Subtle Mimicry of HLA by HIV-1 GP120 – A Role for Anti HLA Antibodies?

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Abstract: Human immunodeficiency virus (HIV-1) infection causes progressive immune deficiency by the targeted depletion of CD4+ T cells. The mechanism by which HIV-1 achieves this is not completely understood, however chronic immune activation is understood to be an essential feature of progressive HIV-1 infection. Although the mechanism by which HIV-1 induces chronic immune activation is also unknown, a number of studies have demonstrated the *in vitro* and *in vivo* protective effects of allo immunization while the presence of antibodies specific for human leukocyte antigen (HLA) class I and II molecules have been correlated with protection from HIV-1. It is currently unclear how allo-immunisation protects the host from HIV-1 or the circumstances under which anti-HLA antibodies are protective. However, a possible mechanism in which anti-HLA antibodies may protect the host, even in the absence of viral neutralization, is by binding to the HLA-homologous regions of the HIV-1 envelope protein gp120. Gp120 demonstrates the structural and functional properties of HLA and this subtle mimicry may endow gp120 with the ability to induce allo-activation of T cells in susceptible hosts, which could increase viral replication and immune dysfunction.

Keywords: HIV-1, HLA, GP120, Allo-immunity, CD4+ T cells.

INTRODUCTION

An estimated 33 million people are now infected with HIV-1, many in poor countries [1]. In 2007 an estimated 2.7 million people were newly infected with HIV-1 and an estimated 2 million HIV-1 positive people died of the disease [1]. There is no effective vaccine to HIV-1 despite the intense research effort in this field and the recent failure of promising vaccine candidates and the toxicity and drug resistance associated with antiretroviral therapy emphasize the need for alternative therapeutic strategies [2]. Even with successful HAART treatment, therapies that allow for HAART breaks and/or enhance host immune responses are highly desirable, particularly when considering that antiviral coverage amongst adults and children was estimated at only 42% in low and middle income countries in 2008 [3]. Many anti-HIV-1 preventative and immunotherapeutic vaccines have been developed in an attempt to generate protective immune responses in the host however these have generally been unsuccessful [4-6]. Other research is pointing towards the use of alternative therapeutic strategies based upon an understanding of the mechanisms by which HIV-1 successfully compromises the host immune response [7]. Currently the mechanisms by which HIV-1 drives the depletion of CD4+ T cells and which ultimately results in the progression to Acquired Immune Deficiency Syndrome (AIDS) are not completely understood, however it is now accepted that generalized chronic immune activation is an essential component of HIV-1 pathogenesis [8, 9]. This lack of basic principles for how HIV-1 manipulates the immune system and causes immune dysfunction is probably why there is still no effective AIDS vaccine. In light of this a number of different hypotheses have been devised in order to explain the occurrence of HIV-1 dependent chronic immune activation [8, 10, 11]. Evidence is mounting which points to a role for autoimmune and allo-immune components of HIV-1 pathogenesis and these findings are being applied to develop novel immunotherapy in order to ameliorate pathogenesis and prevent progression to AIDS [12]. This review details the possible causes of chronic immune activation and discusses how autoimmune responses against human leukocyte antigen (HLA) and HIV-1 gp120 mimicry of HLA may promote immune activation and influence disease progression.

HIV-1 DISEASE PATHOGENESIS

The defining characteristic of HIV-1 infection is the chronic depletion of CD4+ T cells which leads to AIDS. Initially it was thought that increases in viral replication led to increased infection of CD4+ T cells which directly resulted in the observed CD4+ T cell depletion. However, subsequent research has shown that the situation is more complex. Perhaps surprisingly, disease progression was found to be associated with the activation of the immune response, particularly of CD4+ and CD8+ T cells [2, 13-17] and markers of T cell activation such as CD38 and HLA-DR precede increases in viral load and CD4+ T cell decline and have a greater prognostic significance of disease progression compared to increases in viral load [18-22]. During HIV-1 infection the activation of CD4+ and CD8+ T cells is greater than would be expected for HIV-1 specific T cell responses [23] and occurs alongside increases in pro-inflammatory cytokine expression and the activation of other cells including macrophages and dendritic cells [24]. In addition, the level of CD4+ T cell depletion is greater than would be caused by cytopathic infection since only a small number of virions are infective and only a small number of CD4+ T cells are actu-

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ally infected [25-29]. Instead, chronic immune activation precedes T cell depletion predominantly of bystander T cells by activation induced cell death (AICD) [30-32]. Thus, chronic immune activation is a central component of HIV-1 infection.

CHRONIC IMMUNE ACTIVATION IN HIV-1 AND SIV INFECTION

Further evidence that chronic immune activation is essential to HIV-1 disease progression has been observed in a number of different studies. For example, Long term non-progressors (LTNPs), who control HIV-1 disease, can have high viral loads but do not exhibit chronic immune activation [33-35], whilst Chimpanzees are susceptible to cytopathic HIV-1 infection but rarely progress to AIDS; those Chimpanzees that progress appear to suffer from chronic immune activation [36]. A study of simian immunodeficiency virus (SIV) infection of Sooty Mangabeys, the natural host of SIV, indicate that infection is characterised by high viremia but lower levels of immune activation and apoptosis than in pathogenic SIV infection of Rhesus macaques [37]. Differences between HIV-1 and HIV-2 also indicate that chronic immune activation is essential to disease progression. Infection with HIV-2 is associated with lower levels of immune activation, plasma viral load and apoptosis compared to HIV-1 infection [38, 39] despite having similar target cell infectivity, pro-viral loads and antigenic variability [40-42]. Indeed the majority of HIV-2 infected individuals remain asymptomatic [43-45]. Progression of HIV-1 disease has even been observed in some individuals infected with non-cytopathic and non-syncytium inducing HIV-1 strains. This finding further emphasises that factors other than direct viral infection of T cells are responsible for disease progression [46, 47]. Lastly, disease progression can also be independent of cellular immunity since infection of Sooty Mangabeys with SIV does not lead to AIDS despite T cell responses that are lower in breadth and magnitude compared to human T cell responses to HIV-1 [48]. Overall, these studies indicate that viral load, viral cytopathicity and even narrow host immune responses may not be sufficient to cause progressive disease in the absence of chronic immune activation and that viral cytopathicity and viral load are not directly responsible for the activation observed. However the extent of apoptosis observed during HIV-1 infection correlates with increases in viral load while the reduction in viral load upon treatment with HAART reconstitutes controlled immune function [49, 50]. Taken together this research implicates viral gene products in immune activation and disease pathogenesis however despite the clear link between immune activation and HIV-1 pathogenesis the causes have remained elusive. By studying the character of the immune response during progressive infection it is possible to gain insights into how HIV-1 activates the immune system.

Control of HIV-1 by the host is compromised by dysfunction of multiple aspects of immune response including T cell anergy and apoptosis, shifts in the Th1 – Th2 cytokine profile, progressive and selective CD4+ T-cell decline, loss of self tolerance and autoimmune symptoms such as systemic lupus erythematosus, arthritis and graves disease [51, 52]. Importantly, the dysfunction and loss in T-lymphocyte responses begins before significant CD4+ T cell decline in HIV-1 infected individuals [53-56] indicating that the cause of immune dysfunction is responsible for causing CD4+ T cell depletion. HIV-1 has evolved a number of mechanisms to interfere with immune responses [57]. Of these, the HIV-1 envelope protein gp120 plays an important role in T cell dysfunction. T cell anergy induced following gp120 interaction with CD4 contributes to suppression of immune responses and can do so in the absence of HIV-1 virions [58, 59]. The presence of HIV-1 or gp120 during antigen presentation to T cells by APCs also leads to HLA restricted, antigen specific apoptosis of T cells following an additional round of stimulation by uninfected APCs [59-61]. This demonstrates that gp120 can activate T cells and prime them for apoptosis. Defective or inactivated HIV-1 virions expressing gp120 on their envelopes can also activate and induce apoptosis in both uninfected CD4+ and CD8+ lymphocytes [62, 63].

Importantly HIV-1 infection doesn't always cause immune activation despite the presence of replicating virus and gp120. Studies of LTNPs show that these patients have co-ordinated and specific immune responses which are capable of controlling viral replication and delaying progression to AIDS [64-68]. Interestingly, HIV-1 diversity is greater in LTNPs compared to those patients exhibiting progressive disease. This may be in response to strong and effective immune responses against the virus driving the evolution of escape mutants while in progressive disease dominant HIV-1 strains emerge [69-71] upon the dysfunction and chronic activation of the immune response [72]. However it is currently unclear why LTNPs don't suffer from chronic immune activation and are able to control the disease.

The most important aspect of chronic immune activation is the activation, dysfunction and depletion of CD4+ T cells. Most of the immune dysfunction observed during HIV-1 infection is symptomatic of this phenomenon. Therefore it is vital to understand how HIV-1 causes chronic immune activation and how this results in CD4+ T cell depletion.

POSSIBLE CAUSES OF CHRONIC IMMUNE ACTIVATION

The chronic activation of the immune system initiated by HIV-1 is multifaceted and interconnected. HIV-1 virions and/or gene products initiate immune activation by at least one mechanism and possibly by a number of mechanisms (Table **1**). The lack of immune activation in LTNPs indicates that host factors influence susceptibility to HIV-1 dependent immune activation and thus disease progression. A number of possible mechanisms by which HIV-1 may cause chronic immune activation are discussed.

T LYMPHOCYTE RESPONSES TO HIV-1 AND CO–INFECTIONS

Variation in the frequency of T cell activation during HIV-1 infection may provide an explanation for different levels of T cell depletion and chronic immune activation. However, only a small fraction of activated T-lymphocytes are HIV-specific and diversity in the antigen specificity of these responses is more frequently observed in LTNP than in progressors [69, 70, 73]. This indicates that greater variation in the HIV-1 specific T cell populations is part of the controlled immune response that characterises LTNPs rather than part of chronic immune activation. Therefore T cell activation by other sources must be responsible for disease

Table 1. Possible Causes of Chronic Immune Activation

Effects of HIV-1 Infection on Host Immune Responses	Proposed Role in the Activation of Chronic Immune Responses	Questions
Loss of mucosal CCR5+ CD4+ Memory T-lymphocytes following acute infection by HIV-1 [11].	Inability of the host to adequately replace CD4+ T cells in the major site of viral replication and thus control infection. This leads to uncontrolled viral replication.	How important is mucosal depletion of CD4+ T cells relative to depletion of peripheral CD4+ T cells? How might depletion of CD4+ T cells from the MALT relate to chronic immune activation?
Damaged intestinal mucosa allowing the translocation of microbial products such as LPS [103].	LPS activates bystander T cells which primes them for apoptosis	Increases in plasma levels of LPS correlate with chronic immune activation but a direct causative role has yet to be shown.
Depletion of CD25+ CD4+ T regulatory cells by HIV-1 [88].	Uncontrolled activation of T cells.	It is unknown whether depletion of Tregs is a direct cause of chronic immune activation
Stimulation of T cells and APCs by HIV-1 gene products such as gp120 [58, 59].	Increases in viral load result in increased depletion of T cells by viral gene products	This doesn't account for the activation of T cells and breakdown of tolerance observed during chronic immune activation
Co-infection and subsequent hyper activation of the immune system [81].	The immune system fails to control multiple infections and the T cells activated in response to secondary infection promotes HIV-1 replication	Pathogenic HIV-1 or SIV infection can occur in the absence of co infection.
Mimicry of host HLA molecules by HIV-1 gp120 [10].	May promote the breakdown of tolerance and activation of allo-immune responses causing immune dysfunction and increased HIV-1 replication	Although GP120 has been demonstrated to bind peptide epitope and activate T cells the extent to which this occurs during HIV-1 infection is unknown.

progression. HIV-1 proteins contain epitopes that mimic those of other viruses [74] and T cells specific for other viruses that commonly infect humans including EBV, CMV and influenza are also activated during HIV-1 infection [75]. This may be a strategy to increase the frequency of T cell activation in order to provide HIV-1 with a greater number of cells permissible for infection but doesn't offer an explanation for the existence of slow progression in some individuals or the non specific activation of bystander T cells.

HIV-1 specific superantigen has been considered as a cause of chronic immune activation and gp120 contains a super-antigenic epitope which can induce polyclonal B-cell stimulation [76]. However, a lack of consistent enhancement or deletion of the T-cell variable gene repertoire at any stage of HIV infection indicates that a T cell super antigen is unlikely to be responsible for chronic immune activation [77-80].

HIV-1 disease progression is also associated with co-infections with other pathogens or by the activation of microbes that were either latent and/or previously controlled by the immune system [81]. Significant numbers of HIV+ individuals are co-infected with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) [82, 83]. HIV-1 causes greater HBV and HCV replication while HCV generates persistent immune activation including the activation of CD4 and CD8 T cells [84]. Herpes simplex virus (HSV) and cytomegalovirus (CMV) are common viruses which can cause T cell activation and facilitate HIV-1 replication and disease progression respectively [85, 86]. Human herpes virus-6 (HHV6) is an opportunistic virus that is normally controlled by the immune system however, upon HIV-1 infection HHV6 becomes a factor in HIV-1 disease progression. HHV6 also infects activated CD4+ T cells and can induce the expression of CD4+ on CD8+ T cells and NK cells [87].

The activation of specific immune responses to co-infecting pathogens can facilitate HIV-1 replication and may play a part in the chronic activation of the immune system. However experimental SIV infection of macaques and chronic immune activation in HIV-1 infection of humans can be independent of co-infection and no consistent pan-activator of T cells has been identified. This work indicates that other underlying mechanisms of T cell activation must be involved. Among these possible mechanisms is change's in the regulation of immune responses, which may lower the threshold to T cell activation and result in inappropriate immune responses, and damage to the mucosa, the primary site of HIV-1 replication.

T REGULATORY CELLS IN HIV-1 INFECTION

T-regulatory cells (Tregs) are a subset of CD4+ T cells which express CD25 and Foxp3. They are important in regulating the immune response and are also implicated in HIV-1 infection [88]. Increased levels of Tregs in LTNP patients compared to patients on HAART correlates with lower levels of CD4+ T cell activation [89] and Tregs are targeted by HIV-1 and depleted during late stages of HIV-1 disease which may contribute to immune activation. Interestingly HIV-1+ asymptomatic individuals who have functional Tregs specific for HIV-1 antigens have lower viremia and higher CD4 T cell counts than HIV-1+ individuals lacking HIV-1 p24 specific Treg activity who also have a significantly lower CD4:CD8 ratio, an indication of progressive disease [90]. Currently it is unknown whether Tregs directly inhibit chronic immune activation during HIV-1 infection and the antigen specificity of different Treg populations and

their relative contribution to functional anti-HIV-1 immune responses is also unknown. While Treg function may play a role in regulating HIV-1 immune responses another mechanism must be responsible for chronic immune activation.

HIV-1 INFECTION IN THE MUCOSA AND CD4+ T CELL DEPLETION

An important site of chronic immune activation is the mucosa-associated lymphoid tissue (MALT). The gut associated lymphoid tissue (GALT) is a component of the MALT and contains over 40% of the total lymphocyte population [91]. HIV-1, whose natural transmission is through mucosal surfaces, is internalised by APCs and delivered to CD4+ T cells *via* the infectious synapse formed between these cells [92, 93]. In addition experimental SIV infection of macaques has shown that the GALT is the predominant site of SIV infection and exhibits a higher viral load compared to blood and lymph nodes [94, 95]. Early SIV infection of macaques and HIV-1 infection of human patients is associated with rapid depletion of mucosal memory CD4+ T cells especially those expressing the HIV-1 co-receptor CCR5 which implicates HIV-1 infection and/or gp120 binding of these cells [25, 96-98]. However the contribution of CD4+ T cell infection by SIV or HIV-1 to this cell death is unclear. One study has showed that 60% of CD4+ T cells contained SIV DNA by day 10 post infection [99] however another study showed that only 7% of mucosal CD4+ T cells contained SIV RNA at any given time [100]. Both studies indicate that a significant percentage of CD4+ T cells are depleted from the MALT despite being uninfected with SIV. The depletion of CD4+ T cells from mucosal tissue may influence disease progression because of insufficient replacement and migration of the cells [101]. In addition to acute depletion of CD4+ T cells chronic infection is also associated with severe CD4+ T cell depletion in the MALT. However this CD4+ T cell depletion was found in LTNPs as well as in patients with progressive disease so it is difficult to determine how important the chronic depletion of CD4+ T cells in the MALT is to disease progression [102]. A mechanism by which depletion of CD4+ T cells from MALT during HIV-1 infection can cause chronic immune activation has been proposed. This is based upon observations that plasma levels of Lipopolysaccharide (LPS) are significantly increased in chronically infected HIV-1 individuals and SIV infected macaques [103]. LPS is an indicator of microbial translocation from the intestinal lumen and it is thought that depletion of CD4+ T cells in the MALT causes damage to the mucosal barrier which results in the activation of bystander CD4+ T cells *via* signalling by toll like receptors. This may be one mechanism by which pro inflammatory cytokine expression is increased and may contribute towards the non antigen-specific T cell activation. However, a direct causative effect of LPS on chronic immune activation has yet to be demonstrated and the mechanism by which CD4+ T cell depletion causes breakdown of the mucosal barrier is unknown. Finally microbial translocation doesn't clearly explain a number of phenomenon observed during chronic immune activation.

Chronic immune activation is not caused by superantigen or greater diversity in HIV-1 specific T cell responses. While considerable CD4+ T cell depletion occurs in the gut it is unclear how this influences chronic immune activation and the influx of pathogen associated molecular patterns (PAMPs) such as LPS due to damaged gut mucosa does not yet provide an explanation for the numerous phenomenon associated with chronic immune activation. Another explanation for chronic immune activation is based upon observations that indicate that HIV-1 infection shares a number of similarities with Graft versus host disease.

HIV-1 AND GRAFT VERSUS HOST DISEASE

An alternative explanation for chronic immune activation is the HIV-1 dependent priming of an allo-immune response similar to that observed in graft versus host disease (GVHD). The molecular basis for allo recognition is not fully understood [104] however its established that allo-immune responses in GVHD can be either direct or indirect. Direct responses involve the recognition by host T cells of intact donor human leukocyte antigen (HLA) on donor cells [105]. Indirect allo-immune responses involve the recognition of donor HLA derived peptide presented by host APC and restricted by host MHC [106]. The similarities between HIV-1 pathogenesis and GVHD are striking. Prior to the discovery of HIV, it was considered that alloantigen may be involved in the aetiology of AIDS based upon the similarities between AIDS and the immune deficiency observed during experimental graft-versus-host disease in MHC class II mismatched mice [107-109]. Since then a number of studies have documented the clinical and immunological similarities between chronic GVHD and AIDS [110-115]. For example, both diseases are characterized by generalized immune stimulation and dysfunction of numerous cell types, increased pro-inflammatory cytokine profiles, opportunistic infections, and loss of antigen specific responses over a long period of time. Both conditions also have important HLA and autoimmune related components [113, 116]. A large number of studies over the last 20 years have demonstrated the complexity of the interactions between HLA and HIV-1 which implicated allo-immune responses in the pathogenesis of HIV-1 infection.

THE COMPLEX ROLE OF HLA IN HIV-1 INFECTION

A number of studies have identified HLA molecules and combinations of HLA molecules which are linked with either disease progression or non-progression [117-123]. The influence of HLA-B alleles on the interaction between and progression of HIV-1 disease is the most well defined [124]. Of these, HLA-B gene products including HLA-B8, HLA-B35 and HLA-B53 are associated with rapid progression to AIDS whereas others such as HLA-B27 and HLA-B57 are consistently associated with slow or non-progression [125-128]. HIV-1 infected individuals with relatively high expression of HLA-C have also been shown to control viremia more effectively and progress more slowly to AIDS. The increased expression of HLA-C was associated with a -35kb polymorphism upstream of the HLA-C gene [129, 130] and the protective effect may be due to the HLA-C dependent CTL activity identified in LTNPs [131] or to increased lysis of infected cells by NK cells, since there is no clear difference between HLA-C alleles in their ability to control infection. However, the relationship between HIV-1 and HLA-C may be more complex. Optimal HIV-1 infectivity of peripheral blood lymphocytes requires HLA-C expression and HLA-C has been shown to reduce antibody dependent NK cytotoxic-

ity of HIV-1 infected cells [132-134] which offers another explanation for why HIV-1 has evolved to down regulate HLA-A and HLA-B but not HLA-C [135] .

CD4+ and CD8+ T cell immune responses have been shown to control HIV-1 infection and HLA haplotypes have a differential ability to effectively present peptide epitopes in order to generate these responses. Therefore the role of HLA in the selection and maintenance of strong HIV-1 specific immune responses to control viral loads will influence whether a particular HLA predisposes to protection from or progression of disease. In support of this are studies that demonstrate less variability amongst certain HIV-1 epitopes derived from HLA-B27 which is associated with slow progression compared to epitopes derived from HLA-B8 which is associated with rapid progression [136]. Effective CTL immune responses in chimps and humans may be due to the inability of the virus to generate escape mutants to particular T cell epitopes presented by particular HLA however other studies indicate that HLA may play additional roles in HIV-1 infection. In support of this are observations from experiments using SIV infected sooty mangabeys which have shown that the lack of progressive disease, despite a high viral load, is less dependent of cellular immune responses [48] and sooty mangabeys demonstrate reduced CD4+ bystander activation compared to macaques [137]. In addition, Analysis of the HLA repertoire of chimpanzees suggests that there has been strong selection pressure resulting in the depletion in the HLA class I gene repertoire and the loss of a number of HLA class I alleles. This is particularly evident in the diversity of the HLA-B alleles [138, 139]. The selection of certain HLA molecules and the removal of others is probably due to strong evolutionary pressure acting on the immune system of chimpanzees. This may be a factor which influences the reduced susceptibility of chimpanzees to pathogenic HIV-1 infection although it is unknown how reduced HLA diversity might be protective. Heterogenicity in HLA haplotypes and a protective benefit of rare HLA types to which HIV-1 does not evolve escape mutants indicates that a broad array of HLA is beneficial in the control of HIV-1 [118, 122, 140, 141]. If the reduction in the chimpanzee HLA repertoire is due to the selection pressure of HIV-1 infection there must be other, T cell independent, effects of HLA on HIV-1 infection in order to explain the reduced HIV-1 pathogenesis observed in chimpanzees. Taken together the studies in LTNPs, Chimpanzees and Sooty Mangabeys indicate that in addition to mediating T cell activation different HLA have other effects on HIV and SIV infection.

HLA INCORPORATED INTO THE HIV-1 ENVELOPE

Activation of CD4+ T cells greatly facilitates the infection and replication of HIV-1 in these cells. The dual requirement of HIV-1 to evade activated host T cell responses while replicating in activated T cells may be responsible for the HIV-1 dependent chronic immune activation and the complex relationship that appears to exist between HIV-1 and HLA. This includes the incorporation of HLA and a number of other host cell proteins into the HIV-1 envelope when progeny virus particles bud from the cell membrane [142, 143]. In fact the amount of HLA incorporated into HIV-1 envelopes is greater than that of gp120 trimers which form the HIV-1 envelope protein responsible for binding to CD4 and initiating internalization [144]. The incorporation of host HLA is beneficial to the virus. Incorporation of HLA-DR1 or the HLA class I allele Cw4 increases viral infectivity [145-146] and HLA-Cw4 can form complexes with gp120 which can reduce the susceptibility to antibody neutralization [145]. Incorporation of HLA-DR into HIV-1 virions *in vivo* has been associated with the presence of opportunistic infections and during progressive disease [146]. More research on the role of HLA in combination with gp120 in HIV-1 envelope during disease progression is needed to determine whether differences in HLA expression alter the functional properties of gp120.

HLA-DR incorporated into HIV virions or at the surface of infected cells is promoted by immune activation and may trigger inappropriate immune stimulation through the TCR on target CD4+ T cells and promote increased T cell anergy and apoptosis. Virion associated HLA class II has been shown to be functional in the presentation of superantigen [147] and peptides to antigen specific CD4+ T cells [148]. The presence of HLA class II upon inactivated HIV-1 virions can also enhance activation-induced apoptosis in CD4+ and CD8+ T-cells [149] and elevated HLA-DR expression is correlated with CD4+ T lymphocyte depletion [150]. Furthermore the differential incorporation of co-stimulatory molecules CD80 and CD86 by HIV-1 may contribute to inefficient secondary signalling through CD28 on T-cells and ultimately promote anergy or apoptosis [151-152]. Importantly, HIV-1 is selective in the molecules incorporated into the viral envelope since the HIV-1 co receptors CXCR4, CCR5, or CCR3 aren't incorporated when HIV-1 buds from co-receptor expressing cells [153]. Another mechanism by which HLA may effect HIV-1 infection is the demonstration that peptides derived from HLA molecules can interfere with autoimmune and allo-immune responses *in vitro* [154-159] and have the means to promote apoptosis [160, 161]. This may be particularly important in HIV-1 infection due to the auto and alloimmune components of the disease. Clearly incorporation of HLA into the viral envelop represents a strategy by HIV-1 to escape immune responses and activate T cells. Inhibition of these HLA mediated effects may be important in the control of HIV-1 infection.

ANTI-HLA ANTIBODIES IN HIV AND SIV INFECTION

The role of anti-HLA antibodies in HIV-1 infection has been studied in a number of different settings (Table **2**). Studies using macaques immunized with purified HLA class I and II and challenged with SIV cultivated in human cells have showed a strong correlation between anti-HLA responses and protection against SIV [162, 163]. The presence of anti-HLA class I antibodies have also been strongly associated with repeatedly exposed, seronegative (ESN) individuals. However, no correlation was seen between sera neutralising activity and the presence of these anti-HLA class I antibodies [164] indicating that if they are important in resistance to HIV-1, it is based upon other unknown mechanisms. In support of this, sera with anti-HLA antibody were correlated with ESN status.

Additional studies highlight the various effects of HLA on HIV-1 disease. The risk of vertical transmission at birth is decreased with increased HLA discordance between the mother and the infant [165]. This may be due to enhanced

Table 2. Induction of Anti-HLA Antibodies and their Effects on HIV-1 Infection

Study	Anti HLA Antibodies	Effect
Macaques immunized with HLA and protected against SIV infection [162, 163].	Anti HLA class I and II	A strong correlation between anti-HLA responses and protection against SIV was observed.
Exposed, seronegative (ESN) individuals [164].	Anti-HLA class I	No correlation between sera neutralisation and presence of anti-HLA antibody however ESN status correlated with anti cell antibodies.
Sera from polytransfused patients tested for neutralizing activity [224].	Predicted anti- allogeneic HLA	Sera from 2 out of 12 patients had neutralizing activity against HIV-1 while antibody from sera was shown to bind to HIV-1 virions.
Antibodies generated from whole cell allo-immunisation [180].	Anti-HLA antibodies in 2 of 7 recipients	Antibodies from 1 recipient had HIV-1 neutralizing activity.
Anti-HLA antibody from multiparous women and specific for the HLA of their husbands. Used to neutralize virus grown in husband's PBMC (expressing husband's HLA) [166].	Anti HLA class I and II	The HLA antibody did not neutralize HIV-1 *in vitro*.

early immune responses against virus that has evolved to counter T cell responses restricted to different HLA. Another study examined the sera from multiparous women carrying anti-HLA antibodies specific for the HLA of their husbands to determine whether naturally occurring anti-HLA antibodies had HIV-1 neutralizing activity. HIV-1 was grown from the PBMC from each of the participant's husbands which results in the coating of the virus envelope in HLA matching the specificity of the anti-HLA antibody in the sera of their wives. HIV-1 was found to incorporate host HLA into the virus envelope at concentrations greater than that reported for gp160. However binding of the anti-HLA antibody to HIV-1 did not mediate neutralization in this study [166].

In addition, antibodies against HLA homologous regions of gp120/41 have been found to cross-react with the relevant sequences upon HLA and interfere with cellular proliferation [167, 168]. Thus antibodies to HLA and neutralize HIV-1 while antibodies which recognise the HLA homologous C5 region of gp120 cross react with HLA-class I on activated cells [169]. The generation of anti-HLA antibodies and their ability to cross react with gp120 may depend upon the HLA type of the individual.

Anti-HLA antibodies can be protective during HIV-1 infection and/or reduce transmission. However, the circumstances in which these antibodies are generated and the mechanism behind their protective effects is not completely understood. Anti-HLA antibodies may play a role in preventing cross reactive allo immunity either to the HLA incorporated into the HIV-1 envelope or to the HLA homologous regions of gp120. Studies using allogeneic stimulus in therapeutic vaccination are supportive of the theory that controlling adverse immune responses may be as important as generating effective anti-HIV-1 immune responses and the responses to some of these vaccines includes the generation of anti-HLA antibodies [170].

ALLO-IMMUNISATION IN HIV-1 INFECTION

Observations that allo-immune responses may have beneficial affects on HIV-1 infection have lead to attempts to induce these responses in HIV-1+ individuals using a number of different therapeutic vaccine preparations. The first of these was developed in 1986 and consisted of formaldehyde-inactivated autologous lymphocytes derived from HIV-1 individuals and re-introduced into the same patients. This vaccine resulted in increases in CD4+ T cell counts however the effect of re-introducing inactivated autologous cells on HIV-1 infection or on the immune responses is unknown [171]. Later, macaques vaccinated with a preparation using whole SIV infected and killed human cells were observed to be resistant to subsequent infection. Unexpectedly macaques were also protected from challenge with SIV even when vaccinated with killed human cells that didn't contain SIV [172]. Since then further vaccines containing autologous cells reintroduced to HIV-1 patients have been shown to have beneficial clinical effects including increases in CD4+ T cell counts, reductions in viral load and even sero-deconversion however the mechanism of action is still unknown [173, 174].

Another study using an inactivated T cell vaccine, which also didn't contain HIV-1, generated increases in CD4+ T cell counts and clinical improvements in patients [175]. Yet another vaccine based upon peripheral blood leukocytes (PBL) from HIV-1+ donors has been developed and targeted towards gut mucosal immunity which is biased towards the induction of tolerance. Patients treated with this vaccine demonstrated decreased viremia, increased CD4+ T cell counts and a higher survival rate [176, 177]. Live autologous and allogeneic PBL have also been used in therapeutic vaccine trials and showed clinical improvements [178, 179]. In another study 1 x 108 allogeneic irradiated PBMC were used in a single intravenous and three intradermal injections at a single time point. Two of seven patients generated strong anti-HLA class I and II antibody responses specific for the HLA type of the immunised PBMC which were also capable of neutralizing HIV-1 *in vitro* [180]. The use of a fixed inactivated HIV-1 vaccine has also elicited anti-HLA antibodies in HIV-1+ individuals. These antibodies were specific for HLA-B62 and HLA-DR4, the HLA on the host cell line used for vaccine preparation, and wasn't found in individuals expressing either of these HLA alleles which indicate that the vaccine didn't break tolerance to self HLA [181]. Cell based

vaccines seem to have a therapeutic effect even if the cells are dead or come from allogeneic and uninfected individuals who have not been exposed to the virus. Therefore an underlying mechanism may be the induction of tolerance to allogeneic stimuli which reduces immune activation or conversely the activation of allo immune responses that cross react with HIV-1 specific antigen.

These studies of anti-HLA antibodies and allo-immunization indicate that HIV-1 infection or immunotherapy can generate anti-HLA responses and that these responses are capable of neutralizing the virus. Anti-HLA responses can be generated congenitally, by sexual intercourse or by allo immunization. These responses are often, but not always, protective while the mechanism by which they effect HIV-1 infection is incompletely understood (Table **3**). Anti-HLA antibodies can bind to the HLA on the envelopes of circulating virions and have been shown in some studies to have neutralizing activity. However anti-HLA antibodies have also been associated with a LTNP phenotype despite a lack of neutralizing activity while other studies have shown no correlation between the presence of anti-HLA antibody and disease progression [182, 183]. The finding that anti-C5 antibody can cross react with HLA [169], that gp120 has structural and functional homology to HLA [185-187] and that gp120 derived peptides mimic a number of HLA derived peptides[10] adds further layers of complexity to the possible functions of these antibodies. Why does HIV-1 gp120 contain regions that mimic host HLA? How does this benefit the virus? A provocative hypothesis involves the generation of auto-immune or allo-immune responses by HIV-1 mimicry of host HLA which may play an important role in HIV-1 pathogenesis.

HLA MIMICRY BY GP120

Our understanding of the mechanisms by which HIV-1 may cause host allo-immune responses is incomplete. Differences in HLA haplotype are known to influences the extent of allo recognition in GVHD and are also an important factor in the aetiology of HIV-1 [117, 184]. Regions of the HIV-1 genome encode peptides with structural and functional homology to that of various HLA [185-188] while Differences in HLA type correlate with differential susceptibility to disease progression [120-126]. Chimpanzees, despite having a more limited HLA repertoire than humans due to a selective depletion of particular alleles in responses to infection, rarely progress to AIDS [137]. Importantly, antibodies to some of the HLA homologous regions of HIV-1 can cross react with HLA molecules [169]. In fact HIV-1 gp120 can mimic self HLA and activate allo-immune responses. By binding peptide epitopes in the carboxy terminus C5 domain gp120 can activate antigen specific T cell responses using *in vitro* cell culture models [189-191]. This indicates that gp120 has the minimal functional properties of HLA so may be capable of inducing responses similar in character to those of direct allo recognition by inducing a breakdown in tolerance to self-HLA. In fact molecular modelling of the Carboxy terminus of gp120 demonstrates structural features similar to those of T cell allo-epitopes [185]. The C5 region has been shown to bind the flu peptide epitope HA (307-319) PKYVKQNTLKAT [191] however the identity of other peptides and the potential peptide bind motif of gp120 needs to be determined.

In addition to the possibility of causing direct allo recognition, regions within gp120 contain epitopes similar to those of self HLA [10, 188]. This may make gp120 capable of inducing indirect allorecognition by activating T cells specific for the HLA peptide epitopes in which gp120 peptides share homology. Again, the C5 domain of gp120 may be particularly important. This region partially mimics the 3rd hyper variable region of the HLA-DR β chain. Polymorphism in the α-helical region of the HLA-DRβ chain defined by the HVR3 has been shown to be a key region in determining both HLA class II specific alloreactivity *via* direct allorecognition [192-194] as well as being recognized *via* the indirect pathway of allorecognition [195, 196]. Studies have shown that the HVR3 region of the HLA-DR β chain, specifically residues 67-74, selectively affects the expression of the T cell receptor Vβ chain and influences immune activation and allorecognition [197] and polymorphisms in this region have a disproportionate influence upon T cell recognition when compared with other polymorphic residues [198-200]. Allogeneic T cells recognise this HVR3 homologous peptide from the C5 region [201] and CD8+ T cells specific for the C5 sequence TKAKRRVVEREKR, were able to suppress antigen specific proliferation of autologous PBMCs by targeting self-HLA [202]. The C5 peptide is predicted to bind to a number of HLA including HLA-B35, B27 and B8 [203]. As a significant proportion of the endogenous self-peptide repertoire presented to T cells are derived from HLA molecules, these peptides and the corresponding gp120 homologous peptides make likely candidates for allo-epitopes [204, 205].

ALLO-IMMUNE DEPENDENT HIV-1 PATHOGENESIS

The causes and consequences of allo and auto immune responses during HIV-1 infection are still not completely

Table 3. Possible Mechanisms by which Anti-HLA and Allo-Immune Responses may be Protective During HIV-1 Infection

Allo-Immune Response	Possible Mechanism of Action
Anti-HLA antibodies	Binding to HLA on virus envelope which may prevent T cell activation and apoptosis and facilitate neutralisation
Anti-C5 antibodies	Binding to gp120 to inhibit putative allo-activation Cross reactivity to HLA and binding of HLA on virus envelope
Allo-immunisation	Generation of anti-HLA antibodies Activation of CTL targeting HLA homologous peptides derived from gp120 and presented onto infected cells Induction of tolerance to allogeneic stimulus induced by HLA homologous regions of gp120

understood. Up to 10% of T cells are capable of allo-recognition with a higher frequency of T cells implicated in direct allo recognition compared to indirect recognition [206]. CD4+ T cell activation is essential to HIV-1 replication [207] so putative allo-activation during HIV-1 infection could produce a large number of activated CD4+ T cells susceptible to infection by HIV-1. HIV-1 replication in these activated cells would result in greater cell death and the production of pro-apoptotic gene products, including more gp120, and increases viral replication. Activation of CD4+ T cells by gp120 binding to CD4 and also acting as an allo-antigen *via* binding to the TCR would also provide the necessary signals for AICD of bystander T cells observed during HIV-1 infection. In addition, allo-activated CD8+ T cells could interrupt host immune responses by autoimmune targeting of B cells, T cells and APC which present HLA-DR derived peptide *via* MHC class I [202]. In support of this, CTL activity has been detected amongst HIV infected progressor and sero-negative individuals in response to HIV-1 at similar levels to those generated in mixed lymphocyte cultures, a measure of allo immune responses. This indicates that there exists a higher than normal reactivity of T lymphocytes towards HIV-1 [23]. In fact autoreactive cellular responses are also commonly reported in HIV+ individuals including CD8+ CTL responses targeting uninfected activated CD4+ cells [208-210]. These autoreactive responses are not observed in HIV-1+ Chimpanzees highlighting them as a feature associated with AIDS pathogenesis [211]. Chronic immune activation generated from gp120 dependent allo immune activation could benefit HIV-1 by creating an environment that allows for greater viral replication while causing first dysfunction and then deficiency of the immune system as the ability of CD4+ T cells to regenerate becomes exhausted [212]. However more research on gp120 dependent allo-immune responses is needed since the manner and circumstances in which gp120 may activate allo-recognition *in vivo* is currently unknown.

Although the terminal C5 region is recognized as an exposed immunodominant epitope accessible on gp120 associated with virions and gp120 expressed on the surface of infected cells [213-214] it is associated with non-neutralizing antibodies and hasn't been considered as a vaccine target [215-217]. However it is evident that this region is associated with CD4+ T cell responses and antibodies against this region are associated with slower disease progression [89, 217-220]. HIV-1 disease progression has also been linked with the loss of humoral responses against the C5 region [221]. These findings, and the research discussed above, supports the possibility that the beneficial function of non-neutralizing anti-C5 antibodies or anti-HLA antibodies may benefit the host by protecting the immune system from the potential pathogenic effects of gp120 mimicry of HLA.

CONCLUSION

There are a number of possible causes of HIV-1 dependent chronic immune activation however their involvement isn't necessarily mutually exclusive. For example damage to the mucosa may alter the peptide repertoire presented to host T cells which could facilitate allo immune responses. Translocation of PAMPs such as LPS across the GALT may also contribute to gp120 dependent allo immune responses. In fact the onset of severe GVHD, which shares similarities with HIV-1 pathogenesis, is dependent upon the presence of microflora in the gut which facilitates gastrointestinal GVHD due to translocation of TLR ligands [222, 223]. The pro-inflammatory response triggered by translocation of microbial products in the GALT may provide the conditions necessary for breaking tolerance to self during HIV-1 infection. This could be exploited by gp120 in order to specifically break tolerance to self-HLA. Subsequent gp120 dependent allo-activation may be a causative factor behind the depletion of T cells and increases in viral load in the MALT. Co-infection with some pathogens may also influence the microbial translocation and immune activation observed in HIV-1+ individuals. Finally the depletion of Tregs could be responsible for the putative allo-activation of T cells which may otherwise be controlled.

Research on anti-HLA antibodies and allo-immunisation in HIV-1 infection indicate that blocking auto immune or allo immune components of this network of immune activation may be sufficient to control the disease in certain individuals. The homology between gp120 and HLA and the ability of gp120 to activate allo-specific T cells indicates that HIV-1 may have evolved to manipulate this aspect of immune activation however many questions still remain to be answered.

Elucidation of the mechanisms by which HLA molecules have either protective or predisposing effects on progressive HIV-1 disease will be vital in order to better understand how HIV-1 interacts with the immune system and identify which aspects of the immune response are protective or detrimental to controlling disease. Therapeutic activation of certain immune responses may actually be detrimental to controlling disease. Research into the mechanism by which anti-HLA antibodies mediate their protective effect during HIV-1 infection is also needed and should facilitate the use of anti-HLA antibodies in immunotherapy. The consequences of HLA mimicry by gp120 has yet to be studied in the context of HIV-1 infection and the ability of gp120 to induce direct and indirect allo-activation and the circumstances in which it may do so is not well defined. While the C5 region of gp120 can bind peptide epitopes the characteristics of C5 bound peptides is also unknown. It seems unlikely that gp120 would contain the conserved structural and functional properties of HLA without their playing an important role in HIV-1 biology. Finally a greater understanding of how allo-immune responses and anti-HLA antibodies are involved in immune activation during HIV-1 infection will provide novel, targeted opportunities for immunotherapy.

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