes from individuals with asymptomatic HIV infection, but not those with AIDS.^{39,45} Failure to deliver an appropriate accessory signal to TcR-activated CD4⁺ T-cells may constitute a potential mechanism for activation-induced cell death in HIV infection.⁴⁶ HIV induces changes in the surface expression of several adhesion/costimulatory molecules on CD4⁺ T-cells,⁴⁷ monocytes⁴⁸ and dendritic cells.^{49,50} In addition, the enzyme cascades responsible for conveying the message from adhesion co-receptors, such as CD29, to the cell nucleus are blocked to a variable degree in patient-derived T lymphocytes, depending on disease severity, even if receptor expression is normal.^{39,45} A thorough understanding of these processes may provide potential means for restoring or maintaining a more balanced cytokine profile in HIV-infected patients.

Imbalance between Ca²⁺-induced and protein kinase C-mediated signals

The intermediate messengers that mediate the suicidal event in CD4⁺ mature T-cell apoptosis has recently been shown to be Fas (Apo1/CD95).⁵¹ The early biochemical events that cause activated T-cells to undergo apoptosis rather than proliferation, however, remain undetermined. In immature T-cells or thymocytes, an "orphan" signal defined by a sustained increase in intracellular Ca²⁺ (as is

seen in HIV-infected T-cells⁵²⁻⁵⁵) in the absence of concomitant activation of PKC which is physiologically triggered simultaneously, may lead ultimately to programmed cell death.^{41 56} One important function of antigen-presenting cells (APC) is to ensure that there is a balance between intracellular Ca^{2+} release and PKC activation in T-cells, following the primary interaction between the antigen/MHC-complex and TcR, through the generation of accessory signals via surface receptors. Exposure to HIV, or its envelope glycoprotein subunit gp41, inhibits the normal PKC response to lymphocyte activation.¹⁸⁻²⁰ There is also an impaired PKC response to integrin stimulation in T-cells from HIV-infected individuals.^{39 45} This inhibitory effect of HIV or its proteins on accessory cell function will lead to an imbalance of intracellular signals and may indirectly increase apoptosis as well as modify the functional responses of surviving cells.

Effects of HIV gene products on the host immune system

The functions of the major genes and proteins of HIV-1 are summarized in the table. The U_3 region of the HIV-1 LTR (at each end of the viral genome) presents an important site for host-virus interactions at the molecular level and encodes potential binding sites for host transcription factors, such as nuclear factor- κB (NF- κB) and the NF-AT complex (composed of NF-AT $_{\text{p}}$ and AP-1).⁵⁷ In healthy CD4 $^{+}$ T-cells, activation of the TcR and PKC results in increased binding of NF-AT, AP-1 and NF- κB to their corresponding DNA binding sites and induces IL-2 secretion, which increases lymphocyte proliferation. The interaction of HIV gp120 with CD4, however, abolishes the binding activity of these nuclear factors leading to reduced proliferation and cytokine production.^{58 59} This is possibly related to the suppression of TcR-induced Ca^{2+} release and PKC activation by HIV gp120.⁵⁹ The binding activity of these nuclear factors in uninfected CD4 $^{+}$ lymphocytes may also be impaired indirectly through altered cytokine profiles such as an increase of IL-10.⁶⁰

Several viral regulatory and accessory genes interact with components of host cell transcriptional machinery. Nef inhibits the induction of NF- κB DNA-binding activity by T-cell

mitogens⁶¹ as well as TcR-mediated IL-2 gene transcription.⁶² The recruitment of AP-1 DNA-binding activity in stimulated T-cells is also blocked in the presence of Nef.⁶³ In addition, lymphocytes from healthy uninfected donors that had been pretreated with the HIV-1 Nef showed decreased IL-2 receptor expression⁶⁴ and reduced proliferative response to IL-2.²¹ Nef interacts with many of the host cell proteins that are involved in signal transduction and cell cycle control (including CD4, p56^{lck}, p53 {tumour suppressor gene product} and MAP kinase {p44^{mapk}}).²¹ Apart from CD4,^{65 66} the effects of the Nef interaction with these signalling proteins are largely unknown, but may be profound.

A recently published series suggests that, in some instances, specific deletions in the HIV-1 *nef* gene may be related to slower clinical progression.⁶⁷ Nucleotide sequence analysis on viral isolates from an HIV-infected blood donor and six blood or blood product recipients, who remain asymptomatic with stable, normal CD4 lymphocyte counts after 10–14 years, showed similar deletions in the *nef* gene and the *nef*-LTR overlap region (eliminating a number of binding sites for transcription factors including NF-AT) as well as U_3 region rearrangement or duplication. These have been postulated to account for the benign course of infection.

Tat (transactivating factor) interferes with the gene transcription and surface expression of the TcR/CD3 complex,⁶⁸ and inhibits lymphocyte proliferation to antigens.⁶⁹ The synthesis of $\beta 2$ integrins on monocytes and their adhesiveness to endothelium are both enhanced following treatment with HIV-1 Tat.⁷⁰ Tat also decreases the expression of the costimulatory molecule CD28 on T-cells and binds to an integrin expressed on the surface of T lymphocytes.⁷¹ It increases the production of transforming growth factor β (TGF β),⁷² IL-6 and IL-10,⁷³ cytokines which inhibit antigen/IL-2-stimulated T-cell proliferation. Tat can induce apoptosis in cultured lymphocytes from uninfected donors, possibly through a direct effect on a cell cycle-related regulatory enzyme.⁷⁴

Antigen-presenting cell (APC) defects

In preceding sections, we have mentioned some of the alterations in the interactions

Genes and proteins of HIV-1 (adapted from Luciw and Shacklett, 1993⁵⁷)

Gene	Dispensable for replication	Protein	Function
<i>gag</i>	no	Pr55 ^{gag}	polyprotein precursor for virion core proteins: matrix protein p17, capsid protein p24, nucleocapsid protein p9, p7
<i>pol</i>	no	Pr160 ^{gag pol}	polyprotein precursor for virion enzymes: protease p10, reverse transcriptase and RNAase-H p51/66, integrase p32
<i>vif</i>	yes	p23	viral infectivity factor
<i>vpr</i>	yes	p15	virion protein, unknown function
<i>tat</i>	no	p14	transcriptional activator, binds <i>cis</i> -acting Tat-responsive (TAR) RNA (initiation and elongation of viral transcripts)
<i>rev</i>	no	p19	post-transcriptional transactivator, binds <i>cis</i> -acting Rev-responsive element (RRE) (splicing and/or transport and translation of viral mRNA)
<i>vpu</i>	yes	p16	influences virus release, augments turnover of CD4 antigen, downregulates MHC Class I molecule expression
<i>env</i>	no	gp160	precursor for envelope glycoprotein, surface subunit gp120/130—receptor binding, transmembrane subunit gp41/32—membrane fusion
<i>nef</i>	yes	p27	down-regulates viral transcription, downregulates CD4?, inhibits T-cell activation?

between cell surface molecules of antigen-presenting cells and CD4⁺ T lymphocytes. In addition, a number of critical defects in antigen-presenting cell function have been identified in HIV infection. Antigen processing/presentation by dendritic cells (DC, the most potent antigen-presenting cells, and essential for primary immune responses) may be affected by HIV and other retroviruses. Human peripheral blood DC are susceptible to HIV infection^{50,75} and CDC Group II/IV HIV-infected individuals have reduced numbers of DC.⁵⁰ The subpopulation of DC with high-intensity HLA class II antigen expression is preferentially depleted in patients with progressive immunodeficiency.⁴⁹ In addition, the expression of ICAM-1 on DC has been shown to be decreased following retroviral infection.⁷⁶ Functionally, DC from HIV-infected individuals have impaired ability to stimulate uninfected T-cells.⁷⁷ Recent data suggest that the depletion and dysfunction of DC may be reversed by antiretroviral treatment with zidovudine.⁷⁸ Binding and activation of CD4⁺ T lymphocytes by HIV-1-exposed mature DC may result in viral transmission and cytopathic effects, and this may be a critical route of cell-to-cell infection *in vivo*.⁷⁹⁻⁸¹

Towards the later stages of HIV infection, there is an expansion of a subpopulation of CD8⁺ T lymphocytes that are CD28-negative, HLA DR-positive and CD25 (IL-2 receptor α -chain)-negative.^{82,83} This subpopulation of CD8⁺ T-cells has a poor proliferative response to TcR/CD3 stimulation, which may explain the general diminution of cytotoxic T lymphocyte (CTL) responses to other viral antigens (for example of Epstein-Barr virus, cytomegalovirus and influenza).⁸⁴ The primary recruitment of T-cells into immune responses has an absolute requirement for dendritic cells. These specialised APC provide the costimulatory signals required for generation of CTL via their surface adhesion molecules, in particular B7-1⁸⁵ (counter receptor for CD28 and CTLA-4 on T-cells) and the intercellular adhesion molecules ICAM-1 and ICAM-3.⁸⁶ The latter are counter receptors for leukocyte function antigen (LFA)-1 which is involved in antigen-specific CTL-mediated lysis.⁸⁷

Destruction of the APC network in lymphoid organs and subsequent impairment of lymphocyte regeneration

During the asymptomatic stage of HIV disease, active viral gene expression and replication are largely confined to the lymphoid tissues.⁸⁸ A large proportion (up to 30% in one report⁸⁹) of CD4⁺ lymphocytes in the germinal centres of lymph nodes are latently infected during this period of clinical latency. Within the germinal centres, HIV particles are trapped on the surfaces of follicular dendritic cells (FDC)⁸⁹⁻⁹¹ which surround and are intimately associated with lymphocytes as they migrate through lymphoid follicles. The recently discovered ability of FDC to convert neutralised HIV into an infectious form, even in the presence of an excess of neutralising

antibodies,⁹² makes them the ideal vehicle for viral transmission to CD4⁺ lymphocytes. The immunological function of FDC is to capture and retain foreign antigens, which eventually bind to and are presented by germinal centre B-cells to stimulate the memory Th cell population. As disease progresses, the lymphoid organs that provide the APC microenvironment necessary for the renewal of antigen-specific Th cells undergo atrophy, which is characterised by the destruction of the FDC network^{91,93} and possibly the release of entrapped HIV particles into the circulation.⁹⁴

Adhesion and chemokine receptors in HIV infection

Various adhesion receptors play a pivotal role in lymphocyte activation.⁹⁵ The same surface molecules which supply the accessory signal to augment TcR stimulation are also involved in cell-free viral transmission⁹⁶ as well as in syncytium formation^{97,98} in HIV infection. Stimulation of β 1-integrin in infected T-cells may potentially increase the availability of AP-1 for DNA binding and promote HIV transcription by enhancing *c-fos* transcription⁹⁹ through MAP kinase activation.¹⁰⁰⁻¹⁰² There are several HIV-induced defects in β 1-integrin signalling among patient-derived T lymphocytes that involve the expression and/or function of important enzymes such as PKC, MAP kinases and focal adhesion kinase (FAK), a protein tyrosine kinase.^{39,45} At the cellular level, some of these signalling defects correlate with the loss of T-cell proliferative responses. The interactions between lymphocyte activation, adhesion receptor expression and viral replication in HIV disease⁴⁷ may influence viral latency at the postintegration level.¹⁰³

The ability of patient-derived HIV-1 isolates to induce syncytium formation *in vitro* has been shown in several studies to correlate with clinical progression, a more rapid CD4⁺ cell decline and increase in cellular viral load in PBMC.¹⁰⁴⁻¹⁰⁸ The formation of syncytia involves the initial HIV envelope protein-mediated cell membrane fusion between infected and uninfected cells^{109,110} and later events leading to multinucleated giant cell formation which are dependent on the function of adhesion receptors such as LFA-1 and ICAM-1.^{97,98,109}

Recently, additional receptors for HIV have been identified in CD4⁺ cells. These include several receptors for the CC family of chemokines/small cytokines (CCR5, receptor for Rantes, macrophage inflammatory protein-1 (MIP) α and MIP-1 β ; CCR3, receptor for eotaxin, an eosinophil chemoattractant; CCR2b, expressed on monocytes) have been shown to be fusion coreceptors for HIV-1.¹¹¹⁻¹¹⁴ The type of receptor utilised by the virus differs between isolates and appears to be determined by the characteristic of the envelope glycoprotein (syncytium-inducing property). Rantes has been shown *in vitro* selectively to attract (and costimulate) memory T lymphocytes^{115,116} (and K. Bacon, Fourth International Chemokine Symposium,

1995) and inhibit HIV-1 infection by interfering with the virus-cell fusion process.¹¹³ Besides the chemokine receptors, other cell surface molecules that are involved in HIV gp160-mediated cell fusion include the fusion regulatory protein (FRP)-1 and FRP-2.^{117 118} FRP-2 is probably identical to the α chain of $\alpha 3$ integrins¹¹⁸ while FRP-1 (CD98)¹¹⁷ possibly induces fusion by activating the integrins. The induction of syncytium formation in HIV-infected cultures coincides with CD4+ cell depletion *in vitro*.¹¹⁹ Although experiments conducted on human PBL-SCID mice (immunodeficient strains reconstituted with human lymphoid cells) indicate that the loss of CD4+ T cells does not correlate with the cytopathicity of the infecting virus type,¹²⁰ syncytium formation has nevertheless been proposed as an important virus-mediated cytopathic mechanism. Further characterisation of the molecular processes that mediate cell fusion and syncytium formation may provide a possible target for therapeutic intervention.

A hypothetical model and its implications for therapy (figure)

The schematic diagram outlines a possible/hypothetical model that seeks to relate the molecular events involved in antigenic stimulation, viral transactivation, host cell gene expression and cell cycle control as a frame-

work for further analysis. One of the chief obstacles facing the immunological approach to HIV therapy relates to the intricacy of the host-virus relationship. The molecular details of this interaction have been described in the preceding sections and summarised in the figure legend. The enzymatic activities that occur within a T-cell challenged by foreign antigens are indispensable for eliciting a normal immune response, yet these are the same molecular events which may enhance the susceptibility of T-cells to HIV infection and maintain viral replication.^{130 131} HIV transactivation leads to the translation of several viral proteins which may suppress the function and/or expression of intracellular enzymes that are involved in lymphocyte activation and survival. This process may be followed by a shut-down of the host transcription machinery and cell death by apoptosis. Strategies that are designed to restore the integrity of the immune system should be based on agents which are capable of differentiating between HIV-infected and uninfected cells.

For instance, *ex vivo* CD28 costimulation of CD4+ T-cells from HIV-infected donors was recently shown to enhance lymphocyte proliferation but not viral replication.⁴³ One possible explanation is that CD28 costimulation selectively induces the proliferation of a subset of T-cells that do not support infection. Alternatively, this effect could be explained

A hypothetical model depicting the molecular interactions between various pathological processes which may operate simultaneously or asynchronously within an HIV-infected T lymphocyte, depending on the stage of the virus life cycle and activation status of the T-cell. The initial contact of the TcR with antigens (Ag) presented on the surface of APC in association with MHC and other adhesion structures (such as vascular cell adhesion molecule {VCAM}-1) triggers intracellular signals which activate a variety of protein enzymes (including focal adhesion kinase {FAK}¹²¹ and protein kinase C {PKC}¹²²). An enzyme pathway involving FAK(i) may be responsible for the induction of transcription factors (such as c-Fos, part of AP-1) which are imported into the nucleus and bind specific DNA sequences within the gene promoters of various host cell genes.^{123 124} The loss of FAK expression in symptomatic HIV infection is accompanied by the failure of the integrin signal to induce proliferation and rescue T-cells from apoptosis. Transcription factors can be activated alternatively by PKC¹²⁵ which responds rapidly to TcR stimulation¹²² but can be suppressed by HIV gp41 and Nef (ii). Several of the transcription factor binding sites are also contained in the U3 region of the HIV LTR and may be involved in regulating its transcription. The κB site within the U3 region, for instance, binds NF- κB which is moved into the nucleus in response to extracellular stimuli such as IL-1, TNF- α and lipopolysaccharides¹²⁶ (iii). The HIV-related perturbations of Th1 cytokine gene expression and T-cell proliferation may be attributed to the effects of the virus/viral proteins on a transcription factor(s) specific for the Th1 (and not found in the Th2) cytokine induction pathways such as NF-IL2A.¹²⁷ Fas is a surface protein responsible for the induction of apoptosis in antigen-stimulated T-cells.¹²⁸ The surface expression of Fas on T-cells is increased among advanced HIV-infected patients,¹²⁹ leading to an increased risk of apoptosis (iv).

by the CD28-stimulated production of an "endogenous" substance (such as the chemokines) that blocks cell-virus fusion. The problem with the latter explanation in terms of clinical application is, given that some of these substances are produced physiologically in response to a variety of extracellular stimuli (inflammatory ones in particular), a therapeutic strategy that aims to increase their levels may not have additional benefits over what is already achieved physiologically. The effects of these molecules on the expression or function of other cell membrane ligands/lipids which mediate the process of fusion/syncytium formation need to be established. The important message from recent development is that biological substances which are secreted physiologically to modify the immune system may be part of the defence system that deters viral entry into cells. Clearly it is of paramount importance to obtain a better understanding of the mechanisms involved and more importantly, the reason why this defence system fails, in many HIV-exposed individuals, to block virus entry.

Autoimmune reactions in HIV infection

A diverse variety of clinical manifestations of autoimmunity appear quite frequently in individuals with HIV disease.¹³²⁻¹³⁴ These phenomena may be attributed to generalised disruption of regulatory T cell circuits and/or specific cases of molecular mimicry (for example, there are regions of amino acid sequence homology between the *nef* gene product and the MHC DR region,^{134 135} the p17 gag protein and α 1-thymosin,¹³⁶ gp120 and IgG heavy chain,^{133 137 138} and p24 and platelet antigens¹³⁹). Of particular importance to the central theme of this review is that dysfunction and loss of CD4+ cells may be due to specific autoimmune reactions.

The presence of anti-lymphocyte antibodies (ALA) in the sera of HIV-infected individuals has been recognised for over a decade.^{133 134} However, little information was available regarding the specificity of these antibodies and their clinical significance remained uncertain.

Some subsequent studies have attempted to define the cellular and molecular targets of ALA. Stricker and colleagues¹⁴⁰ observed sera from the majority of patients with ARC and AIDS had ALA that bound to an 18 kDa antigen on CD4+ T cells. The anti-18 kDa antibodies reacted with HIV-infected and stimulated CD4+ T cells but not with unstimulated CD4+ cells or stimulated CD8+ cells. *In vitro* studies with affinity-purified antibodies showed that they would lyse cells bearing the 18 kDa antigen in the presence of complement and would also suppress mitogen-induced proliferation of CD4 (but not CD8) cells. A strong association between the presence of antibodies and the clinical status of the infected individual was found: the autoantibody was virtually absent in HIV-infected, asymptomatic individuals and almost always present in patients with AIDS or ARC. We

have determined by *n*-terminal amino acid analysis that the 18 kDa antigen is histone H2B¹⁴¹ (and manuscript in preparation). Furthermore in longitudinal studies of patients with HIV disease, anti-histone antibodies were shown to correlate well with disease activity and the loss of CD4+ cells.¹⁴² It is noteworthy that anti-18 kDa antibodies have also been detected in Rhesus monkeys infected with the simian immunodeficiency virus (SIV) which develop an AIDS-like disease^{143 144} but not in Sooty mangabeys which do not become sick following infection with the virus. Furthermore, asymptomatic HIV-infected chimpanzees do not have anti-18 kDa antibodies in their sera although they were detected in one animal with profound lymphopenia.¹⁴⁵

The origins of the anti-18 kDa antibodies are unknown and their contribution to the pathology of HIV infection remains to be fully elucidated. Nevertheless it is tempting to speculate that they may arise as a result of histones being co-presented to the immune system with HIV, perhaps during the course of apoptosis (see above). Indeed a high incidence of auto-antibodies to nuclear proteins, including histones, occurring in HIV-infected individuals has been described.¹⁴⁶

The presence of antibody with a similar specificity (reactive with a 22 kDa antigen) in the sera of patients with ARC was described in a separate study¹⁴⁷; however, the majority of HIV-infected individuals examined in these investigations had antibodies that reacted with a 73 kDa antigen. Because of the techniques used in this latter study to examine the specificity of the anti-lymphocyte response it is difficult to compare the 22 kDa antigen with the 18 kDa molecule described above.¹⁴⁰⁻¹⁴²

Molecular mimicry and the gp120-CD4 interaction

For some time it has been thought that molecular mimicry arising from structures associated with the gp120-CD4 interface may potentiate autoimmune responses. Ziegler and Stites¹⁴⁸ initially postulated that an autoimmune response could result from antigenic similarities between the CD4-binding receptor site on the gp120 envelope of the virus and HLA class II molecules (HLA DR is the natural ligand for the CD4 molecule, as it interacts in the process of presenting antigen).

The Ziegler-Stites hypothesis has been extended by Hoffmann and colleagues, who consider regulatory T cells bearing internal image idiotypes of class II MHC determinants to be the "center pole" of the immune network.¹⁴⁹⁻¹⁵² The pole is supported and stabilised by a "canvas" of anti-self class II cells. These authors note that the immunological network predicts the existence of both cell types and go on to hypothesise that, while most people do not apparently make pathologically significant responses to their own MHC, it may be easier to develop immunity to cells bearing the subtly different internal image of class II. These authors further propose that the anti-lymphocyte responses are further

exacerbated by allogeneic reactions resulting from lymphocytes present in the blood of or in the ejaculates from contact individuals. Responses directed against the foreign class II molecules may also recognise host class II and act in synergy with the anti-gp120/host class II response. The loss of crucial subsets of regulatory T cells may lead to chaos in the immune system as the "center pole" collapses.

To explore this theory they conducted experiments in alloimmune and autoimmune mice.¹⁵³ Alloimmune animals (mice that had been exposed to cells from another mouse strain) were shown to make antibodies against HIV gp120 and p24 while mice of the autoimmune-prone strains MRL-*lpr/lpr* and MRL-*+/+* made antibodies to gp120. None of these animals had been exposed to HIV proteins. Furthermore, anti-anti-MHC antibodies (immunoglobulins bearing structures similar to those of MHC molecules) were detected in both alloimmune sera and MRL mice. The authors claim that the presence of both types of antibodies in alloimmune sera supports the idea of synergy between immune responses to allogeneic cells and HIV antigenic stimuli as postulated; however these results remain to be confirmed by independent investigators.

Conversely, del Guercio and Zanetti¹⁵⁴ have suggested that autoimmune reactions leading to anti-lymphocyte antibodies may result from the formation of anti-idiotypic antibodies to the gp120 receptor site. The resulting anti-idiotypic antibodies would have specificity for CD4-bearing cells. This hypothesis has been substantiated in part by the finding of anti-CD4 autoantibodies in HIV-infected patients.^{155 156} However, the origin of these antibodies may not have been anti-idiotypic: both groups demonstrated that sera containing anti-CD4 activity did not inhibit the binding of *Leu3a*, a mouse monoclonal antibody which maps very closely to the HIV attachment site on CD4.¹⁵⁷ This conclusion is supported by Wilks and colleagues¹⁵⁸ who failed to find anti-idiotypic antibodies in the sera of 97 HIV-infected subjects.

It is possible that antibodies arising from molecular mimicry of gp120 or anti-idiotypic control mechanisms may have indirect pathological consequences. For example a study by Karpatkin and Nardi¹⁵⁹ noted that autoimmune anti-idiotypic-like antibody (Ab2) directed against anti-HIV-1 gp120 antibody (Ab1) was present in high titre of 21 HIV-infected patients with immune thrombocytopenia. These authors did not perform epitope mapping studies to determine the specificity of these antibodies (therefore they could not necessarily be attributed to originate from images of the gp120-CD4 molecules) but they concluded that they were pathogenic as they were found as Ab1-Ab2 immune complexes associated with platelets and thus involved the destruction of this cell population.

Graft-versus-host (GvH) disease

The hypothesis that HIV could induce a GvH-

like syndrome was first proposed by Shearer and colleagues^{160 161} and indeed similarities in symptoms between HIV disease and GvH reactions have been described.^{162 163} While this theory has undergone re-evaluation and re-interpretation in recent years,^{164 165} its basis is that the immune system of the infected individual responds inappropriately to HIV-infected cells and/or allogeneic lymphocytes (and sperm antigens). The resulting internal conflict ends with the selective destruction of the host's T-cell subsets, particularly the CD4+ lymphocyte population. The GvH model has been extended by Hounsell and co-workers who suggest that a region of the carboxy terminus of HIV gp120 resembles structurally a T-cell alloepitope.¹⁶⁶ Recognition of gp120 expressed on infected CD4+ cells as an alloepitope may thus induce a GvH reaction; a process that would accelerate as the pool of infected cells expands.

Mimicry associated with MHC molecules outside the gp120-CD4 binding site

Deleterious immune responses resulting from structures on the HIV envelope outside the CD4 attachment site of gp120 may also occur. Golding *et al*^{167 168} have described homologous sequence regions of HIV gp41-derived and human MHC class II β 1 domain. Affinity purified IgG antibodies from patients' sera exhibited immunosuppressive activity of lymphocyte proliferation to antigen stimulation.¹⁶⁸ Similarly, a homology between class II MHC molecules and gp120¹⁶⁹ has been noted and reports which describe the presence of anti-class II MHC antibodies and antibody-dependent cellular cytotoxicity (ADCC) reactions which eliminate class II-bearing cells^{170 171} in patients with AIDS reinforce these suggestions and further suggest a role for autoimmunity in the pathogenesis of the disease. More recently Zagury and colleagues¹⁷² using novel software, identified regions of homology between gp120 and sites on both CD4 and HLA (class II β chain) molecules. A synthetic peptide representing this region could inhibit the activation of CD4+ lymphocytes as well as induce humoral and cellular responses from HIV-1-infected individuals. The authors proposed that these gp120 segments may contribute to HIV-induced immunosuppression by two mechanisms affecting CD4-HLA interaction during immune cell activation: (i) an autoimmune reaction against CD4 and (ii) direct interference with the CD4-HLA costimulation signal, thus inducing anergy in the CD4+ cell population. Homology with gp120 (C5 region) has also been found with the α 1 peptide-binding domain of the HLA class I molecule.¹⁷³

Conclusions

The pathogenesis of HIV infection is a dynamic process driven by various mechanisms which may predominate at different points of the virus life cycle. In this paper, rather than giving an extensive review of all the

pathological mechanisms involved, we have focused on a few molecular interactions between HIV and host lymphocytes which may have adverse effects on the survival and/or functioning of the latter. Despite the wide recognition of cellular dysfunction in HIV infection, most of the intracellular signal defects that give rise to changes in lymphokine production and cell cycle regulation remain to be determined. Furthermore, since only a minority of infected CD4⁺ lymphocytes actively produce full-length HIV RNA, it may be necessary to study the effects of latent HIV genome on mechanisms of lymphocyte activation. A better understanding of the complex host-virus interplay will be important clinically in identifying appropriate targets for immune-based interventions.

Addendum added in proof

Recently, another receptor for the chemokine family (CXC-chemokine receptor-4, also known as LESTR/fusin) which specifically binds to the stromal cell-derived factor-1 (SDF-1, a lymphocyte chemoattractant) was identified as a cofactor for HIV entry (Bleul *et al*, *Nature* 1996;382:829–35). Mutations in the genes encoding some of these HIV-1 fusion coreceptors such as CCR-5 generate a non-functional receptor and confer resistance to HIV-1 infection upon individuals bearing the mutant alleles (Samson *et al*, *Nature* 1996;382:722–5; Liu *et al*, *Cell* 1996;86:367–77).

This work is funded by the UK Medical Research Council AIDS Programme Clinical Fellowship Grant No. G106/620 (to T.T.C. Ng.)

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