Toward an Understanding of the Correlates of Protective Immunity to HIV Infection

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Considerable progress has been made recently in understanding the genetic, immunologic, and virologic factors in human immunodeficiency virus (HIV)–infected individuals who either rapidly progress or do not progress to acquired immunodeficiency syndrome (AIDS). In addition, detection of HIV-specific immune responses in HIV-negative individuals who have been exposed to the virus multiple times suggests that natural immune responses to HIV may be protective in rare individuals. Understanding the correlates of protective immunity to HIV infection is critical to efforts to develop preventive HIV vaccines as well as to determine the feasibility of treating HIV infection by boosting immunity to HIV.

A spectrum of clinical courses can occur after HIV infection. Approximately 10% of HIV-infected subjects progress to AIDS within the first 2 to 3 years of HIV infection (rapid progressors) (*1*, *2*); approximately 5 to 10% of HIV-infected subjects are clinically asymptomatic after 7 to 10 years and have stable peripheral blood $CD4^+$ T cell levels (nonprogressors) (*1*, *2*); and the remaining HIV-infected subjects are projected to develop AIDS within a median time of approximately 10 years from initial infection (typical progressors). Data from the Multicenter AIDS Cohort Study suggest that 20 years after infection, 10 to 17% of HIV-infected individuals will be AIDS-free (*1*, *2*).

In this article, we consider recent progress in understanding immunologic and virologic characteristics of HIV-infected typical progressors, rapid progressors, and nonprogressors; summarize data on host genetic factors that may determine the effectiveness of immune responses to HIV; and summarize goals of future research.

Typical Progressors

In typical progressors, within weeks of HIV infection, viremia falls coincident with the induction of anti-HIV cellular and humoral immune responses (*3*). The fall in viremia correlates best with the appearance in peripheral blood of anti-HIV major histocompatibility complex (MHC) class I–restricted $CD8^+$ cytotoxic T cells (CTLs) (*3*).

During acute HIV infection there is oligoclonal expansion of V_β immunoglobulin families, predominantly restricted to $CD8^+$ T lymphocytes; within this population are contained HIV-specific CTLs (*4*). Mobilization of a restricted T cell receptor–for–antigen repertoire may be ultimately associated with a less effective immune response, thus facilitating persistence of HIV (*4*, *5*).

$CD8^+$ T cells are thought to be important in the immune response to HIV during the latent phase of HIV infection for the elimination of productively infected cells and for control of the viral load (*6*). However, HIV-specific $CD8^+$ CTLs may also be involved in the immunopathogenesis of HIV infection; they may contribute to the depletion of antigen-presenting cells either through a direct mechanism (that is, killing of the virus-expressing antigen-presenting cells) or indirectly through tissue damage after the release from CTLs of certain cytokines such as tumor necrosis factor α/β and interferon γ during the process of cytolysis (*5*, *7*–*10*). Nowak *et al.* have hypothesized that patients whose immune systems recognize fewer immunodominant HIV epitopes have a more stable and effective immune response to HIV than those whose CTL responses are against multiple, less dominant epitopes (*11*).

In addition to CTLs, neutralizing antibodies may be a component of the initial control of HIV replication (*12*, *13*). However, as HIV variants emerge over time, new variants frequently are not neutralized by autologous sera, and in some cases, antibodies against newly emerging HIV variants may enhance HIV replication in vitro (*12*, *13*), although the significance in vivo of enhancing antibodies is controversial (*13*). Heath *et al.* have reported that HIV virions coated with neutralizing antibody and attached to tonsillar follicular dendritic cells were still infectious for $CD4^+$ T cells (*14*). This study raised the important question of whether neutralizing antibodies can prevent dendritic cell–associated HIV infectivity in vivo. A randomized trial of passive immunotherapy of HIV-infected patients suggested that the administration of heat-inactivated plasma from HIV-infected individuals every 2 weeks for 1 year could slow the progression to AIDS in the recipients (*15*). Thus, antibodies appear to be involved in protective immunity against the progression of HIV infection, although the specificities of anti-HIV neutralizing antibodies that might be protective in patients remain unresolved.

Progression to AIDS is associated with generalized activation of the immune system, manifested by elevated serum concentrations of neopterin, soluble interleukin-2 receptor, soluble CD8, and β_2-microglobulin, and with activation of a large proportion of $CD8^+$ T cells (*4*, *7*, *8*, *16*, *17*). HIV-infected cells, circulating virions, and viral particles trapped in the follicular dendritic cell network of lymph node and spleen maintain chronic stimulation of the immune system.

Several components of generalized immune activation associated with HIV infection, such as stimulation of different T cell subsets and high levels of antibody production with specificities against a large range of epitopes of different HIV proteins, reflect the efforts of the immune system to control the replication and spread of the virus. However, as the disease progresses, both cell-mediated and humoral immune responses are severely impaired, resulting at least in part from the loss of the regulatory function of $CD4^+$ T lymphocytes and defective or increased production of either immunoregulatory or proinflammatory cytokines or both (*18*). Thus, as a consequence of the impaired regulation of both T and B cell functions, immune activation may ultimately become inappropriate and detrimental effects will predominate.

Rapid Progressors

Rapid progressors have a rapid decline in $CD4^+$ peripheral blood T cell levels, usually within 2 to 3 years after primary HIV infection (*1*, *2*). In general, rapid progressors are characterized by lower levels of antibodies to HIV proteins (*1*, *2*, *19*, *20*) and by low or absent antibodies that neutralize autologous HIV variants (*19*, *21*). High levels of antibodies that enhance the growth of autologous HIV isolates in vitro have been reported in rapid progressors (*22*). Levy *et al.* have found that noncytolytic $CD8^+$ T cell responses that suppress HIV replication are initially present and then decrease in rapid progressors (*23*). Two groups (*24*, *25*) have recently reported identification of

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$CD8^+$ T cell soluble factors that inhibit HIV replication (*23*). Baier *et al.* report that the anti-HIV $CD8^+$ T cell factor is IL-16 (*24*), whereas Cocchi and colleagues showed that $CD8^+$ cell–derived chemokines RANTES, MIP-1α, and MIP-1β synergized to suppress HIV replication (*25*). It will be critical to determine whether production of any of these cytokines is defective in rapid progressors. Others have found anti-HIV $CD8^+$ CTL activity in rapid progressors (*4, 26, 27*). Rinaldo *et al.* reported low levels of memory $CD8^+$ CTLs by precursor frequency analysis in rapid progressors compared with nonprogressors, although anti-HIV CTL effector cell activity was present in fresh peripheral blood cells from rapid progressors that was comparable with CTL activity in nonprogressors (*26*). Other characteristics of rapid progressors include elevated numbers of activated $CD8^+$ $CD38^+$ DR^+ T cells (*27*) and elevated serum markers of immune activation (*1, 2, 28*).

A uniform finding has been a high viral load in rapid progressors that does not fall dramatically after primary HIV infection (Table 1) (*28–32*). But an issue that has yet to be resolved is the amount of heterogeneity of the viral load. Both Delwart *et al.* and Wolinsky *et al.* found more homogeneity in HIV isolates in rapid progressors compared with typical progressors and nonprogressors, implying that the immune response to HIV is ineffective in rapid progressors and is incapable of driving HIV variant diversification (*33*). In contrast, Yu *et al.* found more viral heterogeneity in HIV isolates over time in rapid progressors (*34*).

Nonprogressors

Nonprogressors have high levels of $CD8^+$ $CD38^-$ CTLs (*23*), high peripheral blood $CD8^+$ MHC class I–restricted anti-HIV CTL levels that do not fall over time (*19, 35*), strong $CD8^+$ non-MHC–restricted HIV suppressor activity (*36, 37*), and high levels of antibodies to HIV (*19, 35, 38*). Several investigators have reported increased neutralizing antibodies to HIV or a wide breadth of cross-reactive neutralizing antibodies (or both) in nonprogressors (*19, 21, 35, 39*). Thus, neutralizing antibody levels may well be important for the control of HIV in nonprogressors, although the specificity of such salutary neutralizing antibodies is not known. Stable $CD4^+$ peripheral blood T cell levels are a hallmark of this group with low concentrations of serum and cellular markers of immune activation (*1,2, 27, 35*). Finally, in nonprogressors the structure and function of lymph node germinal centers are maintained and the follicular dendritic cells are preserved (*7, 8, 19*).

It has been proposed that cytolysis of HIV-infected antigen-presenting cells leads to early and severe immunosuppression and is crucial to AIDS pathogenesis (*40*). Zinkernagel and Hengartner have argued that in spite of in vitro cytolytic effects of HIV on susceptible T cell lines, HIV in vivo may not be a cytolytic virus, but rather induces profound $CD8^+$ T cell–dependent destruction of HIV-infected antigen-presenting cells and T cells (*41*). This hypothesis predicts that rare individuals will be able to eliminate HIV-infected cells with potent HIV-specific $CD8^+$ T cells (*41*). Similarly, if AIDS is primarily mediated through pathogenic CTL immune responses to HIV, then in this scenario an asymptomatic carrier state should exist in which there are high viral loads and essentially no anti-HIV $CD8^+$ T cell responses (*41*). The fact that recent data have demonstrated that the viral load is low and that anti-HIV CTL levels are generally high in nonprogressors argues against this latter hypothesis.

In contrast to rapid progressors, HIV variants in nonprogressors have been reported by some investigators to be diverse, suggesting that HIV variant heterogeneity may be a reflection of effective immune responses to HIV (*33*). Thus, in nonprogressors, it appears that immune responses are sufficently effective to maintain or at least markedly prolong the clinically latent phase of HIV infection.

There is also evidence that some nonprogressors are infected with constitutively less pathogenic or nonpathogenic HIV strains (Table 1). Thus, nonprogressors likely represent a heterogeneous group in whom host responses and the level of pathogenicity of the virus variably contribute to the state of nonprogression of HIV infection.

Multiply Exposed, HIV-Seronegative Individuals

Studies of individuals who have been exposed multiple times to HIV and are persistently HIV-seronegative have raised the possibility that, although these individuals show T cell responses to HIV proteins, a small percentage of them may be resistant to HIV, or may have been able to clear the infection without making antibodies to HIV (*37, 42, 43*).

Clues to the explanation of multiply exposed HIV-negative individuals comes from observations in rhesus macaques and chimpanzees of resistance to low doses of HIV or simian immunodeficiency virus (SIV) given intrarectally or intravaginally (*44*). Primate studies have suggested that there may be local cellular mucosal immune responses capable of protecting against low-dose mucosal HIV or SIV challenges (*44*). However, given the rapidity with which anti-HIV circulating CTLs arise in primary HIV infection of humans and yet do not usually prevent the development of AIDS (*3, 4*), and the fact that anti-HIV CTLs develop in vertically infected children without usually protecting against progression of HIV infection (*45*), complete clearance of HIV infection by HIV-specific CTLs (if it occurs at all) must be a rare event (*45*). The timing and regional location of the appearance of CTLs may be important. If CTLs develop after the initial dissemination of the virus, they may not be capable of curtailing the progression of disease, whereas if CTLs are present at the site of challenge, that is, the genital mucosa before virus dissemination as in the case of preimmunization, adequate control of infection may be achieved. Arguing against this latter point is the fact that SIVgag-immunized rhesus monkeys with no antibodies to SIV but with high levels of anti-SIVgag CTLs were not protected when challenged with intravenous SIVmnc in vivo (*46*). However, the intra-

Table 1. Characteristics of HIV in typical progressors, rapid progressors, and nonprogressors to AIDS.

Clinical course	Comments
Typical progressors	Monocytotopic homogeneous HIV strains are transmitted during primary infection (*58*).
	HIV isolates during the clinically latent stage are initially monocytotopic, nonsyncytium-inducing, slowly replicating variants (*29*).
	HIV isolates during progression to AIDS are frequently more rapidly replicating, T cell–tropic variants (*6, 29, 58*).
Rapid progressors	High viral load in primary HIV infection that generally does not fall dramatically to the levels seen with typical progressors (*28–32*).
	Rapid progressors have higher levels of unspliced HIV mRNA compared to nonprogressors or typical progressors (*31, 59*).
	Some rapid progressors may be infected with more rapidly replicating, virulent HIV strains (*29, 30*).
Nonprogressors	Viral load is generally lower in nonprogresors than in rapid progressors (*19, 29, 31, 32, 35*).
	Some, but not all, nonprogressors may be infected with constitutively less pathogenic HIV variants (*60, 61*).

venous nature of the challenge might have overcome any protection afforded by CTLs, whereas it is possible that these monkeys may have withstood a mucosal challenge.

Genetic Factors Implicated in Modulating Host Immune Responses to HIV Infection

The MHC class I and class II genes play a major role in determining the specificity of T and B cell antiviral immune responses. A number of MHC alleles as well as other host genetic factors have been described that may influence predisposition or protection against HIV infection or disease (Table 2).

There are several mechanisms whereby MHC-encoded molecules might predispose an individual to rapid or nonprogression to AIDS. First, having a certain MHC class I or class II allele could protect against HIV progression by serving as a restricting element for one or several immunodominant HIV T helper or CTL epitopes, thus promoting a salutary immune response to HIV and protection from progression to AIDS. Such a protective effect of the MHC class II E_{α}^{d} gene in the development of murine AIDS has been documented (*47*). Similarly, the lack of protective MHC alleles could predispose to developing AIDS because of a lack of salutary responses to HIV (*48*).

Second, having a certain MHC class I or class II allele could predispose an individual to pathogenic immune responses against a viral epitope in certain tissues such as the central nervous system or lungs, or against certain HIV-infected cell types such as monocyte (or macrophage) and dendritic cells. Similarly, the lack of an AIDS-promoting MHC allele would protect against pathogenic immune responses to HIV.

Third, having rare MHC class I and class II alleles could facilitate the rapid recognition of HIV-infected allogeneic cells during the early stages of HIV infection, thus promoting rejection of HIV-infected cells by means of alloreactive T cell responses (*49*). Sheppard and colleagues have shown that human sera from alloimmunized individuals neutralized HIV in vitro (*50*). Similarly, having common MHC alleles could promote less effective anti-HIV alloantigen responses and thus promote HIV infection or progression.

Fourth, human leukocyte antigen (HLA)–HIV disease associations are not absolute; thus, the data in Table 2 might reflect the association of genes linked to or within the MHC (*51*). For example, genetic markers linked to the *HLA-A1*, *CW7*, *B8*, and *DR3* haplotype, such as the complement C4 null allele (*C4AQO*) and a polymorphism in the tumor necrosis factor α promoter, have been suggested as MHC-linked gene candidates that might participate in a multigene effect on outcomes of HIV infection (*51*).

Fifth, the recent discovery that the level of MHC class I expression on virus-infected cells regulates the susceptibility of these cells to natural killer cell–mediated lysis provides a new area of investigation into the role of host MHC I genes in regulating the effectiveness of natural killer cell responses to HIV (*52*).

Finally, roles for transporter-associated with antigen-presenting (*TAP*) gene alleles have been proposed in determining the outcome after HIV infection (*48, 53*). Data have suggested that combinations of MHC-encoded *TAP* and class I genes may synergize either in providing certain salutary anti-HIV responses or in avoiding pathogenic anti-HIV immune responses, or both.

Table 2. Genetic factors implicated in modulating host immune responses to HIV infection.

Factor	Effect	Reference
	Major histocompatibility loci-encoded genes	
B35, C4, DR1, DQ1	Associated with Kaposi's sarcoma	(*62*)
DR1	Associated with Kaposi's sarcoma	(*51, 63*)
DR2, DR5	Associated with Kaposi's sarcoma	(*63*)
DR5	Associated with Kaposi's sarcoma	(*63*)
Aw23, Bw49	Associated with Kaposi's sarcoma	(*63*)
B62	Associated with fever, skin rash in primary HIV infection	(*51*)
Aw19	Associated with HIV seropositivity in HIV multiply exposed individuals	(*49*)
A1, A24, C7, B8, DR3	Associated with rapid progression to AIDS	(*51, 64*)
*DR4, DQB1*0302*	Associated with rapid progression to AIDS	(*65*)
DR3, DQ1	Associated with rapid progression to AIDS	(*66*)
B35	Associated with rapid progression to AIDS	(*51, 67*)
TAP2.1	Promotes HIV progression to AIDS	(*48*)
DR5	Associated with thrombocytopenia and lymphadenopathy in HIV infection	(*68*)
DR5, DR6	Association of diffuse infiltrative $CD8^+$ lymphocytosis with Sjogren's-like syndrome in HIV	(*69*)
Bw4	Associated with slow decline in $CD4^+$ cell numbers	(*65*)
*B13, B27, B51, B57, DQB1*0302,0303*	Protects from progression to AIDS	(*48*)
A26, B38, TAP1.4, TAP2.3	Associated with ability to clear HIV infection in transiently infected HIV-seronegative individuals	(*53*)
A28, Bw70, Aw69, B18	Associated with protection from HIV infection	(*49*)
A32, B4, C2	Associated with long-term survival in HIV infection	(*70*)
*A11, A32, B13, C2, DQA1*0301, DQB1*0302, DRB1*0400, DRB4*0101*	Associated with long-term survival in HIV infection	(*70*)
	Other genes	
p53 tumor suppressor gene	Controls HIV replicative patterns and determinant of viral latency	(*71*)
Unknown inherited trait	Associated with PB mononuclear cell resistance to HIV infection in vitro	(*72*)

Summary and Future Directions

A pattern is emerging that many nonprogressors to AIDS have an immune response to HIV that is quantitatively and qualitatively superior to anti-HIV immune responses that occur in HIV-infected individuals who rapidly progress to AIDS. The HIV load in peripheral blood mononuclear cells varies widely from patient to patient and generally increases within individual patients as the disease progresses (*32*). Recent studies now suggest that the cellular viral load level is established early on in HIV infection and is a predictor of the subsequent clinical course, with smaller viral loads after serconversion predicting longer survival (*32*). The initial key unanswered question is whether a small viral load after seroconversion in nonprogressors is related to low pathogenecity of the infecting HIV strain, to a particularly effective anti-HIV immune response, or to both. The answer to this question may not be the same for all patients.

A second important issue that must be explored quickly is that of the role of the host genetic background in determining the rate of progression of the clinical course. Though HIV proteins are of sufficient size to contain many immunogenic epitopes, HIV proteins contain strongly immunodominant regions, as well as a myriad of regions with sequence similarities to a wide spectrum of host proteins. Thus, it is critical to determine if MHC-encoded or other host genetic factors are responsible for a qualitatively more effective anti-HIV immune response in nonprogressors. If, in fact, nonprogressors are genetically programmed to successfully

control HIV, then immune reconstitution to rebuild a "better immune system" with allogeneic bone marrow and thymus grafts becomes a theoretical possibility.

Third, the need for determining the specificity of both CTL responses and protective neutralizing antibodies in nonprogressors is extraordinarily important for understanding both the biological basis of the nonprogressor status and the design of effective HIV vaccine immunogens. It is critical to determine the specificity of serum antibodies in nonprogressors that neutralize HIV primary isolates grown in peripheral blood mononuclear cells.

Fourth, the role of viral factors in determining nonprogressor status must be better understood. Although recent data demonstrated that *nef*-deleted mutants are not a common finding in nonprogressors (*61*), some investigators have found that HIV is more difficult to isolate from nonprogressors compared with typical progressors (*19*). The key question is whether a particular virus type or strain interacts with a particular host genotype to eventuate in nonprogressor status.

Fifth, the types of anti-HIV immune responses that are generated by small- and large-inoculum HIV infection through genital mucosa are critical to understand. More sensitive and inexpensive assays of HIV viral load are needed to determine the levels of HIV infection in various tissues. Studies are needed that profile mucosal and systemic immune responses to HIV after both genital and systemic routes of HIV infection, and that determine what immune responses are protective for systemic and genital challenges in animal models such as SIV infection of rhesus macaques.

Sixth, although the use of attenuated HIV strains as a vaccine remains controversial, attenuated SIV strains have protected adult rhesus monkeys against SIV challenge (*54*), and primary infection with HIV-2 may confer some protection against HIV-1 in humans (*55*). It is important to understand the correlates of protective immunity in these settings. Of note is the fact that although live-attenuated *nef*-deleted SIV is not pathogenic in adult rhesus monkeys, it may be pathogenic in neonatal animals (*56*). The immune and other factors in neonatal and adult rhesus monkeys that lead to protection in adults and to disease in neonates are critical to understand.

Finally, the role of pathogenic compared with salutary $CD8^+$ T cell responses to HIV in determining the various clinical courses of HIV infection must be defined. The role of $CD8^+$ T cell cytokines in suppression of HIV replication in long-term nonprogressors is particularly important to study. The fact that nonprogressors have high levels of anti-HIV CTLs strongly suggests that CTL responses to HIV may be important in the control of virus replication over time. However, the question of whether qualitative differences among anti-HIV CTLs, including the possibility of pathogenic effects, has not yet been resolved. Resolving this question is critical to HIV vaccine immunogen design and to the design of novel strategies to induce protective immune responses in those patients early in the clinical course of progression to AIDS. It has been hypothesized that CTL immune responses may be more effective if they are targeted at a major immunodominant epitope of HIV rather than at several less dominant regions (*11*). If this were true, it is possible that successful immunotherapy of a HIV-infected patient might boost the CTL response to a single conserved epitope, making it immunodominant by increasing the frequency of reacting T cells and inducing a more stable and effective CTL response (*11*). Such a trial of peptide-based immunotherapy has just begun in HIV-infected patients (*57*).

We are clearly entering a new era of understanding the pathogenesis of HIV infection and of appreciation of the novelty and complexity of the cellular and molecular mechanisms of HIV-host interactions. This new knowledge has reinforced the conviction that to develop effective anti-HIV drugs and vaccines, viral pathogenesis and the correlates of protective immunity must be understood.

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