Pathogenesis of HIV: non-specific immune hyperactivity and its implications for vaccines

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ABSTRACT – More than a decade ago, the pathogenesis of AIDS was reviewed in this journal, using the subtitle 'classical and alternative views', when evidence was accumulating that HIV could not cause AIDS simply through direct cytopathic mechanisms alone. Generalised immune activation after infection with HIV is now understood to be associated with and predictive of disease progression and probably represents the single most important difference between rapid progression and slow or non-progression. However, the fundamental source of this phenomenon remains undetermined. Do pathogenic events after acute infection promote an environment susceptible to increased hyperactivity or does inherent reactivity towards HIV in susceptible individuals ultimately influence these processes? New strategies aimed at eliminating HIV-induced immune activation are required, as is investigation into the clinical and immunological influence of antibodies that target HIV epitopes associated with disease and that are not necessarily neutralising. Therapeutic vaccines to prevent disease may be more practical and effective than classic prophylactic vaccination.

KEY WORDS: AIDS, autoimmunity, graft-versus-host disease, HIV, HLA, immune activation, immune evasion, long-term non-progressors

Introduction

More than a decade ago, this journal published an article which reviewed knowledge of the underlying mechanisms of HIV pathogenesis and pointed out that HIV was not so much a rampant cytopathic killer virus (with regard to how the disease was induced) but rather one that induced chronic immune hyperactivity.[1] In the subsequent years, more and more evidence has accumulated to support the causative role of this hyperactivity in the development of AIDS.[2] Here the latest data is reviewed in an attempt to understand why this process occurs so readily in some individuals but is completely absent in others. The possibilities of a therapeutic vaccine aimed at reducing this chronic stimulation are then explored.

Current treatment status

Current therapeutic strategies are able to reduce the viral load to extremely low levels and reduce HIV-driven immune activation, but they do not eliminate this immune activation entirely, which leads to continued immunological degradation and incomplete functional restoration of the immune system in many cases.[3,4] Although current vaccine approaches are aimed at inducing effective neutralising antibodies, an increasing number of reports is documenting the lack of clinical efficacy of such antibodies in influencing the immunopathogenic processes triggered by HIV.[5] Even non-infectious virions and shed viral proteins can induce partial activation and apoptosis of lymphocytes.[6]

The immune genetics of the host clearly play a major role in determining HIV-induced disease, as chimpanzees and a significant number of infected patients who do not seem to progress (long-term non-progressors (LTNPs)) have an apparent resistance to inappropriate immune activation despite highly variable viral loads and the continual presence of cytopathic virus (Table 1).[7] The fact that some individuals can live with the virus without pathogenic immune activation suggests that the immune system may be manipulated to inhibit those viral epitopes or features that trigger the process in susceptible individuals.

Stealth paradox

HIV employs numerous mechanisms to avoid the immune response, such as antigenic variability, carbohydrate masking of target structures, conformational changes, downregulation of host human leucocyte antigen (HLA) in infected cells, latency, and the use of cell-to-cell transmission. It also incorporates a variety of host-cell proteins into the virion to provide additional protection from complement – for example, CD55, etc. It therefore is paradoxical that such covert efforts to hide from the immune response should provoke the exact opposite, activating not only HIV-specific T lymphocytes but also T lymphocytes that bear completely unrelated specificities, as well as B cells, natural killer (NK) cells, and antigen-presenting cells (APCs).[8] This activation is then associated with anergy and apoptosis involving

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uninfected cells, which leads to a loss of antigen-specific responses that can be detected long before the number of CD4+ T lymphocytes declines.[9] In spite of recognition of the importance of non-specific immune activation many years ago in classic and alternative views, the concept that immune activation is somehow at the heart of the pathogenesis of AIDS only recently has been recognised. Longitudinal studies have reported that immune activation markers have greater prognostic significance than viral load or CD4 counts,[10] and advances in primate studies clearly show that high viral loads do not lead to disease unless accompanied by inappropriate immune stimulation and that the latter can lead to disease even in the presence of low viral loads.[11] Similarly, the reduced pathogenesis of infections with HIV-2 has been linked to a lower immune activation status. The absence of chronic activation and apoptosis in LTNPs infected with HIV-1 suggests that these individuals lack susceptibility or an appropriate receptor to engage in such inappropriate responses or possess an immune response that specifically targets and neutralises the fundamental triggers of such inappropriate activation, thereby preventing engagement of the pathogenic process. Despite the recent surge in publications with regard to immune hyperactivity induced during progression to AIDS, not a single publication has identified the fundamental source of this phenomenon.

Chronic hyperimmune responsiveness

A transgenic mouse model, in which there is persistent triggering through CD27–CD70 interactions, leads to exhaustion of the naive T-cell repertoire, lack of immune responses, and susceptibility to opportunistic infections.[12] The fact that this does not normally occur is because T-cell responses are regulated tightly to avoid persistent cellular replication. None of the number of views as to how HIV may cause this immune activation has been proved or necessarily disproved. HIV destroys a large number of CCR5 CD4 memory T lymphocytes in the intestinal mucosa during acute infection through cytopathic and apoptotic mechanisms, and it is proposed that the immune system is wounded fatally during this early stage and that chronic activation is a direct consequence of this damage.[13] Exactly how such a big loss leads to chronic activation is unclear, as other well-known T-cell killers, including measles virus and human herpes virus 6, have the capacity to cause massive losses of T lymphocytes and transient immunodeficiency during acute infection, with neither of them causing an AIDS-like syndrome. Although derivatives of the 'big-hit' theory primarily implicate events during the acute phase of infection as critical to disease outcome, other theories support the long-term influence of virions of HIV and its gene products in promoting chronic immune stimulation. Some viral proteins, such as Tat and Nef, are known to induce environments that facilitate immune activation; however, the envelope glycoprotein gp120 is implicated primarily in pathogenic processes involved in immune activation given its known interactions with cell surface CD4 and chemokine receptors.[15] CD4 signalling is a crucial part of normal T-cell activation but does not explain why LTNPs remain immune to chronic activation processes. Similarly, chemokine receptor interactions may influence activation but do not represent an obvious explanation for variable responses in different individuals. It is possible that signals induced as a result of these interactions may trigger activation, possibly by promoting events that decrease the stimulation requirements of these cells, although susceptibility to an additional inappropriate stimulus may represent the difference between progressors and LTNPs.

Known mechanisms of inappropriate signalling include super antigens that bypass the normal regulatory mechanisms. HIV initially was reported to be a super antigen, but careful cohort analysis has shown no specific effect on the T-cell repertoire and that the previously reported losses were due purely to declining CD4 counts.[15] Another hypothesis is that HIV may be triggering innate immune stimuli, such as toll-like receptors, or other unidentified receptors by gp120 or other products. This could easily explain the susceptibility or resistance to immune stimulation among different individuals. The gp120 of HIV is able to

Table 1. Disease categories.

Characteristic	Rapid progressors	Long-term non-progressors	Chimpanzees
Immune activation status	Chronic and generalised	Low or moderate and specific	Low or moderate and specific
Viral load	High	Low or moderate	Variable
CD4 count	Rapid or progressive decline	Stable	Stable
Cytopathic virus	Present	Present	Present
Viral variability	Low	High	High
Anergy or apoptosis	High	Low	Low
Bystander cell death	High	Low	Low
CD8 activity	High	Low or moderate	Low or moderate
Autoimmune phenomenon	Present	Absent	Absent
Quality of immune response	Early loss of antigen-specific responses	Sustained specific responses	Sustained specific responses
Susceptibility to opportunistic infection	High	Low	Low

interact throughout the course of infection with a number of molecules, including multiple chemokine receptors such as chemokine (C–C motif) receptors (CCRs) 1, 2b, 3, 8, and 9. It is also able to bind the high-affinity dendritic cell-specific intercellular adhesion molecule 3 grabbing non-integrin (DC-SIGN, CD209) on dendritic cells, and variants have been found to infect CD8 cells.[16] It is conceivable that the envelope could trigger other cellular molecules that have nothing to do with access to cells but may inappropriately activate the immune response and that, by their nature, are refractory to the affects of neutralising antibodies (Fig 1).

Molecular mimicry and conserved pathogenic features

Numerous publications have documented the similarity of various cellular proteins and epitopes from HIV-encoded sequences, and autoimmune responses have long been suggested to contribute to the pathogenesis of AIDS.[17] The role of molecular mimicry in pathogenesis has suffered from the stringent view that the viral sequence and structural features in question must represent an exact replica of the relevant host molecule. Partial sequence mimicry can be sufficient, however, as has been demonstrated specifically for the triggering of autoreactive T cells that target myelin basic protein in patients with multiple sclerosis.[18] Indeed, partial structural mimicry is also sufficient for the task, as is evident in the case of structural mimicry between a small region of the HIV-1 gp120 V3 loop and a short β-hairpin structure found on the receptor-binding regions of certain chemokines that are able to resist neutralisation by variability but retain the ability to interact with the coreceptor.[19] However, any autoreactive response triggered in such instances would promote only select activation of a few autoreactive T lymphocytes against the select host protein and would not be in keeping with the widespread activation reported.

Of all the components of the immune system, the one that has been shown to determine disease outcome is the HLA repertoire.[20] Although it is argued primarily that certain HLA types may present antigenic peptides more suitable to long-term viral suppression and therefore resistance, it is also possible that the HLA type of an individual selects a T-cell repertoire more inherently responsive to particular pathogenic epitopes or structural features presented by HIV. When HIV was first sequenced, reports highlighted the sequence and structural homology between the conserved regions of the HIV envelope and HLA. As many of these were partial homologies and were based in non-neutralising sections of the envelope, however, they have not received any significant attention. This is particularly bizarre given that the pathogenesis of AIDS on numerous occasions has been compared clinically and immunologically with chronic allogeneic activation, as seen in chronic graft-versus-host disease, even before the causative virus – HIV – was identified.[21] Nevertheless, certain epitopes from the C2 and C5 conserved regions have been reported to stimulate alloreactive T-lymphocytes,[22,23] promote autoreactive T-lymphocyte activation,[24] and induce CD8 T-lymphocyte suppressor responses against uninfected but activated HLA-DR-expressing cells.[25]

The conserved C5 region is of particular interest, as it has reported serological and structural homology with peptide-binding domains of HLA molecules.[26] Soluble gp120 has been shown to interact specifically with peptides in a manner similar to soluble HLA monomers and to promote activation of an antigen specific T-cell clone[28] – a feature eliminated by prior incubation with antibodies targeted to the C5 domain. The α helix of this region has conserved residues with the third hypervariable domain of the HLA-DR β-chain, which is a polymorphic region in the native HLA molecule that is involved in peptide interactions and T-cell selection and has a prominent influence on direct and indirect alloactivation. More recently, the peptide-binding properties of gp120 were shown to be functionally sensitive to mutation and antibody targeting of the C5 region that mimics the HLA-DR β-chain.[29] Moreover, it is known that soluble single HLA-chain peptide complexes can stimulate peptide-specific T cells and induce antigen-specific apoptosis, and the peptide-binding domain structure of α or β-chain peptide complexes alone is able to promote T-cell activation.[30] As gp120 mimics

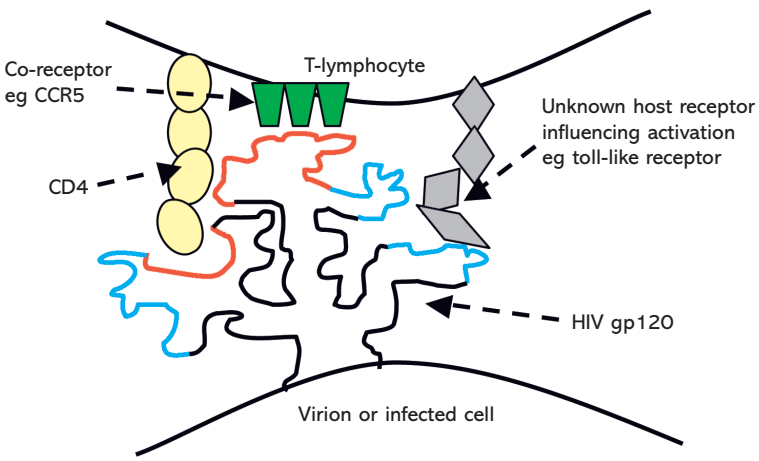

Fig 1. Potential interactions between HIV gp120 and the immune system that influence chronic immune activation. The diagram shows interactions of virion or cell-associated HIV gp120 with the immune system – in this instance, T lymphocytes. The HIV gp120 structure is represented by unexposed/hidden regions (black) and exposed neutralising domains (red) alongside exposed non-neutralising regions (blue). The neutralising domains are shown interacting with target cell receptors for viral entry, including CD4 (yellow) and the coreceptor chemokine (C-C motif) receptor 5 (CCR5) (green) and represent major vaccination targets. It is proposed that chronic immune activation might be triggered through interactions between gp120 and additional host receptors (grey), such as toll-like receptors, which may influence disease susceptibility or resistance. A role for the exposed non-neutralising domains of HIV gp120 in such interactions is proposed.

HLA-DR by binding a similar face of the CD4 receptor, it was proposed previously that these additional HLA-like sequences could provoke alloactivation in individuals with susceptible HLA types (Fig 2). Although difficult to prove, evidence is consistent with such a scenario, as antibodies against the C5 region strongly correlate with slower disease progression, and loss of antibody responses to this region is associated with progression.[31] Antibodies against the C5 region are also evident in patients who are heavily exposed but uninfected.[32] This thus raises the question of whether inducing responses to non-neutralising epitopes could reduce activation and progression to disease.

Non-neutralising antibodies as disease treatment

It is argued that therapeutic success should be measured not so much by a drop in viral load but principally through changes in the immunological environment associated with damping inflammatory immune responses and activation. The very existence of LTNPs provides evidence that elimination of AIDS does not necessarily require complete removal of HIV. The probability that a protein with the shape-shifting properties of gp120 may interact with yet unidentified receptors that provoke non-specific immune activation should not be underestimated, as nearly a decade passed between the discovery of the CD4-binding properties of gp120 and the discovery of its interaction with chemokine coreceptors. Multiple interactions between gp120 and cellular proteins primarily are associated with cellular infection, and the sequences involved remain priority targets for neutralisation. Non-neutralising antibodies, however, may have a major role in preventing disease. Non-neutralising antibodies have been shown to interfere with replication of HIV and can play a prominent role in reducing virus loads during acute viraemia.[33,34] This is in addition to numerous independent reports, over many years, that have associated clinical benefits with the presence of non-neutralising antibodies that target the gp120 C5 domain.

Conclusions and the future

An ideal scenario would be to reduce the viral load of HIV to as close to zero as possible and induce an appropriate immune response against the immunopathogenic epitopes. Such a scenario may lead to a massive reduction in the amount of antiretroviral drugs required during a patient's lifetime and also promotes the possibility of patients remaining off treatment for months to years. A 2006 trial of a therapeutic vaccine showed that it delayed viraemia after cessation of antiretroviral drugs and induced weak anti-gag responses, and the additional targeting of pathogenic epitopes with this approach may ultimately lead to long-term control of the disease.[35] Many experts on vaccines for HIV acknowledge that complete protection is impossible for such a virus and that the best that can be hoped for is partial population protection. Therapeutic vaccination is a much more practical and readily tested goal.

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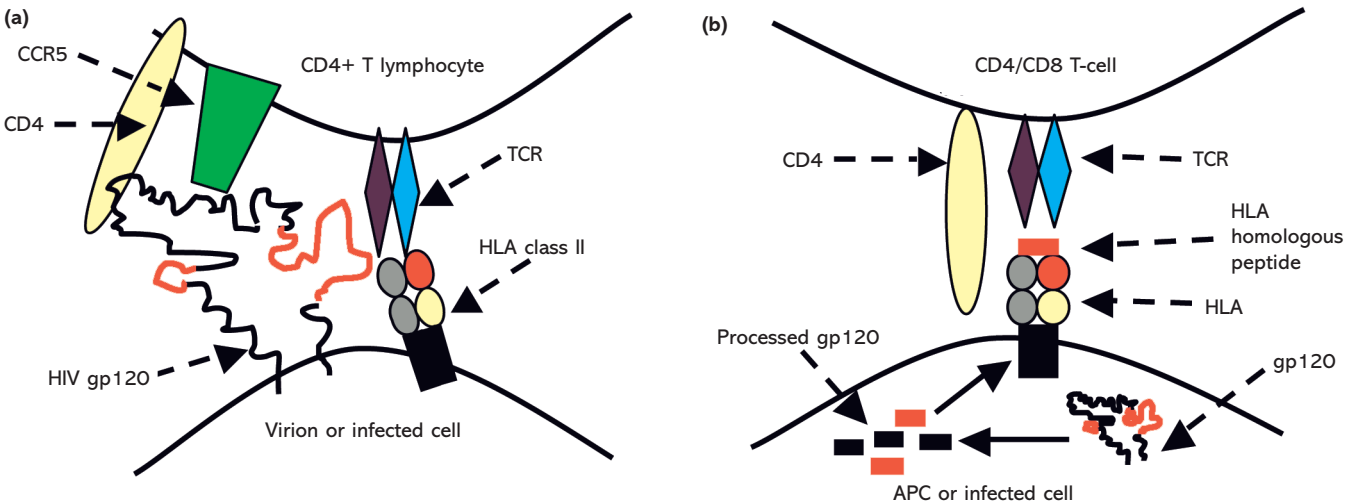

Fig 2. Models for potential mechanisms through which HIV-1 gp120 could influence alloactivation. (a) Alloactivation might be provoked by direct immune recognition of gp120 domains bearing structural homology with human leucocyte antigen (HLA) (represented by red regions of gp120). Alternatively, the close association of gp120 HLA homologous structures with host HLA might be mistaken for an allogeneic or hybrid complex by the host and may trigger a response. (b) Processing of cellular expressed or phagocytosed gp120 may lead to the presentation of HLA homologous sequences (red) by host HLA on infected or uninfected cells and provoke indirect alloactivation of CD4 and CD8 T lymphocytes. Furthermore, activation of CD8 T lymphocytes by a HLA homologous sequence might provoke an autoimmune response towards the native HLA-derived sequence when presented as a peptide as part of the host self repertoire and lead to immunosuppressive responses towards uninfected cells bearing that sequence. CCR5 = chemokine (C-C motif) receptor 5; TCR = T-cell receptor.

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