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www.publish.csiro.au/journals/sh *Sexual Health*, 2005, **2**, 53–62

Review

Genetic influences on HIV infection: implications for vaccine development

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ABSTRACT. Human HIV infection is characterised by great variability in outcome. Much of this variability is due either to viral variation or host genetic factors, particularly major histocompatibility complex differences within genetically diverse populations. The study of non-human primates infected with well characterised simian immunodeficiency virus strains has recently allowed further dissection of the critical role of genetic influences on both susceptibility to infection and progression to AIDS. This review summarises the important role of many host genetic factors on HIV infection and highlights important variables that will need to be taken into account in evaluating effective HIV vaccines.

Additional keywords: MHC, T-cells.

Introduction

Despite over 20 years of intensive research on HIV pathogenesis, treatment and vaccination, the HIV pandemic continues its assault on human populations, spreading into new regions and leaving a trail of devastation. Antiretroviral therapy has come a long way in prolonging the asymptomatic period of HIV infection, however side effects, the emergence of drug resistance, high costs and limited availability mean that a vaccine is still the best hope for bringing the HIV pandemic under control.

There are two major strains of human immunodeficiency virus, designated HIV-1 and HIV-2. HIV-2 is more closely related to the simian immunodeficiency viruses than it is to HIV-1, and most likely represents a separate cross-species transmission.[1] HIV-1 is the predominant cause of human AIDS, and is divided into three major phylogenetic groups, M, N and O.[2] In this review, we will focus on the M group of HIV-1, which includes over 95% of defined global isolates, including the defined viral subtypes (A–J) that characterise the HIV-1 epidemic within distinct geographic regions.[2] This population-level viral variation is augmented by the existence of viral quasi-species within each infected individual.

The extensive viral variability within an HIV-positive individual is a combined result of an error-prone viral replication mechanism,[3] viral recombination[4] and evolution within human populations.[5] Sequence variability confers an advantage on the virus, allowing it to continually thwart host immune responses. Although this viral diversity is a key consideration, many host factors strongly influence the outcome of HIV infection. To achieve maximal effectiveness, antiviral therapies and vaccines must address both the viral and host factors that result in divergent outcomes of infection.

Studying host factors in HIV-infected humans remains difficult since each subject effectively carries or evolves a different virus strain. Fortunately, several outbred non-human primate models are available to dissect host genetic factors influencing progressive lentiviral disease. Rhesus, cynomolgus and pigtail macaques are all susceptible to AIDS-like diseases with high levels of viral replication and depletion of CD4+ T-cells following infection with simian immunodeficiency virus or chimeric SIV/HIV (SHIV).[6,7] Using defined viral isolates, these models provide a valuable opportunity to understand the effects of genetic factors on AIDS disease progression more thoroughly.

Defined genetic influences on HIV infection

Numerous genes have been implicated in the outcome of HIV infection, leading to the characteristic variability of disease progression seen following HIV infection.[8] The genes that have been identified are involved in several stages of HIV replication, including viral entry, immune regulation following infection and adaptive immunity to HIV (see Fig. 1). Many of these genetic associations have evolved within particular ethnic or geographic populations, potentially due to the different pathogen burdens these groups have experienced throughout history.[9] This section provides an overview of some of the genetic variations affecting viral entry and immune

10.1071/SH04057 1448-5028/05/020053

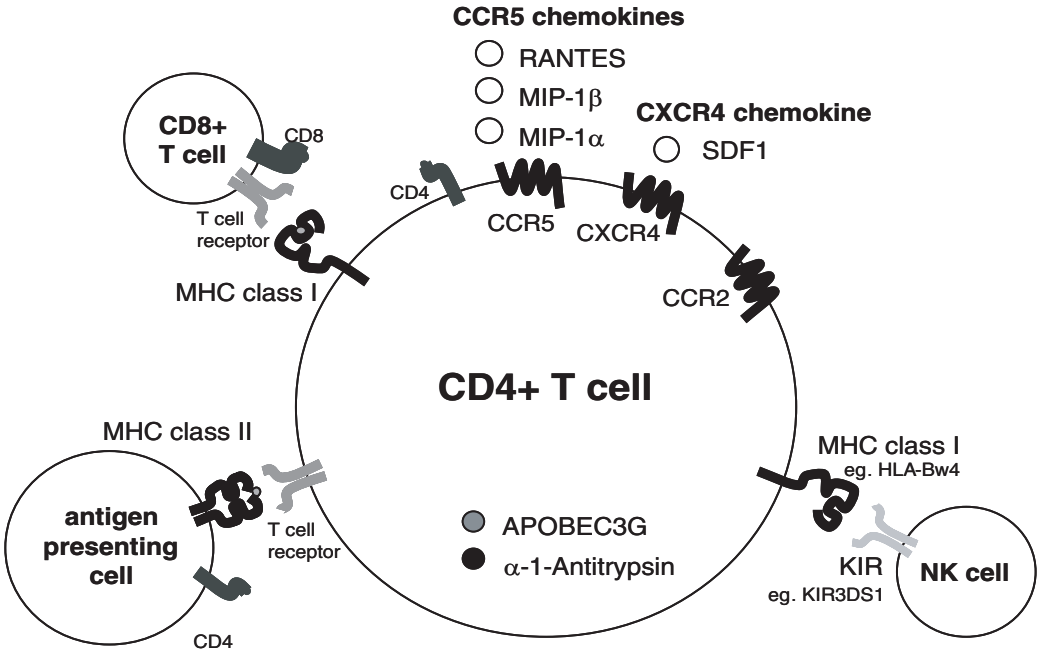

Fig. 1. An illustration of a CD4+ T-cell highlighting the regions of genetic variability implicated in HIV infection. CCR5 = CC chemokine receptor 5; CXCR4 = CXC chemokine receptor 4; CCR2 = CC chemokine receptor 2; RANTES = regulated on activation, normal T-cell expressed and secreted; MIP = macrophage inflammatory protein; SDF1 = stromal cell-derived factor-1; APOBEC3G = APOprotein B mRNA editing enzyme, catalytic polypeptide-like 3G, NK = natural killer; KIR = killer cell immunoglobulin-like receptor; MHC = major histocompatibility complex; HLA = human leukocyte antigen.

regulation following HIV infection in humans. The following section focuses on the major histocompatibility complex (MHC) and its critical role in both humans and non-human primates.

Variant genes for chemokine receptors such as CCR5, CXCR6 and CCR2, which act as co-receptors for HIV entry, have been found to affect the natural history of HIV infection in humans.[10–12] The CCR5-Δ32 mutation, a 32 bp deletion present in at least one allele in ~10% of Caucasians (and in about 2–5% of the population throughout Europe, the Middle East and India [13]), results in a premature stop codon and a knockout phenotype, leading to protection from HIV infection in homozygotes and a delayed onset of AIDS in heterozygotes.[9,10,14] A different CCR5 allele (+.P1.+) is associated with CCR5 up-regulation and accelerated progression to AIDS.[9] It has been suggested that CCR5 haplotypes may have different effects on AIDS progression in different ethnic groups.[15] A variant of the CCR2 gene, V64I, is often associated with the CCR5-Δ32 mutation and results in slower progression to AIDS.[12] Polymorphisms in the chemokine receptors CXCR6 and CX3CR1 have also been linked to disease progression.[11,16,17]

Variants of chemokine and cytokine genes, such as Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES), stromal cell-derived factor-1 (SDF-1), interferon-γ (IFNγ) and interleukin-10 (IL-10) have also been implicated in modulating HIV-induced disease.[18–21] In general, genetic variants of these genes cluster in regulatory regions, resulting in changes in expression levels. Elevated levels of the CCR5 chemokine RANTES or CXCR4 chemokine SDF-1 result in delayed progression to AIDS, most likely due to receptor competition with nascent HIV virions for cell entry.[9,17] A gene variant resulting in a 2–4-fold reduced production of the viral replication inhibitor IL-10 is associated with more rapid progression to AIDS.[21] The IFNγ allele –179T is inducible by tumour necrosis factor α, leading to very high levels of IFNγ production, rapid depletion of HIV-infected CD4+ cells, and a much more rapid progression to AIDS.[9,22]

There are a number of other genes that have been implicated in the modulation of HIV infection. The natural killer cell receptor KIR3DS1 interacts with the Bw4 motif on some HLA-B molecules, and is implicated in slowing the progression to AIDS.[23] Variants of cellular factors such as the cytosine deaminase APOBEC3G (APOprotein B mRNA Editing enzyme, Catalytic polypeptide-like 3G) and the protease inhibitor α-1-Antitrypsin may also contribute to susceptibility to AIDS.[24,25] Linkage disequilibrium could be complicating the analysis of many of these

gene polymorphisms, and the resistance or susceptibility phenotypes observed could be due to (or affected by) other, linked genes.[17] In addition, there are likely to be as yet unidentified host factors that are important in determining the outcome of HIV infection.

The major histocompatibility complex

The MHC contains highly polymorphic genes encoding classical MHC class I and class II molecules that present antigen to CD8+ and CD4+ T lymphocytes respectively.[26] The influence of both MHC class I and class II variants on HIV infection has been extensively studied in both humans and non-human primates.[27–31] While some MHC class II alleles have been connected with progression to AIDS, for example *HLA-DRB1*01* was associated with delayed progression to AIDS in a Kenyan cohort,[32] the majority of associations have been made with MHC class I.[29,33,34] Since CD8+ T-cells have been shown to be a critical component of anti-HIV and anti-SIV immunity,[35–37] the association between MHC class I and HIV progression is a logical and important focus for enquiry.

There is strong evidence that heterozygosity at MHC class I loci is advantageous in mounting effective cellular immune responses to HIV infection.[9,38,39] This heterozygosity facilitates a broader immune response to sequence-diverse HIV isolates by providing a larger selection of MHC binding specificities for a range of viral epitopes.[8,9] MHC class I heterozygosity is important for delaying the progression to AIDS, particularly in the absence of the 'rapid progressor' molecules HLA-B*35 and HLA-Cw*04.[38] HLA-B alleles are more frequently associated with effects on AIDS disease progression than HLA-A alleles.[40] Interestingly, there is evidence that homozygosity at the HLA-B locus is not necessarily detrimental if there is Bw4 motif homozygosity.[41] The Bw4 motif is a series of amino acids located between residues 77–83 in the α1 domain of MHC class I molecules, forming part of the peptide binding pocket, and known to interact with killer inhibitory receptors on NK cells.[42–44] The Bw6 motif, an alternative sequence at the same location, is expressed in a mutually exclusive pattern in HLA-B molecules.[42] Intriguingly, the Bw4 motif is not present on either HLA-B*8 or HLA-B*35 which are both associated with accelerated disease (both instead display the Bw6 motif).[41] This evidence suggests that the Bw4 motif itself may contribute to an improved outcome of disease, though further studies are required to prove this somewhat controversial observation.[23,41,45] Recent research also indicates that people with less common HLA types are more likely to mount immune responses to HIV, since the virus does not mutate at a population level to escape less common alleles.[30,46]

A number of MHC class I alleles have been shown to associate with either rapid or slow progression to AIDS in both humans and non-human primates,[47,48] summarised in Table 1. In humans, the HLA-B*35Px allele group (*B*3202, B*3503, B*3504* and *B*5301*) is associated with accelerated progression to AIDS.[9,47] HLA-B*35Px differs from HLA-B*35PY by a single amino acid within the binding pocket, and the B*35PY molecules are not associated with a more rapid progression to AIDS.[47] This example indicates the specificity with which MHC class I type can influence disease progression. In rhesus macaques, expression of both Mamu-A*1304 and Mamu-A*1403 is associated with rapid progression to AIDS following SIV infection, providing a potential model for the further study of MHC class I influence on rapid progression.[49]

A better understanding of protective cellular immunity to HIV may be gained through the study of MHC class I

Table 1. MHC class I alleles that are associated with the outcome of HIV/SIV infection in humans and macaques

Species	Allele	Association with disease	Reference
Human (*Homo sapiens*)	*HLA-B*35Px*	Rapid onset of AIDS	9,47
	*HLA-B*57*	Delayed onset of AIDS	51–57
	*HLA-B*27*	Delayed onset of AIDS	28,51,58,59
	*HLA-A*32*	Delayed onset of AIDS	52
	*HLA-B*44*	Delayed onset of AIDS	41
	HLA-A2/6802 supertype	Delayed onset of AIDS	48
Rhesus macaque (*Macaca mulatta*)	*Mamu-A*1304*	Rapid onset of AIDS	49
	*Mamu-A*1403*	Rapid onset of AIDS	49
	*Mamu-A*01*	Delayed onset of AIDS	31,34,60
	*Mamu-A*1303*	Delayed onset of AIDS	34
	*Mamu-B*17*	Delayed onset of AIDS	31
	*Mamu-B*03*	Delayed onset of AIDS	33,50
	*Mamu-B*04*	Delayed onset of AIDS	33,50
Pigtail macaque (*Macaca nemestrina*)	*Mane-A*10*	Lower viraemia during acute infection	61

alleles that are associated with slower progression to AIDS in both humans and non-human primates (Table 1). It has been noted that humans and non-human primates carrying MHC types associated with slow progression to AIDS generally respond to a larger proportion of known mapped epitopes for their particular alleles than people with alleles associated with rapid disease.[46,50] In humans, the MHC class I alleles *HLA-B*57* and *HLA-B*27* are both strongly associated with an attenuated progression to AIDS.[8] *HLA-B*57* is present in 4–6% of the population,[51] and a strong correlation between *HLA-B*57* and delayed progression to AIDS has been shown in a number of studies, including an analysis of subjects infected with *nef*-deleted attenuated HIV.[51–54] Epidemiological studies have shown carriers of *HLA-B*57* have longer survival following HIV infection compared to *HLA-B*57* negative individuals.[51] The precise mechanism for this observed clinical advantage has yet to be fully determined, though *B*57* variants have been shown to have a flexible peptide-binding specificity, potentially enabling these molecules to elicit broad CD8+ T-cell responses.[55–57] In the study of subjects infected with *nef*-deleted attenuated HIV,[54] while the *B*5701* allele was present in 85% of people with long-term non-progressive infection, it was still present in 9.5% of people who did succumb to AIDS. This suggests that the *B*5701* allele merely delays the onset of AIDS and that there may be some other requirement aside from *B*57* that is necessary to generate the protective phenotype. *HLA-B*27* is another MHC class I allele associated with delayed progression to AIDS.[28,51] *HLA-B*27* is found in around 5% of Caucasians, though is significantly more rare in African Americans suggesting an unequal distribution between ethnic groups.[51] *HLA-B*27* carriers develop an immunodominant response to an epitope derived from the structurally constrained Gag p24 protein.[58,59] While *B*27* is associated with long-term nonprogressive infection, the p24 epitope is susceptible to viral escape, most likely resulting in an abrogation of the CTL response directed to this epitope.[59] This escape correlates with an increased viral load and the development of syncytium-inducing HIV.[59] The story of B*27 demonstrates that even carriers of alleles associated with delayed progression are still susceptible to eventual disease. There are a number of other MHC class I alleles and types that have been associated with an attenuated disease course in humans, including *HLA-A*32*,[52] *HLA-B*44*[41] and the HLA-A2/6802 supertype.[48]

In rhesus macaques, the well-characterised MHC class I allele *Mamu-A*01* has been associated with slow disease progression.[31,34] Dominant acute-phase CD8+ T-cell responses are generated towards Gag and Tat epitopes presented by Mamu-A*01, leading to lower set-point viral loads and more favourable disease outcome following SIV infection.[31] Further evidence suggests that Mamu-A*01-positive animals are able to control viral replication to a level which prevents the destruction of lymph node tissue seen in Mamu-A*01-negative animals.[60] Mamu-A*1303 shares binding pocket specificity with Mamu-A*01 and is associated with a longer survival time following SIV infection, but not necessarily with lower viral loads.[34] *Mamu-B*17* is another rhesus MHC class I allele associated with slow disease progression, and similar to Mamu-A*01, it presents epitopes generating important CD8+ T-cell responses during acute infection.[31] The study of MHC class II-identical rhesus macaques has also identified Mamu-B*03 and Mamu-B*04 as being associated with slower disease progression.[33,50] In pigtail macaques, the recently identified MHC class I allele *Mane-A*10*, which restricts an immunodominant Gag epitope, has been associated with lower set-point viral load during acute SIV infection.[61] The correlation of these non-human primate MHC class I alleles with disease progression provides an exciting opportunity to explore the mechanisms of disease attenuation in a controlled setting, something that is impossible in the human population.

There are a number of techniques currently in use for the MHC class I typing of non-human primates. Serological methods are not commonly used, since antibody screening is often unable to distinguish closely related alleles, and many of the reagents are specific for human or murine MHC.[62,63] Instead, current typing techniques focus on molecular methods such as polymerase chain reaction (PCR) amplification and sequencing, which enable the detection of even extremely closely related MHC class I alleles. Polymerase chain reaction with sequence-specific primers (PCR-SSP) is used for the detection of common and well-characterised alleles in rhesus macaques, such as Mamu-A*01 and Mamu-B*17,[64–66] as well as numerous human MHC alleles. Using PCR-SSP typing requires an exact knowledge of the sequence of the allele to be identified, and also entails comprehensive assay validation to ensure that false positives are minimised. Another emerging technique for MHC class I typing is reference strand-mediated conformational analysis (RSCA).[61,67–69] The RSCA technique involves the use of fluorescently labelled reference alleles, which form conformational heteroduplexes with the uncharacterised alleles to be typed (Fig. 2).[68,70] These heteroduplexes have a characteristic mobility on a non-denaturing acrylamide gel, and can be identified through comparison with the mobility of MHC class I allele clones.[70] The advantage of this technique is that in addition to enabling the identification of well-characterised alleles, it is able to distinguish between multiple sequences differing by as little as one nucleotide.[61,67]

Once MHC class I alleles have been identified, the research focus can be shifted to the CD8+ T-cell responses that are generated by MHC–peptide complexes. MHC class I tetramers comprise four identical MHC class I molecules, their specific bound epitopes and a linked

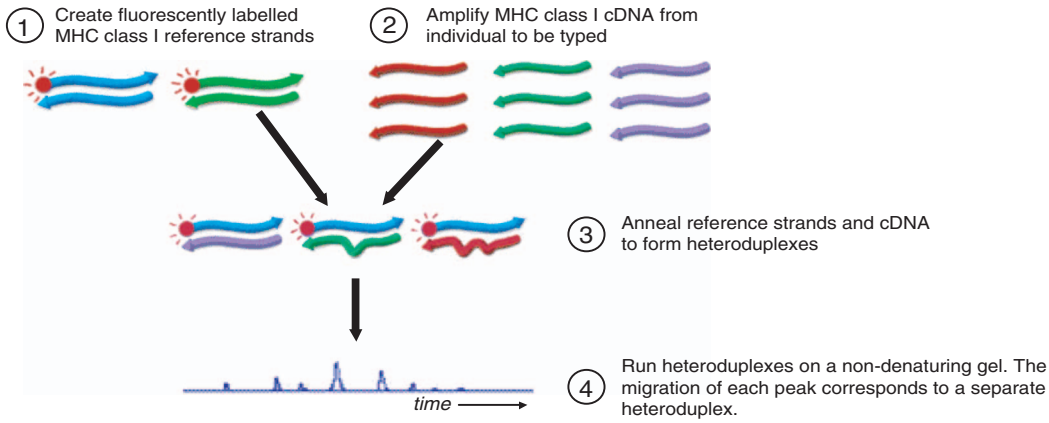

Fig. 2. A schematic of the MHC class I typing technique Reference Strand-mediated Conformational Analysis (RSCA). RSCA is an emerging technique for MHC class I typing of humans and non-human primates, involving the formation of conformational heteroduplexes between fluorescently labelled reference strands and uncharacterised MHC class I alleles. These heteroduplexes have a characteristic mobility when electrophoresed on a non-denaturing gel.

fluorochrome, facilitating the study of antigen-specific CD8+ T-cells by flow cytometry.[71,72] The development of this technology has opened up the investigation of CD8+ T-cell immunity, providing new insights into the quantity, distribution and phenotype of antigen-specific CD8+ T-cell responses to HIV in humans and SIV/SHIV in non-human primates.[57,72–77]

Viral escape

An understanding of HIV pathogenesis not only requires knowledge of host genetic factors, but also of the ability of the virus to escape immune recognition. Viral escape, where the virus mutates at targeted residues to reduce or abrogate immune responses, has been demonstrated during both acute and chronic HIV and SIV infection.[58,78–84] Escape occurs at both T-cell and neutralising antibody epitopes,[81,82] although this review will focus primarily on T-cell immune escape.

T-cell immune escape mutations can occur at residues that are important for MHC binding, at residues recognised by the T-cell receptor of responding T-cells, or even at residues that are implicated in antigen processing (Table 2 and reviewed in [85]). It is predicted that as much as 75% of the sequence diversity across HIV/SIV genes may be attributable to viral escape (O'Connor *et a*l, unpublished data).[30] The majority of HIV escape mutations have been shown to associate with particular MHC class I alleles and it appears likely that HIV is evolving at a population level to avoid immune responses restricted by common MHC class I types in humans.[30] Many MHC class I epitopes in both HIV and SIV are found within functionally constrained regions of the virus, for example the immunodominant epitopes for HLA-B*57 and Mane-A*10

Table 2. Mechanisms of T-cell viral escape employed by HIV

Mechanism	Impact on immune recognition	Example	Reference
Mutation in MHC binding residues	MHC–peptide interaction primarily involves 'anchor' residues that bind deep within the MHC binding cleft. Mutation at these residues can abrogate epitope binding to the MHC molecule.	Gag CM9 epitope in Mamu-A*01 + rhesus macaques Gag KP9 epitope in Mane-A*01 + pigtail macaques	[61,86,88]
Mutation in T-cell receptor (TCR) recognition residues	Even single residue mutations can abrogate epitope recognition by the TCR of antigen-specific CTL.	Tat TL8 epitope in Mamu-A*01 + rhesus macaques	[102]
Mutation affecting antigen processing	For presentation on MHC class I molecules, viral antigens must be processed via the proteosome into minimal epitopes. Mutations in proteosomal enzyme motifs can alter antigen processing.	Gag KK9 epitope in HLA-A3 + humans	[103]

both map to the same region of the Gag p24 protein,[54,61] suggesting that this region may be relatively restrained in its ability to escape. In HLA-B*27 positive humans and Mamu-A*01 positive macaques, viral escape at a single immunodominant epitope restricted by the protective allele corresponds with loss of immune control, and progression to AIDS.[58,86]

The astonishing effect of viral escape at an immunodominant epitope, and the abrogation of a single antigen-specific CD8+ T-cell response, combined with the high error rate of HIV replication, is discouraging for the prospects of generating a sustained, protective immune response. Fortunately, many escape mutations come at a fitness cost to the virus,[87,88] constraining the number and location of mutations that can be tolerated, and resulting in reversion to wild-type sequence once immune pressure has been removed.[59,88–90] It may be that the most effective T-cell responses are those that are directed towards a broad range of antigens, and that lead to large reductions in viral fitness if and when escape ensues.

Consequences for vaccine development

The development of a successful HIV vaccine will rely heavily on harnessing knowledge of the complex genetic factors that influence HIV infection. HIV vaccines will need to elicit responses to multiple epitopes in order to be effective in a genetically diverse population, and to minimise the impact of viral escape. Comprehensive knowledge of MHC diversity should allow the selection of vaccine modalities that deliver the best epitopes for the elicitation of effective T-cells and which either efficiently control viral replication on their own or at least result in viral escape variants that confer a large fitness cost.[30,83,89] Alternatively, vaccines could be designed to elicit T-cell immunity targeting escape variants that otherwise subvert T-cell immunity.[91] Since certain NK receptor genes are also linked to lower levels of viral load, there is the potential to harness the innate immune response and augment any adaptive immunity that follows.

Genotypic variation is a key consideration for the evaluation of vaccine trials in both humans and non-human primates. Since the various genetic factors described here have such a marked influence on the outcome of HIV or SIV infection, vaccine trials may need to be carefully designed to control for genetic factors. It is conceivable that some human subgroups will be more readily protected by vaccines than others.

Understanding lentiviruses that evolve to become non-pathogenic within non-human primate populations could reveal insights into effective immune or genetic control of these viruses. Various SIV strains do not generally cause AIDS in their natural hosts — chimpanzees, sooty mangabeys and African green monkeys all carry SIV strains and largely remain healthy despite high levels of viral replication.[92–95] SIV isolates become pathogenic when taken from their natural hosts, for example SIVsm (from the sooty mangabey) causes AIDS in Asian monkeys such as the rhesus and pigtail macaque and AIDS (as HIV-2) in humans.[96–99] Similarly, SIVcpz (from chimpanzees) causes AIDS (as HIV-1) in humans.[100] These examples indicate the potential for the natural host species to become well adapted, presumably over many centuries, to otherwise pathogenic primate lentiviral infection. HIV has likely only recently been introduced to the human population[101] and has given humans relatively little time to adapt to HIV at a population level. A better understanding of the genetic factors and innate and adaptive immune responses to non-pathogenic lentivirus infections should lead to insights applicable to inducing more effective immune responses by vaccination.

Conclusions

HIV has continued to spread across the globe, despite attempts by the medical and scientific communities to curb the epidemic. The huge variability of the virus itself contributes to different outcomes of infection, however it appears that variations in several key immune genes in humans have an even larger impact on the progression to AIDS. In particular, genes of the major histocompatibility complex, the centre of the adaptive immune response, can confer either a protective or a susceptible phenotype in people exposed to HIV.

While multiple associations between MHC and other immune-related genes have been demonstrated in humans and non-human primates, much of what influences the progression to AIDS in any one individual is still poorly understood. Further, as novel T-cell based vaccination strategies evolve that are at least partially effective, understanding the subgroups of people most (or least) likely to benefit from vaccination will be an important priority.

Conflicts of interest

None exist.

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Received 7 December 2004, accepted 24 February 2004