Host Genes Important to HIV Replication and Evolution

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Recent years have seen a significant increase in understanding of the host genetic and genomic determinants of susceptibility to HIV-1 infection and disease progression, driven in large part by candidate gene studies, genome-wide association studies, genome-wide transcriptome analyses, and large-scale in vitro genome screens. These studies have identified common variants in some host loci that clearly influence disease progression, characterized the scale and dynamics of gene and protein expression changes in response to infection, and provided the first comprehensive catalogs of genes and pathways involved in viral replication. Experimental models of AIDS and studies in natural hosts of primate lentiviruses have complemented and in some cases extended these findings. As the relevant technology continues to progress, the expectation is that such studies will increase in depth (e.g., to include host whole exome and whole genome sequencing) and in breadth (in particular, by integrating multiple data types).

Host genetics has been of considerable interest to the field of HIV/AIDS since the identification of the role of CCR5 Δ 32 (Dean et al. 1996; Huang et al. 1996; Liu et al. 1996) in resistance to infection and of human leukocyte antigen (HLA) alleles in disease progression (Kaslow et al. 1996). Further observations confirm that there is a significant component of heredity in the susceptibility to HIV-1. Identical twins infected with the same viral strain progressed at a similar pace, whereas their fraternal twin had a different clinical course (Draenert et al. 2006). In vitro, the study of cells from large pedigrees—immortalized B lymphocytes from multigeneration families—

allowed the identification of a host genetic contribution to >50% of the observed differences in cell susceptibility to transduction with a vesicular stomatitis virus (VSV)-pseudotyped HIV-1 vector (Loeuillet et al. 2008). In the larger context of infection by simian immunodeficiency viruses, host genetic variation influences transmission between species as well as replication and pathogenesis within individuals of the same species (Kirmaier et al. 2010). Host genetic variation includes fixed differences between species (divergence) and variation within populations (polymorphism). Genetic barriers to viral transmission and spread can arise owing to variation in genes required

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for optimal viral replication (e.g., receptors, transcription factors, chaperones, etc.) as well as variation in genes that actively thwart viral replication and pathogenesis (e.g., innate and adaptive immune effectors such as antibody and cytotoxic T lymphocyte (CTL) responses, and restriction factor loci such as *TRIM5α*, the *APOBEC3* cluster, and *tetherin*). The influence of host selection on viral evolution manifests as changes in primary sequence (escape and reversion variants) in the viral genome structure, and over the long term, in the acquisition of accessory functions. In this article, we begin with an overview of the current understanding of genes and gene variants influencing susceptibility to HIV-1 in humans, and susceptibility to HIV/simian immunodeficiency virus (SIV) in nonhuman primate models of infection. This includes data from candidate gene studies, genome-wide association studies, and other genome-wide screens. We then analyze notable data on host genome pressure on the viral genome structure. Finally, we present a global view on the evolutionary genomics of susceptibility to HIV-1 and other retroviruses.

KEY ADVANCES

Human Genomics

Genome-Wide Association Studies

The HIV field was one of the first to embrace the opportunities offered by new technologies that allowed genome-wide association studies (GWASs). This approach, which assesses 500,000 to 1 million genetic variants (single nucleotide polymorphism, SNP) for each individual, had advantages and limitations (Telenti and Goldstein 2006). First, it allowed for the first time the non-a priori analysis, at genome-wide scale, of possible genetic determinants of a trait. This would allow discovery, unbiased validation of all previously reported variants, and scoring the contribution of the genetic variant in the context of other possible genome influences. However, the limitations of the approach include the need for sufficient power, requiring large numbers of subjects, and the identification

of very precise study traits (Evangelou et al. 2011). In addition, only common variation (present in >5% in a given population) is investigated in GWASs. The need for large populations (power) is determined by the statistical requirements that impose a very strict threshold of significance (i.e., defined by $P < 5 \times 10^{-8}$ owing to correction for multiple comparisons) and by the limited contribution of any given genetic variant to the population phenotype. The study traits need to be defined by strict criteria to avoid heterogeneity in the phenotype—an important consideration because the field uses study outcomes, such as time to AIDS or death, which represent composite end points. Finally, the genotyping arrays used in GWASs target common variants that tag other variants; the actual causal variant or functional polymorphism is unlikely to be interrogated directly. Current arrays are generally adequate to capture common variation in Caucasians and Asians, although less effective in individuals of African ancestry.

Eight GWASs have been published during the period 2007–2010 (Table 1). The first study (Fellay et al. 2007) investigated the genomic determinants of viral set point after seroconversion—the relatively steady state of viral replication in the 3 years following a documented infection. As a secondary end point, the study evaluated disease progression, as defined by time to CD4⁺ T-cell count less than 350 cells/μL, or else initiation of treatment. This study identified three variants in chromosome 6: a variant in *HCP5* that tagged the protective allele *HLA-B*5707*, a variant upstream of *HLA-C* associated with difference in HLA-C expression levels, and a variant in *ZNRD1* that may be merely associated with other influences from the major histocompatibility complex (*MHC*) locus, or contribute directly to pathogenesis (Ballana et al. 2010). Extension of this work by the same group of researchers (Fellay et al. 2009) confirmed the various associations and ruled out major variants elsewhere in the genome with the exception of those in the *CCR5-CCR2* locus (Fig. 1). The overall variance explained by the genome-wide significant hits was close to 20%—much larger than what has

Table 1. Genome-wide association studies, 2007–2010

Study/year	Trait	N	Population	Genome-wide significant hits ^a	Comment
Fellay et al. 2007	Viral load set point, disease progression	486 (seroconverters)	Caucasian	rs2395029 (<i>HCP5/HLA-B*57:01</i>), rs9264942 (<i>HLA-C</i>), rs9261174 (<i>ZNRD1</i>)	
Dalmasso et al. 2008	Plasma HIV-RNA levels and cellular HIV-DNA levels	605 (seroconverters)	Caucasian	rs10484554, rs2523619, and rs2395029 (<i>HLA-C</i> , <i>HLA-B</i> locus)	
Limou et al. 2009	HIV nonprogression	275 (HIV-1 ⁺ nonprogressors), and 1352 (negative controls)	Caucasian	rs2395029 (<i>HCP5/HLA-B*57:01</i>)	Subset study (Limou et al. 2010) used to validate candidate rs2234358 (<i>CXCR6</i>) in three independent cohort studies ($n = 1028$)
Le Clerc et al. 2009	Rapid disease progression	85 (HIV-1 ⁺ rapid progressors), and 2049 (negative controls)	Caucasian	–	
Fellay et al. 2009	Viral load set point, disease progression	2554 (seroconverters and seroprevalent)	Caucasian	rs2395029, rs9264942, rs259919, rs9468692, rs9266409 (<i>MHC</i> locus), and rs333(<i>CCR5Δ32</i>)	Failed to validate previously reported candidate genes with the exception of <i>CCR5/CCR2</i> variants
Herbeck et al. 2010	Disease progression	156 (rapid, moderate, and nonprogressors)	Caucasian	–	Among the 25 top-ranking variants, rs17762192 (<i>PROX1</i>) was validated in an independent replication cohort of 590 seroconverters
Pelak et al. 2010	Viral set point	515 (seroconverters)	African American	<i>HLA-B*57:03</i> (rs2523608)	In contrast with the tagged <i>HLA</i> , rs2523608 does not reach genome-wide significance
International HIV Controllers Study 2010	HIV nonprogression	974 (HIV controllers), 2648 (HIV progressors)	Caucasian, African American, and Hispanics	313 SNPs in the <i>MHC</i> locus captured by rs9264942, rs2395029, rs4418214, and rs3131018 as independent markers	Arg97, Cys67, Gly62, and Glu63, all in <i>HLA-B</i> ; Ser77 in <i>HLA-A</i> ; and Met304 in <i>HLA-C</i> collectively explain 20% of the observed variance in Caucasians

^aVaries between $p < 10^{-7}$ and $p < 10^{-8}$ depending on the study design.

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Figure 1. Distribution of the protective alleles according to viral or clinical phenotypes. The bar graphs show the allelic distribution of three variants that have a genome-wide significant association with HIV-1 set point (left-hand-side graphs) and disease progression (right-hand-side graphs) in a population of 2362 HIV-infected individuals. The data on *HCP5*, a perfect tag of *HLA*B57:01*, illustrate the nature of the association between protective alleles and long-term nonprogression: although 31%–37% of elite controllers carry *HLA*B57:01*, only 6%–22% of *HLA*B57:01* carriers are elite controllers. (Adapted, with permission, from Fellay et al. 2009; reprinted, with permission, from *PLoS Genetics* © 2009.)

been observed in GWASs of other diseases or in studies of anthropomorphic diversity (height, weight) but still a small percentage of the total. Although the overwhelming message is one of confirmation of the critical importance of the *HLA-B/HLA-C* locus, some studies have reported additional candidate loci (Table 1).

A significant step forward in the understanding of the complexity of signals emerging from the *MHC* locus came from the International HIV Controllers Study (2010). This large consortium compared the genetic data of 974 subjects defined as viral controllers and 2648 progressors. After an initial step that confirmed the critical importance of the *MHC* region in the trait of nonprogression, the study proceeded to mapping putative causal variants within the *HLA* locus. This step is complex because this gene-rich region has high levels of genetic diversity and a complex pattern of linkage disequilibrium. The linkage disequilibrium reflects the measurement of nonrandom association between two or more alleles that occur together on a chromosome. The International HIV Controllers Study developed analytical tools that specified unique residues in the *HLA-B* groove as putative causal variants. These included Gly62, Glu63, Cys67, and Arg97, all in *HLA-B*. In addition, the study identified Ser77 in *HLA-A* and Met304 in *HLA-C*. With the exception of Met304 in the transmembrane domain of *HLA-C*, these residues are all located in the *MHC* class I peptide binding groove, underscoring that the conformational presentation of class I restricted epitopes to T cells play a key role in host control. Chimpanzees can be infected with HIV-1; however, most do not develop AIDS. The contemporary *MHC* class I repertoire of chimpanzees targets analogous conserved domains of HIV-1/SIV_{cpz} to those targeted by human protective alleles *HLA-B*57* and *B*27*, in particular, of the Gag protein (de Groot et al. 2010). The functional characteristics of the chimpanzee *MHC*-repertoire may be the result of a selective sweep caused by lentiviruses (de Groot et al. 2010). The consistent identification of *HLA-B*57*, *HLA-B*27*, and *HLA-B*51* in host genome studies is attributed to fitness cost of mutating in the targeted viral

epitopes and to the patterns of viral escape from CD8⁺ T-cell recognition. Differences in prevalence of the restricting *HLA* allele in different human groups consequently lead to HIV-1 adaptation to *HLA* at a population level (Kawashima et al. 2009).

Following the completion of the GWASs mentioned above, the field is planning a joint meta-analysis of all available data sets combining information presented in Table 1 and new GWASs. This approach can address issues of insufficient power and thus facilitate the identification of common variants that would be associated with smaller effects, or more rare variants included in the typing arrays. Follow-up of GWASs includes resequencing and functional analysis of the main hits and putative causal variants. This has been performed for *HCP5* (Yoon et al. 2010), *HLA-C* (Thomas et al. 2009), and *ZNRD1* (Ballana et al. 2010) hits. Of particular interest is the recent work that identifies the –35 SNP in *HLA-C* as a marker of variation at the binding of microRNA Hsa-miR-148a to its target site within the 3' untranslated region of *HLA-C* (Kulkarni et al. 2011). This mechanism of posttranscriptional regulation results in relatively low surface expression of alleles that bind this microRNA and high expression of *HLA-C* alleles. The exact role of the individual *HLA-B* amino acids identified by the International HIV Controllers Study on epitope presentation, T-cell receptor binding, and CTL activity is the subject of intensive research in the field.

Vaccine Genomics

A particularly attractive use of GWASs is in the understanding of differences between individuals in the response to immunogens. Although vaccine genomics is in its infancy, some initial applications have been reported. A GWAS assessed determinants of HIV-specific T-cell responses to the MRKAd5 HIV-1 gag/pol/nef vaccine (Fellay et al. 2011) tested in 831 subjects of the Step HIV-1 vaccine trial, as measured by IFN- γ ELISpot assays. No genetic variant reached genome-wide significance, but polymorphisms located in the *MHC* showed the

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strongest association with response to the HIV-1 Gag protein. HLA-B alleles known to associate with differences in HIV-1 control were found to be responsible. The authors concluded that the host immunogenetic background needs to be considered in the analysis of immune responses to T-cell vaccines. Increasingly, vaccination studies will include host genetic analysis, informed consent, and DNA storage for later analysis.

Vaccine genomics can also address the selective pressure from vaccine-induced T-cell responses on HIV-1 infection in humans. Rolland et al. (2011) analyzed HIV-1 from 68 infected volunteers in the STEP trial to identify signatures distinguishing vaccine from placebo recipients. Gag amino acid 84, a site encompassed by several epitopes contained in the vaccine and restricted by HLA alleles common in the study cohort, was identified by this approach. Viral genome regions excluded from the vaccine components did not carry distinctive signatures of selective pressure from vaccine-induced T-cell responses on HIV-1 infection in humans.

Advanced Genome Analyses

Although the platforms and analytical tools for genome-wide genotyping are well established, it is clear that the GWAS approach will not capture some aspects of the host influence on the pathogenesis of HIV infection. Additional types of data include the transcriptome and proteome of the infected cell or individual. Further techniques use evolutionary and comparative genetic tools for the identification of host genes involved in genetic conflicts with lentiviral or retroviral pathogens, or large-scale functional genomics using loss-of-function (siRNA) and gain-of-function screens (Bushman et al. 2009; Telenti 2009).

Expression analyses have generated a collection of data from *in vitro* and *in vivo* studies on cell lines, whole blood, and cellular subsets. Many publications were based on earlier technologies interrogating small gene subsets, were limited by the number of samples, and rarely captured the dynamic nature of the transcriptome (Giri et al. 2006). Globally, this body of literature has described a number of features

of the infectious process that massively modulates the antiviral defense systems (the interferon response, including the antiretroviral intrinsic cellular defense apparatus), as well as genes involved in the cell cycle and degradation/proteasome pathway (Rotger et al. 2010). Particularly relevant is the observation that elite controllers have CD4⁺ T-cell transcriptome profiles that are similar to those from individuals receiving effective treatment (Rotger et al. 2010). The transcriptome profile of a subset of elite controllers is indistinguishable from that of the uninfected individuals—at least in HLA-DR-CD4⁺ T-cell subsets that were the object of a recent study (Vigneault et al. 2011).

Increasingly, studies are successfully using expression data to single out genes for functional analyses. Notable examples include observations on SOCS1 (Rotger et al. 2011), BATF (Quigley et al. 2010), and CXCR6 (Paust et al. 2010) that originated in transcriptome analyses. The suppressor of cytokine signaling 1 (SOCS1) suppresses interferon signaling by direct binding to phosphorylated type I interferon and active JAK kinase and by orchestrating the events leading to proteasomal degradation of a number of target proteins. Although viruses such as HTLV-1 may use induction of SOCS1 to evade the antiviral effects of interferon signaling, it is differentially up-regulated in the nonpathogenic primate models (Bosinger et al. 2009; Jacquelin et al. 2009; Lederer et al. 2009) and in HIV-1 infected humans that tolerate high levels of viral replication and do not progress (Rotger et al. 2011). The basic leucine transcription factor, ATF-like (BATF), a transcription factor in the AP-1 family, was identified during the study of exhausted CD8⁺ T cells. PD-1 coordinately regulates a program of exhaustion genes in humans and mice, including up-regulation of BATF. Silencing BATF in T cells from individuals with chronic viremia rescues HIV-specific T-cell function (Quigley et al. 2010). The third example, CXCR6, emerged from the study of natural killer (NK) cells in mice (Paust et al. 2010). Hepatic NK cells, but not splenic or naive NK cells, develop specific memory of vaccines containing antigens from HIV-1 and other viruses (Paust et al. 2010).

NK cell memory depends on CXCR6, a chemokine receptor on hepatic NK cells that is required for the persistence of NK memory.

Additional efforts are also directed at comparative transcriptomics, which is the cross-species analysis of expression patterns of human and nonhuman primates during infection and disease (Rotger et al. 2011). HIV-infected subjects with rapid disease progression have gene expression patterns in CD4⁺ and CD8⁺ T cells similar to that in pathogenic SIV infection of rhesus macaque (Fig. 2). In contrast, humans that do not progress despite prolonged and extreme levels of viral replication share transcriptional features with the sooty mangabey model of natural infection, including a common profile of regulation of a set of genes that includes *CASP1*, *CD38*, *LAG3*, *TNFSF13B*, *SOCS1*, and *EEF1D* (Rotger et al. 2011).

Next-generation sequencing offers an unprecedented opportunity to jointly analyze cellular and viral transcriptional activity. This approach served to show that at peak infection of SupT1 cells—a T-cell line—one transcript in 143 is of viral origin (0.7%), including a small component of antisense viral transcription (Lefebvre et al. 2011). Deep sequencing also

showed very active transcription of repetitive elements and endogenous retroviruses: Approximately 0.4% of all cellular transcripts are of such origin whether the cell is infected or not (Lefebvre et al. 2011).

Proteomic studies analyzed 2000–3200 proteins and identified 15%–21% to be differentially expressed on infection (Chan et al 2007; Ringrose et al. 2008), including changes in the abundance of proteins with known interactions with HIV-1 viral proteins. The NCBI HIV-1 Human Protein Interaction Database (<http://www.ncbi.nlm.nih.gov/RefSeq/HIVInteractions/>) summarizes >3000 interactions with almost 1500 human genes (Fu et al. 2009). A complete library of viral-host protein coimmunoprecipitation relevant to the early innate immune responses to HIV is being built by the HINT consortium (HIV Networks Team, www.hint.org) and will be publicly available.

Genome-wide siRNA and shRNA screens have generated a comprehensive view of genes required for efficient viral replication (Brass et al. 2008; König et al. 2008; Zhou et al. 2008; Yeung et al. 2009). Individually, each published screen has identified a few hundred such candidate genes. However, there is a limited overlap

Figure 2. Schematic representation of the parallelism between human and nonhuman primate (NHP) models of HIV/SIV pathogenesis. EC, elite controllers; RP, rapid progressors; VNP, extreme viremic nonprogressors. (Adapted, with permission, from Guido Silvestri 2010.)

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across studies that has been attributed to differences in study design and to the type and source of the si/shRNA library (Bushman et al. 2009). The studies were also not specifically designed to identify restriction factors; no hits resulted in increasing levels of viral replication. Despite these limitations, meta-analysis of the data convincingly identified sets of genes and pathways that are common to two or more studies. A pattern emerged among the 34 shared genes that involve the nuclear pore machinery, the mediator complex, a number of key kinases, and components of the NF- κ B complex. Studies under way address those various technical issues by the systematic comparison of multiple siRNA libraries, the development of experimental approaches that can identify restriction factors, the integration of these data with other sources of experimental data, notably with gene expression (Fellay et al. 2010), and by the use of primary cells.

One gain-of-function screen used a cDNA library representing 15,000 unique genes in an infectious HIV-1 system (Nguyen et al. 2007). A more recent overexpression screening approach aimed at characterizing the antiviral activity of more than 380 interferon-stimulated genes (ISGs) against a panel of viral pathogens (Schoggins et al. 2011). Broadly antiviral effectors included *IRF1*, *C6orf150/MB21D1*, *HPSE*, *RIG-I/DDX58*, *MDA5/IFIH1*, and *IFITM3*. In addition, anti-HIV activity was proposed for *MX2*, *IFITM2*, *CD74*, *TNFRDF10A*, *IRF7*, and *UNC84B*. Several ISGs, including *ADAR*, *FAM46C*, *LY6E*, and *MCOLN2*, enhanced the replication of certain viruses, highlighting the complexity in the type I interferon responses.

Primate Genetics

Nonhuman primates (NHP), whether naturally or experimentally infected with simian immunodeficiency viruses (SIVs), display phenotypic variation on multiple levels, including differences in relative susceptibility to infection, variability in both acute and long-term viral replication levels, differing rates of disease progression, and differences in degree of pathogenesis (see Klatt et al. 2011; Lifson and Haigwood

2011). NHP populations, including both wild populations and captive-bred colonies, comprise genetically variable, outbred individuals, and it is reasonable to assume that variation in virological phenotypes reflects, in part, host genetic variation. Phenotypic variation in SIV-infected NHPs provides a considerable but largely unexplored opportunity to examine the influence of host genetics on primate immunodeficiency virus replication and disease. In the case of rhesus macaques, the most commonly used NHP in AIDS research, the availability of whole genome sequence (WGS) data has facilitated discovery and cataloging of SNPs and copy-number variants that may prove useful for genetic and genomic analyses (Malhi et al. 2007; Lee et al. 2008). WGS data are also available for chimpanzees and a variety of other NHPs representing all main primate lineages (www.ensembl.org). Thus, comparative studies of the different SIVs and their respective primate hosts have the potential to identify and characterize genes that govern the transmission of viruses within and between populations.

Relevance to HIV infection and human disease exists on multiple fronts. For many gene products with well-established roles in HIV-1 infection or replication, there is evidence for an analogous or similar role for other SIV, and in such cases, the existence of animal models can confirm and even extend understanding of the biological relevance of such interactions (Fig. 2). Humans are frequently exposed to retroviruses of other, nonhuman primates (Wolfe et al. 2004), and SIV from chimpanzees and sooty mangabeys have made the jump several times (see Hahn et al. 2000; Apetrei et al. 2004; Sharp and Hahn 2011). Thus, in addition to reconstructing the natural history of the primate lentiviruses, comparative studies can reveal the role of genetics in determining which retroviruses jump from primates into humans, and allow us to ask whether adaptation to the human genetic landscape is a prerequisite for emergence of new viruses. As a practical matter, identification and molecular analysis of genes that interfere with cross-species transmission are also helping pave the way toward improved animal models of HIV infection and AIDS

(Hatzioannou et al. 2006; Kamada et al. 2006; Ambrose et al. 2007; Igarashi et al. 2007; Hatzioannou et al. 2009). Finally, understanding the role of genetics in promoting the non-pathogenic outcome in natural hosts of SIV could some day suggest pharmacological strategies for uncoupling HIV infection from disease in humans.

Studies in Macaques (Macaca sp.)

In a striking parallel to the emergence of HIV-1 and HIV-2 in humans, the first SIV was isolated as an emerging pathogen in colonies of captive Asian macaques in the early 1980s (Daniel et al. 1985; Mansfield et al. 1995; Gardner 2003; Apetrei et al. 2004). The SIV-infected macaque has since served as the primary model for pre-clinical AIDS research, in part because there is still no practical, small animal model that faithfully recapitulates HIV infection and AIDS in all essential parameters. Among the practical difficulties encountered in the SIV/macaque model are animal-to-animal variability in susceptibility to infection, viral replication levels, and disease progression (not unlike the variation observed among HIV-infected humans). Although this variability can confound small-scale animal studies (for practical reasons, studies in NHPs are often underpowered), it also means that nonhuman primate models can be used to investigate the influence of host genetics on viral replication, emergence, and pathogenesis.

As a model system for understanding the influence of host genetic variation on virological outcomes, SIV-infected macaques have several advantages over analysis of human cohorts. Initial infection is established either by a cloned viral isolate of known sequence, or by a biological isolate that can be genetically defined by sequencing. Unlike naturally occurring infection in humans, most macaque cohorts consist of animals infected in parallel with identical or very similar viruses. Both the time and route of infection are known precisely. Because most or all animals in a study are under the care of a specific team of investigators following a set of standardized protocols, sample collection,

evaluation, and care of animals in SIV cohorts are inherently more uniform. Furthermore, end points (such as definition of AIDS) are consistently applied. Finally, and most importantly, hypotheses can be tested or confirmed in either prospectively or retrospectively genotyped animals. Familial relationships are also often known for captive-bred animals, raising the possibility that approaches incorporating pedigree analysis might ultimately be applied to macaque cohorts. The primary disadvantage of macaque cohorts as subjects for genetic association studies is the relatively small size of any given study (typically <50 animals). Nonetheless, given the extensive use of the SIV/macaque model for the past 25 years and the widespread use of a limited number of closely related SIV strains, it should be feasible to assemble sufficiently large study cohorts by combining samples from multiple SIV studies. To date, GWASs have not been reported for SIV/macaque cohorts. However, studies focusing on specific genes/loci serve to illustrate the potential contributions of SIV cohorts to our understanding of host genetics and AIDS.

The MHC Locus in Primate Models

Perhaps the most significant contributions of SIV animal models to understanding the role of host genetics have been in elucidating the influence of MHC class I genes on lentiviral replication and disease progression, and the potential for vaccine-induced CTL responses. The first robust correlations between specific MHC genotypes and epitope-specific viral escape from CTL emerged from studies of SIV-infected rhesus macaques (Evans et al. 1999; Allen et al. 2000). For example, Evans et al. documented emergence of epitope-specific escape variants by tracking SIV sequences in MHC-defined macaques (Evans et al. 1999). Similarly, Allen et al. reported rapid emergence of CTL-escape variants in a *Mamu*-*A01-restricted Tat epitope during the first 8 wk of infection, corresponding to the primary onset of acute-phase virus-specific CTL responses (Allen et al. 2000). Such studies were corroborated by monoclonal-antibody-based depletion of CD8⁺ T cells in SIV-infected macaques,

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which led to transient increases in viral replication levels and provided confirmation that cellular immune responses have a major influence on viral replication (Schmitz et al. 1999). Later studies also revealed significant correlations between specific MHC alleles and control of SIV replication levels; most notably, *MHC B*-locus alleles *Mamu-B*08* and *B*17*, which are associated with elite control of SIVmac infection in rhesus macaques (Yant et al. 2006; Lofredo et al. 2007a,b).

More recently, O'Connor and colleagues took advantage of a unique population of animals, the Mauritian cynomolgus macaques, to analyze the impact of *MHC* diversity on viral replication levels in vivo (O'Connor et al. 2010). Because Mauritian cynomolgus macaques display a limited number of *MHC* haplotypes, *MHC*-homozygosity is fairly common—a situation enabling direct comparison of viral replication in homozygous and heterozygous individuals, many with shared *MHC* haplotypes. In this study, *MHC*-homozygous animals infected with SIVmac239 had chronic-phase plasma viral RNA levels 80 times higher on average than *MHC*-heterozygous animals analyzed in parallel, suggesting that the increased breadth of potential virus-specific CD8⁺ T-lymphocyte responses in heterozygous individuals on average gave rise to significantly enhanced control of viral replication. These results provided strong experimental confirmation of prior studies describing heterozygous advantage in human HIV/AIDS cohorts (Carrington et al. 1999; Tang et al. 1999). As a practical matter, evidence of heterozygous advantage in these animals also lends credence to the hypothesis that an effective HIV-1 vaccine will be one that induces a broad range of virus-specific immune responses.

MHC class I molecules also interact with killer immunoglobulin-like receptors (KIR), influencing NK cell responses to HIV infection (Martin et al. 2002, 2007). Several candidate *MHC*-KIR interactions have been reported for rhesus macaques based on in vitro binding assays (Rosner et al. 2011). Colantonio and colleagues made the serendipitous discovery that a recombinant soluble *MHC* tetramer folded around certain SIV-derived peptides could bind

to the surface of lymphocytes from a subset of uninfected animals with no prior exposure to SIV or SIV antigens (Colantonio et al. 2011). This observation led to the identification of a specific *MHC*-KIR interaction (Mamu-A1*00201/Mamu-KIR3DL05) and the first functional demonstration of ligand-mediated NK cell inhibition in primary macaque cells (Colantonio et al. 2011). Further investigation also revealed that the particular SIV peptide/epitope bound by the Mamu-A1*00201 tetramer influenced the ligand/KIR interaction. Although the impact of *MHC*-bound peptide on *MHC*-KIR interaction has been reported (Malnati et al. 1995; Peruzzi et al. 1996; Mandelboim et al. 1997; Rajagopalan et al. 1997; Zappacosta et al. 1997; Hansasuta et al. 2004; Thananchai et al. 2007), the analysis by Colantonio et al. pointed toward specific involvement of residues in the KIR molecule. By taking advantage of polymorphic variants of the rhesus macaque *KIR3DL05* gene that differed in peptide selectivity, they pinpointed residues in the third loop of the KIR D1 domain that influence the peptide dependency of the *MHC*-KIR interaction (Colantonio et al. 2011). Structural models of *MHC*-KIR interaction place this loop in close proximity to the *MHC*-peptide surface (Boydington et al. 2000; Fan et al. 2001; Sharma et al. 2009). Importantly, genetic characterization of the rhesus macaque *KIR* locus and the development of reagents specific for macaques will permit incorporation of *KIR* genetics into animal models of AIDS and preclinical vaccine research.

Restriction Factors

The discovery of the host restriction factor TRIM5 α illustrates the benefits of a comparative approach to the study of HIV and AIDS. The antiviral activity of TRIM5 α was first identified by Stremlau and colleagues by screening a rhesus macaque cDNA library for genes that conferred resistance to HIV-1 infection of human cells (Stremlau et al. 2004). Similarly, an unusual Trim5 ortholog was identified as the source of a genetic block to HIV-1 infection in cells from South American owl monkeys (*Aotus sp.*)

(Nisole et al. 2004; Sayah et al. 2004). It is now widely assumed that TRIM5 is a major modulator of cross-species transmission of retroviruses, and as a practical consequence, *TRIM5* poses a significant genetic barrier to development of a NHP model of HIV-1 infection (Hatzioannou et al. 2006; Kamada et al. 2006; Ambrose et al. 2007; Igarashi et al. 2007; Hatzioannou et al. 2009).

Two independent association studies in SIV-infected rhesus macaques have shown the ability of TRIM5 to suppress lentiviral replication levels in vivo (Kirmaier et al. 2010; Lim et al. 2010a). It is noteworthy that both studies uncovered significant associations with relatively few animals ($n < 100$ animals in both cases). This differs from *TRIM5* studies in human HIV/AIDS cohorts, where reported associations have been modest (Goldschmidt et al. 2006; Javanbakht et al. 2006; Spielmon et al. 2006). The Lim et al. study (Lim et al. 2010a), which focused on a cohort of SIVmac251-infected rhesus macaques, most closely resembles the situation in human cohorts. Just as HIV-1 is only weakly susceptible to human TRIM5, SIVmac strains are relatively resistant to rhesus macaque TRIM5. The enhanced ability to detect a significant effect in macaques was owed, in part, to the presence at high frequency of functionally distinct TRIM5 alleles in the rhesus macaque *TRIM5* locus (Newman et al. 2006; Wilson et al. 2008). Lim et al. also revealed that complete viral resistance to TRIM5 is not required for pathogenesis—animals with restrictive alleles displayed lower but significant levels of SIVmac251 replication and developed AIDS—a fact that could not have been appreciated from tissue culture experiments alone.

Goldstein and colleagues first reported evidence for variation in inherent susceptibility of T lymphocytes from naïve, uninfected rhesus macaques to infection with SIV strain SIVsmE543-3 (Goldstein et al. 2000). They further showed that susceptibility of an animal's cells to infection in tissue culture correlated with in vivo susceptibility to SIVsmE543-3 infection. These results argued for the existence of an intrinsic cellular block to infection unrelated to virus-specific adaptive immunity. More

recently, Kirmaier et al. found that this inherent resistance to SIVsmE543-3 was due to rhesus macaque TRIM5, and that variation in susceptibility of animals to SIVsmE543 infection correlated with allelic variation in the rhesus macaque *TRIM5* gene (Kirmaier et al. 2010). Compared to SIVmac251, which is well adapted to rhesus macaques as a host, the impact of rhesus TRIM5 polymorphism on SIVsmE543 was far more dramatic (2–3 log differences in viral loads). The greater susceptibility of SIVsmE543-3 to multiple alleles of rhesus TRIM5 likely reflects its derivation by brief passage of a sooty mangabey virus (SIVsm) through only two rhesus macaques (Hirsch et al. 1997).

Restriction of HIV-1 by the most common alleles of rhesus macaque TRIM5 also poses a barrier to development of simian-tropic strains of HIV-1 (Ambrose et al. 2007). However, additional genetic barriers remain, including those imposed by the *APOBEC3* and *BST2/Tetherin* loci. Although intraspecies surveys of NHP *BST2/Tetherin* and *APOBEC3* loci have been limited, some reports suggest that these genes may also be polymorphic in rhesus macaques (Weiler et al. 2006; Jia et al. 2009; McNatt et al. 2009). Whether allelic variants of tetherin and *APOBEC3* have an impact on viral infection or pathogenesis in the macaque model remains to be seen (a weak correlation between *APOBEC3G* variation and SIVmac replication levels in vivo has been reported [Weiler et al. 2006]). In contrast to rhesus macaques, pig-tailed macaques (species *Macaca nemestrina*) uniformly carry a single allele of *TRIM5* (*TRIM5^{CypA}*) that does not restrict HIV-1 infection in tissue culture assays (Liao et al. 2007), raising the possibility that this species may provide a more permissive host for developing an experimental model of HIV-1 infection (see Igarashi et al. 2007; Hatzioannou et al. 2009; Lifson and Haigwood 2011).

Although SIV-infected macaque cohorts have not been routinely subjected to gene association or GWASs, the impact of host genes and genetic variation on SIV replication and disease is disclosed by adaptive countermeasures acquired by viruses during replication in vivo. Kirmaier et al. identified specific amino acid

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alterations in the SIVsmE543 CA protein that emerged in vivo in several animals bearing suppressive *TRIM5* genotypes. Such changes also appeared during the emergence of SIV in rhesus macaque colonies in the 1970s (Kirmaier et al. 2010). Among its many functions, the SIVmac Nef protein clearly prevents viral inhibition by rhesus macaque tetherin in tissue culture assays (Jia et al. 2009; Zhang et al. 2009). Compelling evidence in support of a similar role in vivo came from retrospective analysis of animals infected with a *nef*-deleted variant of SIVmac239. Replication of the SIVmac239 *nef* mutants was initially attenuated in vivo, and strains that eventually grew out in these animals had acquired novel anti-tetherin activity through adaptive changes in the viral Env protein (Serra-Moreno et al. 2011). Taken together, the emergence of adaptations to overcome CTL and restriction factors in animals with defined genotypes provides evidence that expression of these host genes (e.g., *MHC*, *TRIM5*, and *tetherin*) has biological relevance, by inhibiting viral replication in vivo, consistent with their observed mechanisms of action in the laboratory.

Chemokine Receptors and Chemokines

Mutations analogous to the $\Delta 32$ base-pair deletion in the CCR5 coding sequence in humans have also been found in two closely related nonhuman primates that serve as natural hosts of SIV infection (Chen et al. 1998; Palacios et al. 1998; Riddick et al. 2010). At least two distinct mutations are found in the CCR5 gene of sooty mangabeys (*Cercocebus atys*), the natural hosts of SIVsm (Riddick et al. 2010). Both are deletion mutations, encompassing 2 and 24 nucleotides of coding sequence, respectively. In one colony of captive sooty mangabeys, the frequencies of the $\Delta 2$ and $\Delta 24$ alleles were reported to be 26% and 3%, respectively (Riddick et al. 2010). The $\Delta 24$ variant is also present at high frequency in red-capped mangabeys (*Cercocebus torquatus*), and the naturally occurring SIV that is endemic to these animals (SIVrcm) can use a different molecule (CCR2b) as a coreceptor for viral entry (Chen et al. 1998).

Only as recently as 2004, researchers came to recognize that copy-number variation (CNV) is a major source of human genetic diversity (Iafate et al. 2004; Sebat et al. 2004). CNV, which can encompass expansions and contractions of large segments of chromosomal DNA (and the genes contained therein), can result in phenotypic diversity. Nonhuman primates with relevance to AIDS and AIDS research, including chimpanzees and Indian origin rhesus macaques, also display significant levels of genome-wide CNV (Perry et al. 2006; Lee et al. 2008). In 2005, Gonzalez et al. reported an inverse correlation between copy number of *CCL3L1*, which encodes a ligand for CCR5, and susceptibility to HIV-1 infection (Gonzalez et al. 2005). Interestingly, a similar link between *CCL3L1* copy number and disease progression in SIVmac-infected macaques has also been described (Degenhardt et al. 2009). The correlations have intuitive appeal, as ligands of CCR5 have been shown experimentally to inhibit HIV-1 replication (Cocchi et al. 1995; Menten et al. 1999, 2002; Nibbs et al. 1999; Xin et al. 1999). However, the link between *CCL3L1* copy number and HIV-1 infection has been called into question by subsequent, independent studies, which have failed to reproduce the correlation (Bhattacharya et al. 2009; Urban et al. 2009). Likewise, after correcting for known influence of the MHC class I and *TRIM5* loci on SIV infection, Lim et al. did not find a significant correlation between *CCL3L1* copy number and replication of SIVmac in rhesus macaques (Lim et al. 2010b). At present, the original claims remain controversial and additional work may be needed to resolve the discrepancies; the fact that *CCL3L1* is copy number variable in rhesus macaques raises the possibility that some issues may be addressable experimentally.

Joint Viral-Host Genome Analysis

A particularly attractive application of genomics is in the analysis of the reciprocal genetic signals resulting from the interaction between the host and the pathogen. The HIV-1 genome is conducive to such analyses because the expected plasticity and mutability would effec-

tively reflect the genetic signals of escape. However, there are constraints to viral escape, which reflect RNA and protein structural requirements (Watts et al. 2009) that may translate into loss of fitness. Although the HIV-1 genome is considered to be highly variable, 77% of amino acid positions are conserved, whereas 10% of the genome is under positive selection. This class of sites defines critical residues in host-pathogen interaction, whether resulting from CTL or other host-selective pressures. Although half of the sites under positive selection in the HIV-1 genome are mapped to CTL epitopes, there is considerable interest in identifying the nature of the pressures that are driving evolution in nonpeptide sites. These may reflect pressure from KIR or host restriction factors. Figure 3 depicts the superposed signals and influences that may account for conservation and variation in the viral genome.

Studies of monozygotic twins infected with the same viral strain (Draenert et al. 2006) showed the power of the host genome to control and drive viral diversity. The initial CD8⁺ T-cell response targeted 17 epitopes, 15 of which were identical in each twin. Three years after infection, 14 of 15 initial responses were still detectable, whereas of four responses that declined in both twins, three showed mutations

at the same residue. The antibody responses cross-neutralized the other twin's virus, with similar changes in the pattern of evolution in the envelope gene. These results indicate a considerable concordance of cellular and humoral immune responses and HIV evolution in the same genetic environment (Draenert et al. 2006). To discover a larger number of host HLA-viral genome mutual associations at the population level, Moore et al. (2002) and Bhattacharya et al. (2007) searched for signatures of selection driven by specific HLA alleles across the viral genome. The challenge here is to expand the analysis to identify all possible driving forces, which may include mechanisms in addition to CTL pressure. Eventually, there is a need to conduct a full discovery effort that considers both the viral and the corresponding host at the genome level.

NEW RESEARCH AREAS

Next-Generation Sequencing

The field of host genomics is facing a change in paradigm (Fellay et al. 2010). GWASs served to understand the role of common variants in HIV-1 disease. However, the extent of variance explained—around 20% of viral load or disease

Figure 3. Multilayer representation of HIV-1 clade B Gag. The various information layers align the sites under positive selective pressure (red), conservation scores (<90% conserved, black), the structured domains at the protein (dark blue), and viral RNA level (light blue) (Watts et al. 2009), the position of CTL (dark green), antibody (light green), and T helper epitopes (turquoise) compiled in the Los Alamos HIV database, and the Gag region overlapping with the viral protease (purple).

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progression—indicates that other factors are yet to be discovered. New technology in genome sequencing now allows the study of rare variation, whether through the capture and sequencing of the whole exome (the 2% of the genome that is protein coding), or increasingly through the deep sequencing of the whole genome or transcriptome (RNA-seq). These sequencing and resequencing tools associated with effective decoding bioinformatic support are also becoming affordable. A number of projects are under way in the HIV field that use next-generation sequencing for the study of extremes of disease (elite controllers vs. rapid progressors), and of unique populations that are resistant to infection (noninfected exposed hemophiliacs). Next-generation sequencing also offers an unprecedented opportunity to jointly analyze cellular and viral transcriptional activity (Lefebvre et al. 2011).

Evolutionary Genomics

The close association of retroviruses with the human, primate, and mammalian genome supports the notion that there has been significant coevolution, which results in signals of selection in both genomes. The availability of complete genomes for dozens of mammals and, as of 2010, nine primates representing all main primate and prosimian groups permits screening for signals of genetic conflict genome-wide. The analyses can extend from the comparative assessment of the coding regions of single individuals, to the analyses of whole genome signatures and the inclusion of multiple individuals. When applied to human diversity, genome evolutionary studies mark regions that likely reflect the impact of pathogens and population bottlenecks. These genes and genetic regions can inform next-generation sequencing projects (King et al. 2010), as analysis of the latter will need to be supported by priors—functional or other—because they test a very large sampling space. That is, genome sequencing generates very large numbers of variants that cannot be prioritized based solely on statistics. A new range of tools are now available for the identification of evolutionary signals during

human population diversification (Grossman et al. 2010).

Paleovirology and Protein Reconstruction

The infection of the germline can lead to viral genes becoming inherited as host alleles. A broad range of retroviral and nonretroviral virus groups are now recognized as part of modern genomes (Johnson 2010; Katzourakis et al. 2010). The long-lasting association of retroviral genomes with the mammal genome, as well as exogenous retro/lentiviral infections, could influence contemporary susceptibility to HIV-1 in humans. Paleovirology is a novel field of research that uses genome data to reconstruct extinct viruses and the ancestral state of restriction factors (Emerman et al. 2010). Specific examples include the reconstruction of the core protein of PtERV, a 4-million-year-old endogenous retrovirus identified in the chimpanzee and gorilla genomes (Kaiser et al. 2007). The resurrection of this virus could show that the human variant of TRIM5 α actively prevented infection by this virus. A second example of reconstruction, this time of 20-million-year-old TRIM5 α , suggested that restriction of HIV-1 has decreased during evolution leading to humans (Goldschmidt et al. 2008). Soll et al. investigated two chimpanzee endogenous retrovirus-1 and -2 (CERV1 and CERV2) relatives of modern murine leukemia viruses (MLVs) that are present in the genomes of Old World primates, but absent from the human genome (Soll et al. 2010). Using CERV2 Env-pseudotyped MLV vectors, Soll et al. identified copper transport protein 1 (CTR1) as a receptor that was presumably used by CERV2 during its ancient exogenous replication in primates. CTR1-inactivating mutations may represent an evolutionary barrier to the acquisition of CERV2 resistance in primates. In addition, the reconstruction of the first examples of endogenous lentiviruses, PSIV in lemurs (Gilbert et al. 2009) and RELIK in rabbits (Katzourakis et al. 2007; Keckesova et al. 2009), opens the door to the study of the activity of restriction factors on these ancient elements (Rahm et al. 2011).

Data Integration, Network, and Systems Biology

There is an urgent need to design experiments that will allow the incorporation of multiple types of genomic information with function. An excellent example from immunology is the identification of regulatory networks that control the transcriptional response of mouse primary dendritic cells to toll-like receptor agonists (Amit et al. 2009). This network model identified 24 core regulators and 76 fine tuners that explain how pathogen-sensing pathways achieve specificity. This study established a broadly applicable approach to dissecting the regulatory networks controlling transcriptional responses in mammalian cells. A second paradigmatic use of systems biology is the study of heterogeneity in cell populations during viral infection (Snijder et al. 2009). Much of the variation in viral infection, endocytosis, and membrane lipid composition is determined by the adaptation of cells to their population context. Perturbation screens, combined with quantitative modeling of single cells, revealed the molecular networks that underlie the heterogeneous patterns in cell populations that likely mediate collective behavior. Although developing system and network approaches in *in vitro* models is reductionist, the next challenge is to set the conditions for HIV-1 systems biology *in vivo* that can create series of perturbations, implement the iterative acquisition of high throughput data, and model the observed variation.

CONCLUSIONS

The field of host genomics is at a crossroads thanks to the availability of new technology and sequences of human and primate genomes. Some steps have been completed, such as clarifying the role of common variants in HIV viral load and disease progression, and the description of transcription in infected individuals. The next studies will be technology driven, but will also be designed to capture and integrate multiple types of data. These include the study of the genetics of resistance to infection and disease mediated by rare human variants, the use of deep RNA sequencing to improve

the quantification of transcriptome changes in specific cell populations, and the capture of the dynamic processes in gene expression. At the postgenome level, there is a need for completing functional analysis of human variants or of candidate regulatory genes identified through the novel approaches. The integration of data and system biology will generate new lists of candidates for such functional studies.

Primate genetics is also progressing, led by the identification of important variants that stratify the susceptibility to infection in the macaque model. Live-attenuated SIV mutants and chimeric viruses (SIV-HIV hybrids, or SHIVs) first revealed the presence of dominant-acting genetic barriers to lentiviral replication in nonhuman primates, some of which have been identified. However, despite more than 25 years of work, cohorts of SIV-infected macaques have yet to be analyzed by large-scale gene association or GWASs.

Understanding of the host genome should inform the study of the viral genome, and vice versa. The plasticity of the viral genome provides several kinds of information: from the structural requirements for viral function, to the faithful reflection of host pressures exerted during cross-species transmission, adaptation to a new host, and spread in a genetically diverse population. Research priorities include the mapping of all sites in the viral genome that are the likely result of host-selective pressure, followed by the identification of the host factors that exert those pressures, and their characterization. A general framework needs to be designed that will address whether the role of the respective host factors is to act as cross-species and interindividual barriers of transmission, to exert control of viral replication in the infected individual, or to limit pathogenicity. Progress in the HIV-1 field will benefit from improved understanding of the evolution of the innate immunity against retroviruses, and this should clarify the genetic conflicts between retrovirus and the host.

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