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Host genetic determinants of HIV pathogenesis: an immunologic perspective

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Abstract

Purpose of review—The purpose of this review is to highlight recent advances in our understanding of host genetic determinants of HIV pathogenesis and to provide a theoretical framework for interpreting these studies in the context of our evolving understanding of HIV immunopathogenesis.

Recent findings—The first genome-wide association analysis of host determinants of HIV pathogenesis and other recent studies evaluating the interaction between killer cell immunoglobulin-like receptors and human leukocyte antigen alleles have implicated both adaptive and innate immune responses in the control of HIV replication. Furthermore, genetic variation associated with the expression of CCR5 and its ligand have been strongly associated with both decreased susceptibility to HIV infection and delayed clinical progression, independent of their effects on viral replication, suggesting a potential role for CCR5 inhibitors as immune-based therapies in HIV disease.

Summary—Host factors associated with the control of HIV replication may help identify important targets for vaccine design, while those associated with delayed clinical progression provide targets for future immune-based therapies against HIV infection.

Keywords

CCR5; HIV pathogenesis; HLA; host genetic variation; KIR

Introduction

The past decade has seen a dramatic expansion in our understanding of the host genetic determinants of HIV pathogenesis. The recent mapping of the human genome enabled the first genome-wide analysis of polymorphisms associated with the control of HIV replication and disease progression earlier this year [1^{**}]. Furthermore, advances in our understanding of receptor-ligand interactions through in-vitro studies and animal models have facilitated ‘next generation’ candidate gene analyses that evaluate biologically important interactions between genes [2,3,4^{**}]. Ultimately, insights from such studies may help identify targets for both vaccine development and immune-based therapeutics. The purpose of this review is to highlight these recent advances, and to provide a theoretical framework for interpreting these studies in the context of our evolving understanding of HIV immunopathogenesis.

The germane outcome: viral control or clinical progression or both?

One important consideration for studies evaluating host genetic determinants of HIV pathogenesis is whether to choose plasma HIV RNA level or progression to AIDS as a primary outcome of interest and pertinence. These two outcomes are not independent in that higher plasma HIV RNA levels during early HIV infection strongly predict rapid clinical progression to AIDS and death [5], explaining up to 50% of the variability in time to AIDS [6*]. A few patients, however, have been shown to maintain clinically undetectable plasma HIV RNA levels in the absence of antiretroviral therapy ('elite' controllers) while still progressing to AIDS [7,8,9*], whereas others with high plasma HIV RNA levels may maintain normal CD4+ T cell counts and remain healthy for years in the absence of antiretroviral therapy [10*,11]. Thus, host factors independent of the level of viral replication can contribute to HIV disease progression.

Given this distinction between the control of viral replication and clinical progression to AIDS, the most appropriate outcome for genetic association studies really depends on the ultimate goal of the research. If the focus is on host determinants of viral control to inform vaccine design, then plasma HIV RNA set-point is probably the most relevant outcome. Conversely, if the goal is to identify host targets for immune-based therapies for patients with persistent immunodeficiency despite treatment-mediated viral suppression, then clinical progression is a more relevant outcome. By assessing both outcomes concurrently, one can begin to discern whether factors associated with delayed clinical progression are mediated through the control of viral replication, independent mechanisms, or both. We will use this framework to interpret recent developments in the host determinants of HIV pathogenesis throughout this review.

Host determinants of viral control

Perhaps the most consistent host factor associated with the control of HIV replication and disease progression in prior candidate gene analyses is the human leukocyte antigen (HLA) allele B*57 [12–18]. These studies were further validated by the first genome-wide analysis of host polymorphisms associated with viral control and clinical progression, published earlier this year [1**]. In this study, Fellay *et al.* [18,19] used a chip containing over 550 000 single nucleotide polymorphisms (SNPs) spanning the genome to identify SNPs associated with lower plasma HIV RNA level set-points among 486 recently HIV-infected patients from the multisite EuroCHAVI cohort. Among all evaluable SNPs, the SNP most strongly associated with low plasma HIV RNA set-point was the HLA-complex P5 (HCP5) gene, which is in virtually complete linkage disequilibrium with the HLA allele B*5701. B*5701 has long been associated with the ability to maintain clinically undetectable plasma HIV RNA levels in the absence of antiretroviral therapy. Furthermore, viral escape from B*57-restricted cytotoxic T cell responses results in a poorly fit virus, which reverts in the absence of B*5701 pressure [20,21]. These observations have suggested that enhanced CD8+ T cell control of HIV replication is a major mechanism mediating this association [18].

Several lines of evidence suggest that the association between the HLA B*57 allele and clinical progression may also be mediated in part by mechanisms other than cytotoxic T cells. For example, B*57 is associated with lower plasma HIV RNA levels and fewer symptoms during acute HIV infection, prior to the development of adaptive HIV-specific T cell responses [17]. Furthermore, many B*57+ individuals fail to control HIV replication despite the absence of HLA-B*57-specific epitope escape mutations [22]. HLA B*57+ individuals controlling viral replication may also continue to control viral replication even after the emergence of HLA B*57-specific escape mutations [23].

One possibility supported by a growing body of evidence is that the HLA B*5701 allele is associated with a stronger innate immune response against HIV. Natural killer cells are tightly regulated by an array of both activating and inhibitory killer immunoglobulin-like receptors (KIRs), whose target cell ligands are HLA-class I molecules. Loading of viral-derived peptides into an HLA-class I molecule may modulate its binding to an activating KIR, resulting in natural killer cell activation, target cell lysis and inflammatory cytokine elaboration, all contributing to the control of viral replication (Fig. 1a). In a recent analysis of data from five natural history cohorts from the pre-highly active antiretroviral therapy (HAART) era, Martin *et al.* [3] found that in the absence of its presumed HLA ligand, homozygosity of the activating KIR3DS1 allele is associated with rapid progression to AIDS and death. In the presence of its presumed HLA ligand, however, HLA-B Bw4-80I (a group of HLA alleles that includes B*57), KIR3DS1 is associated with significantly delayed clinical progression and decreased susceptibility to opportunistic infections (Fig. 1b) [3,24*]. The interaction between KIR3DS1 and HLA-Bw4-80I also appears to be associated with lower plasma HIV RNA levels, suggesting that a stronger natural killer cell response to HIV results in improved control of viral replication [24*]. While this protective KIR3DS1 and HLA-Bw4-80I interaction has not been observed for other types of outcomes in two clinically distinct cohorts [25,26], functional data show that natural killer cells isolated from KIR3DS1+/HLA-Bw4-80I+ individuals suppress HIV replication in autologous CD4+ T cell cultures much more efficiently than natural killer cells from donors who are missing this specific compound genotype [27**], suggesting that the protective KIR3DS1 and HLA-Bw4-80I mediates its effect through improved natural killer cell-mediated control of HIV replication.

While the KIR3DS1/HLA-Bw4-80I interaction suggests that activation of natural killer cells results in delayed clinical progression in HIV-infected individuals, recent evidence also suggests a role for inhibitory KIRs in delaying progression to AIDS. The presence of KIR3DL1 alleles encoding highly expressed, highly inhibitory KIR3DL1 allotypes along with their cognate HLA-Bw4 ligands (including B*5701) is also strongly associated with both control of plasma HIV RNA levels to below 2000 copies/ml (an identified target for vaccine studies) and delayed progression to AIDS and death in the absence of therapy (Fig. 2a) [4**]. Why would a highly inhibitory KIR allele be associated with viral control and delayed clinical progression when previous data indicate that activation of natural killer cells is protective against HIV? Recent studies have suggested the concept that receptor–ligand pairings associated with strong natural killer cell inhibition under homeostatic conditions will be associated with stronger effector cell responses when the interaction between that inhibitory receptor and its ligand is lost, for example upon viral infection [28–32]. Thus, natural killer cells expressing strongly inhibitory KIR3DL1 subtypes are predicted to confer more vigorous effector cell responses than weakly inhibitory KIR3DL1 subtypes when the Bw4 ligand is downregulated by HIV nef or altered in a manner such that KIR3DL1 no longer recognizes it (Fig. 2b). Ongoing phenotypic and functional studies will be necessary to prove these mechanisms.

HLA B alleles may not be the only class I alleles associated with control of viral replication. For example, a SNP in the HLA-C promoter region is also associated with viral control even after adjustment for other HLA alleles associated with viral control including B5701 [1**]. This SNP was previously associated with HLA-C expression levels [33], suggesting some biological plausibility. There are at least two mechanisms by which this association may be explained. The HLA-C SNP might be associated with increased cytotoxic T cell-mediated control since HLA-class C-restricted HIV epitopes have been defined and appear to be capable of inducing cytotoxic T cell mediated lysis [34]. While the HIV accessory protein nef may help evade cytotoxic T cell responses by decreasing HLA A and B expression in infected cells, it has no effect on HLA-C expression, so these HLA-C-restricted T cell

responses may be particularly important *in vivo* [35]. Another potential explanation for the HLA-C association with viral control relates to its interaction with natural killer cells. HLA-C allotypes also serve as the ligands for activating and inhibitory KIRs on the surface of natural killer cells and could presumably modify the ability of natural killer cells to lyse HIV-infected cells. Indeed, some combinations of HLA-C and KIR alleles have been associated with resistance to HIV infection in cohorts of highly exposed individuals, presumably as a consequence of a higher natural killer cell activation state [36,37].

It is also noteworthy that while strongly associated with plasma HIV RNA set-point, the HLA-C SNP was not significantly associated with clinical progression in the EuroCHAVI cohort. This might simply reflect methodological issues. Since this genome-wide analysis was performed on a modern cohort of HIV-infected individuals who often initiate antiretroviral therapy before they are at significant risk for AIDS, clinical progression was defined as the time to treatment initiation or time to an estimated CD4 count under 350 cells/mm³ (often projected by an individual's calculated slope of CD4 decline). This may not be a particularly accurate or precise measure of disease progression since the decision to start antiretroviral therapy may be influenced by factors unrelated to immunodeficiency (i.e., patient choice and readiness to start). Patient-specific CD4 slope is also an imprecise measure, poorly correlated to clinical progression to AIDS [6]. Thus, failure to detect an association between HLA-C SNPs and clinical progression may simply reflect poor accuracy and precision of the outcome measurement. Repeating this analysis using samples from pre-HAART era natural history cohorts that have directly measured the rate of clinical progression to AIDS would address this possibility.

Biologic factors might also explain how some polymorphisms, particularly those associated with stronger innate immune responses, could have beneficial effects on viral replication without discernable effects on clinical progression. For example, strong innate immune responses likely help control HIV replication directly through natural killer cell-mediated lysis or indirectly as adjuvants for HIV-specific B and T cell responses [38,39], delaying clinical progression. These same innate immune responses, however, may also result in the 'unintended' negative consequences of generalized immune activation and bystander T cell apoptosis [40,41], contributing to more rapid disease progression and counteracting their beneficial effects on viral control. This paradox is perhaps best illustrated by our recent observation that HIV-infected 'elite' controllers who maintain undetectable plasma HIV RNA levels in the absence of antiretroviral therapy occasionally experience CD4+ T cell depletion and progression to AIDS, an effect strongly associated with abnormally high T cell activation levels [9]. These potentially negative consequences of the innate immune response in HIV pathogenesis are further supported by the observation that sooty mangabeys and African green monkeys have attenuated innate immune responses to SIV infection, minimal increases in T cell activation despite high levels of SIV replication, and rarely progress to immunodeficiency and AIDS [42,43]. Thus, the balance between positive and negative effects of the innate immune response may explain why some factors like the recently described SNP in the HLA-C promoter region can have significant effects on viral control without significant effects on clinical progression.

Host factors affecting HIV progression independent of viral replication

While most protective host factors presumably mediate their effects by decreasing HIV replication, some genetic factors are associated with delayed clinical progression independent of plasma HIV RNA levels. These factors may be less important for the purposes of vaccine development, for which the control of HIV replication is the outcome of interest, but their independent effects on clinical progression make them particularly important targets for immune-based therapies. The most extensively studied factor in this

category is the CCR5 $\Delta 32$ mutation. Associated with a nonfunctional HIV co-receptor CCR5, this mutation dramatically decreases the risk of acquiring HIV infection among individuals homozygous for the mutation [44–46], and delays clinical progression in heterozygous individuals [44,47–51]. In addition to the genetic determinants of CCR5 expression, more recent work suggests that higher CCL3L1 gene copy numbers (encoding the natural ligand of CCR5, MIP-1 α) further decrease the risk of HIV acquisition and delay clinical progression in HIV-infected individuals [2]. While decreased CCR5 and increased MIP-1 α expression likely blocks HIV from entering target cells, thereby decreasing viral replication, these genes also appear to have beneficial immunologic effects independent of their effects on viral replication. For example, adjustment for plasma HIV RNA levels only partially attenuates the relationship between CCR5 $\Delta 32$ heterozygosity and delayed clinical progression [52]. Furthermore, groups of polymorphisms associated with decreased CCR5 expression and higher CCL3L1 copy numbers are associated with improved cell-mediated immune responses to vaccines and immunogens in HIV-negative individuals and delayed clinical progression in HIV-infected individuals even after adjustment for plasma HIV RNA levels [53**].

These viral load-independent effects might relate to the fact that CCR5 has other functions besides its role as an HIV co-receptor. Since CCR5 is also a mediator of chemotaxis [54], decreased CCR5 availability might decrease T cell trafficking to inflamed mucosal and lymphoid tissues, reducing both target cell availability and bystander T cell death at sites of highest HIV replication. CCR5 signaling may also facilitate cellular activation directly [55], potentiating activation-induced apoptosis, a central feature of HIV pathogenesis. This latter mechanism is supported by the observation that the natural hosts of nonpathogenic SIV infection, which exhibit very low levels of T cell activation despite high levels of viral replication, consistently express extremely low levels of CCR5+ CD4+ T cells [56,57]. These coreceptor-independent functions of CCR5 might also explain why a recently FDA-approved CCR5 inhibitor significantly increases CD4+ T cell counts in HIV-infected individuals harboring drug-resistant CXCR4-using viruses despite negligible effects on plasma HIV RNA levels [58]. This clinical study further demonstrated how insights from the host genetic determinants of HIV disease progression can be translated into potential immune-based therapeutics.

Other host polymorphisms associated with delayed HIV disease progression recently identified include polymorphisms in the ring finger protein 39 (RFP39) and the zinc ribbon domain containing 1 gene (ZNRD1) [1**]. While the function of RFP39 is unknown, ZNRD1 encodes an RNA polymerase subunit, so could conceivably be involved in the inhibition of HIV transcription. Neither of these genes, however, was strongly associated with plasma HIV RNA level set-point in the EuroCHAVI cohort, so if these genes truly modify HIV pathogenesis, the mechanism is unlikely to be solely mediated by the inhibition of viral replication. Replication of these findings in other natural history cohorts and further characterization of the function of these genes will be necessary to confirm the importance of these genes in HIV pathogenesis.

Conclusion

In conclusion, recent genetic association studies have identified several novel host determinants of HIV pathogenesis. The HLA B*57 allele, HLA-C gene polymorphisms, as well as HLA/KIR interactions are all strongly linked to the control of viral replication, implicating a role of both the adaptive and innate immune systems in the control of HIV replication and suggesting potential targets for future vaccine development. Furthermore, genes associated with the expression of CCR5 and its ligand have been strongly associated with both decreased susceptibility to HIV infection and delayed clinical progression,

independent of their effects on viral replication, suggesting a potential role for CCR5 inhibitors as immune-based therapies in HIV disease. Future functional studies will be needed to fully characterize these mechanisms and translate these associations into clinically useful interventions.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 411–412).

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Figure 1. Protective effect of *KIR3DS1*+ *HLA-B Bw4-80I* on AIDS progression

(a) Model illustrating the possible mechanism for the protective effect of *KIR3DS1*+*Bw4-80I* against HIV. In the presence of a normal target expressing normal levels of human leukocyte antigen (HLA)-Bw4 with self peptide sitting in its peptide binding groove, there is no interaction with KIR3DS1 and therefore no natural killer (NK) cell activation (upper cartoon). Conversely, KIR3DS1 may recognize HLA-Bw4 on an HIV-infected target, potentially because of lower expression of HLA-Bw4 or alterations in the HLA molecule, such as viral or self-stress peptides sitting in the peptide-binding groove. Binding of KIR3DS1 to altered HLA-Bw4 results in natural killer cell activation and killing of the infected target. (b) Kaplan-Meier survival analysis comparing the effects of *KIR3DS1* and *Bw4-80I* (solid line) versus individuals homozygous for *HLA-Bw6* (*Bw6/Bw6*; dotted line) using Cox proportional hazards model. Relative hazard=0.53, $P<0.001$.

Figure 2. Protective effect of *KIR3DL1*H*Y* + *HLA-B Bw4-80I* on AIDS progression

(a) Effect of *KIR3DL1*+*HLA-B* genotypes on progression to AIDS. Kaplan–Meier survival curves showing the effect of high (*KIR3DL1*H*Y*) and low (*KIR3DL1*I*x*) expressing *KIR3DL1* alleles in combination with *Bw4-80I* on survival relative to the *Bw6/Bw6* comparison group, which is not recognized by *KIR3DL1* allotypes. The *KIR3DL1*H*Y* group includes individuals with *KIR3DL1*H*H* or *KIR3DL1*H*004* (*KIR*004* is not expressed on the cell surface) and the *KIR3DL1*I*x* group includes individuals with *KIR3DL1*I*I* or *KIR3DL1*I*H* or *KIR3DL1*I*004*. (b) Model for how expression levels of *KIR3DL1* could affect strength of natural killer (NK) cell activation. *KIR3DL1*H* allotypes are expressed at a higher density per cell and on a greater number of natural killer cells relative to *KIR3DL1*I* allotypes. On the left, natural killer cells that are strongly inhibited by *KIR3DL1* receptors in response to a normal target will respond strongly to an HIV infected target when the ligand for the inhibitory *KIR3DL1* ligand is lost on the target. On the right, natural killer cells that are only weakly inhibited by alternative *KIR3DL1* allotypes will respond weakly to an infected target when the ligand for the weak inhibitory *KIR3DL1* ligand is lost. Thus, the larger the contribution of receptor–ligand pairing to natural killer cell inhibition under ‘normal’ conditions, the more vigorous an effector cell response will be when the interaction between that inhibitory receptor and its ligand is disrupted. — *Bw6/Bw6*; — *Bw4-80I+3DL1*I*x*; — *Bw4-80I+3DL1*H*H*. Strong activation: V, activating receptor; ▲, activating receptor ligand; =, class I ligand. Weak activation: ∅, 3DL1*H; ∅, 3DL1*I.