

# MHC-based vaccination approaches: progress and perspectives

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The major histocompatibility complex (MHC) harbours genes whose primary function in regulating immune responsiveness to infection is to present foreign antigens to cytotoxic T lymphocytes (CTLs) and T helper cells. In the case of infection by human immunodeficiency virus (HIV), defining the optimal HIV epitopes that are recognised by CTLs is important for vaccine design, and this in turn will depend on the characteristics of the predominant infecting virus. Moreover, the particular MHC human leukocyte antigens (HLAs) expressed by a geographical population is important since these are likely to determine which HIV epitopes are immunodominant in the anti-HIV immune response. Consideration of these aspects has led to the dawn of a new era of MHC-based vaccine design, in which the CTL epitopes are selected on the basis of the frequency of restricting MHC alleles. This article reviews data on the distribution patterns of molecular subtypes of HLA class I and class II extended haplotypes, discussing distribution among Asian Indians but with reference to global distributions. These data provide a genetic basis for the possible predisposition and fast progression of HIV infections in the Indian population. Since there is selective predominance of different HLA alleles and haplotypes in different populations, a dedicated screening effort is required at the global level to develop MHC-based vaccines against infectious diseases. It is hoped that this might lead to the development of multivalent, poly-epitope, subtype-specific HIV vaccines that are specific for the target geographical location.

Unravelling the sequence of the human genome together with advances in understanding the molecular aspects of immunology have been

remarkable achievements of recent times and have had a considerable impact on developing new perspectives in molecular medicine. An

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understanding of the genetic basis of complex, multifactorial diseases is crucial for identifying predisposing factors, discovering new targets for drug development, assessing the effect of interactions between genes and the environment, and predicting individual responses to specific drugs. Among the tools available for disease prevention and control, vaccines rank high with respect to effectiveness and feasibility. With the considerable progress made in immunology, functional genomics and proteomics, new strategies have been developed for the design of universal molecular vaccines that can elicit specific immune responses (Ref. 1).

### MHC-based vaccination

The major histocompatibility complex (MHC) functions in regulating immune responsiveness. The tripartite interaction of the T-cell receptor (TCR) with the MHC bound to an antigenic peptide derived from the pathogen is crucial for eliciting a specific immune response against the pathogen (reviewed in Ref. 2). The extreme degree of polymorphism in the MHC poses limitations for the development of a potentially global vaccine for infectious diseases because the ability to mount an effective T-cell response is partly determined by the MHC phenotype of the individual and different individuals have different MHC allotypes (Ref. 3). In humans, the MHC system is represented by the human leukocyte antigen (HLA) loci, which has more than 1500 alleles known in its 12 classical polymorphic loci (Ref. 4). HLA molecules not only present peptides in order to elicit an effector function (e.g. cell death or cytokine release) but are also crucial for T-cell repertoire selection and deciphering self versus nonself for T cells in the thymus (Ref. 5).

In an epitope approach to vaccine development, a prior knowledge of the HLA supertypes is useful; the HLA supertypes are characterised by largely overlapping peptide-presenting specificities based on structural similarities in the antigen-binding groove or shared peptide-binding anchor motifs. These supertypes provide an alternative to serological or phylogenetic classification. The alleles in a given HLA supertype often present the same epitopes (termed 'supertopes') for T-cell recognition (Ref. 3). The HLA supertype expressed by an individual or cohort of individuals could determine the epitopes of the infecting agent to which cytotoxic

T lymphocytes (CTLs) respond (Ref. 6). Thus, if the HLA types present in a target population are known, together with the particular epitopes that are restricted by these HLA types (i.e. the immunodominant epitopes), then a so-called MHC-based vaccine can be generated (Ref. 6).

In the example of infection by human immunodeficiency virus (HIV), defining the optimal HIV epitopes that are recognised by CTLs is important for vaccine design, and this in turn will depend on the characteristics of the predominant infecting virus. For an effective HLA-based preventive vaccine that could induce both anti-HIV T-cell responses and anti-HIV neutralising antibodies, it is implied that: (1) depending on the immunogen, not all members of a cohort may have an immunogenic HIV epitope present to bind to their particular HLA antigens; (2) not all relevant HIV variants would probably be represented in an immunogen; (3) vaccines might need to be designed for specific geographical locations, and perhaps even for specific ethnic groups within them; and (4) such vaccines would almost certainly be less than 100% effective in the vaccinated cohorts (Ref. 6). The strategy of creating an MHC-based vaccine has raised the possibility of designing global vaccines that would be equally efficient for all MHC supertypes (i.e. a combination of alleles in an extended haplotype). In particular, the HLA supertype concept provides a means of designing vaccines that are universally effective in ethnically diverse populations (Refs 3, 7). Thus, an HLA-based vaccine designed against HIV could not only impart a sterilising immunity (i.e. inducing complete protective immunity without persistent latent infection) but also could reduce the initial multiplication of HIV and lower the viral set-point (baseline virus load) that precedes the progressive development of AIDS. It could thus lead to a less-severe infection and an increased number of 'long-term nonprogressors (LTNPs)' (individuals infected with HIV who fail to progress to AIDS). Another important criterion that a vaccine against infectious agents needs to fulfil is ultimately to reduce its transmissibility through seminal fluid or blood plasma.

Recently, new evidence for the crucial involvement of proteins of the human MHC in shaping variations in HIV proteins, and possibly evolution of the virus itself, has emerged (Ref. 8). HIV vaccines will therefore

have to match the relevant circulating virus, but also must elicit very broad responses to multiple epitopes in order to stay one step ahead of HIV variation (Ref. 9).

### Vaccine development in HIV/AIDS: a major challenge

According to estimates by the World Health Organization (WHO), more than 40 million people have been infected worldwide with HIV (Ref. 10). As many as 15 000 infections are being reported per day, an equivalent of 5.6 million per year. In India, at least 4 million people are infected and 2.6 million die of AIDS per year, which is proportional to diseases such as tuberculosis and malaria (Ref. 11). In several African and other countries, the life expectancy of humans has been reduced drastically by more than 20 years. AIDS is therefore a major challenge for both developed and developing countries alike. Furthermore, it is an excellent model to highlight how knowledge of the molecular diversity of HLA can drive us closer to vaccine design.

There are four major scientific challenges for the rational development of HIV vaccines: (1) the lack of information on the immunological correlates of protection against HIV/AIDS (i.e. how protection in some individuals is mediated by the immune system); (2) the genetic variability of HIV clade antigens universally (i.e. the fact that even HIV strains show variability in their antigenic proteins) and the constant development of escape mutants of the virus; (3) the lack of good animal models within which to test vaccines; and (4) the diverse repertoire of HLA molecules with the ability to bind a wide array of HIV epitopes (Ref. 12). Of these, the vast diversity of HLA molecules across various ethnic groups constitutes the major limitation for an effective peptide vaccine. Since different MHC alleles recognise different structural motifs on HIV, individual HLA alleles from a small geographical region could present only a very restricted set of epitopes and hence cannot be generalised for the whole population. A sequence analysis of other alleles therefore becomes mandatory to determine the structural coordinates of principal peptide-binding pockets and to identify the optional 'motifs' or 'supermotifs' for peptide binding. The specificities of these sequences of different HLA phenotypes could thus predict the recognition patterns of a possible repertoire of CTL epitopes derived from antigens.

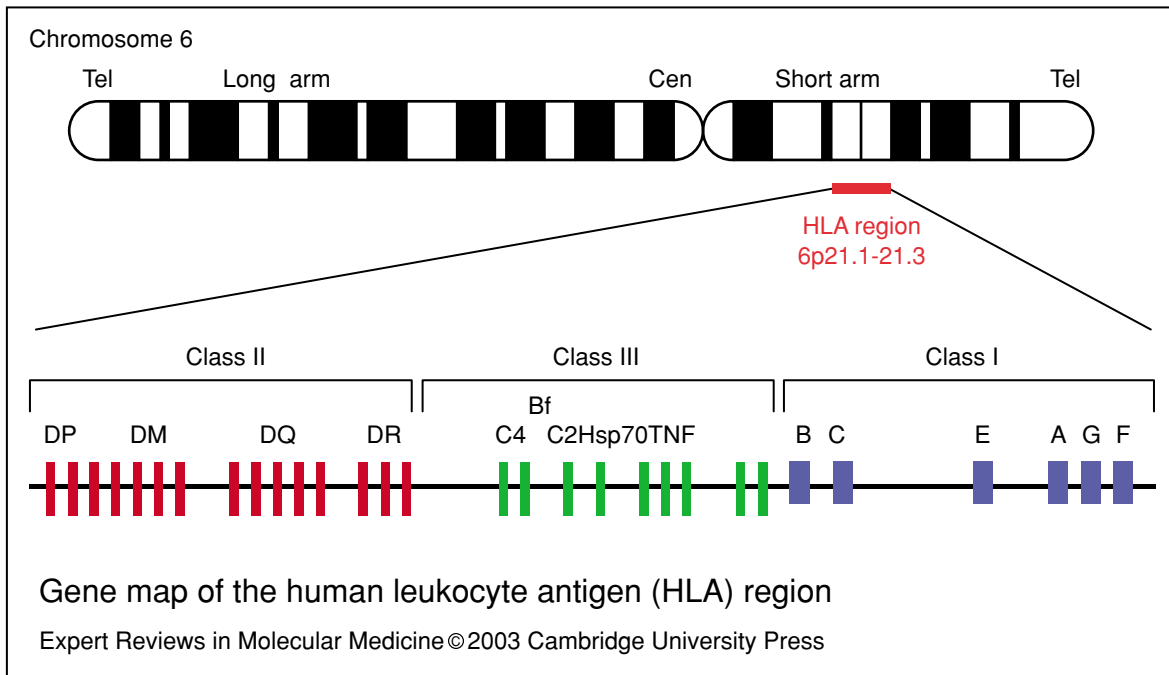
The extreme degree of polymorphism concentrated within the human MHC (which has many allelic variants of several functional genes, yielding billions of possible phenotypic combinations) presents a formidable obstacle in the development of peptide-based vaccination programmes. The first step to develop HLA-based vaccine strategies would thus require sufficient knowledge of the following variables: (1) the common HLA molecules expressed in the population to be immunised; (2) the HLA-restricted T-cell epitopes present in the immunogen; and (3) the HIV types present in the population to be vaccinated.

### The HLA system

#### Genetics

The HLA region spans  $4 \times 10^6$  nucleotides on chromosome 6p21.1 to p21.3, with class II, class III and class I genes located from the centromeric to the telomeric end (Fig. 1) (reviewed in Ref. 2). Most of the genes are in linkage disequilibrium and are therefore inherited as a combined block or a haplotype. Recombination occurs rarely, at a frequency of 1–3%, mostly at the HLA-A or HLA-DP ends. The HLA genes are co-dominantly expressed and follow the Mendelian pattern of inheritance. Sequencing of MHC (Ref. 13) has revealed that there are more than 128 expressed genes, out of which at least 40% have one or more designated immune functions. The gene densities are very high, with approximately one gene every 14.1 kb in the HLA class I region, every 25 kb in the class II region and every 14.3 kb in the class III region (Refs 13, 14).

Currently, a total of 1496 alleles in the HLA region have been defined according to the ImMunoGeneTics (IMGT)/HLA database statistics (<http://www.ebi.ac.uk/imgt/hla>), updated by the European Bioinformatics Institute. Of these: in the MHC class I region, 237 alleles have been identified in HLA-A, 472 in HLA-B and 113 in HLA-C; in the MHC class II region, 304 alleles have been identified in HLA-DRB1, 49 in HLA-DQB1, 22 in DQA1 and 96 in DPB1. The amino acid differences that account for molecular diversity in the class I region occur mainly in the  $\alpha 1$  and  $\alpha 2$  domains within any of the seven hypervariable sequences (i.e. amino acid sequences 9–12, 40–45, 62–83, 94–97, 105–116, 137–163 and 174–194). The hypervariable regions in the class II region genes are located in the  $\alpha 1$  and  $\beta 1$  domains of



**Figure 1. Gene map of the human leukocyte antigen (HLA) region.** The HLA region spans  $4 \times 10^6$  nucleotides on chromosome 6p21.1 to p21.3, with class II, class III and class I genes located from the centromeric (Cen) to the telomeric (Tel) end. HLA class I molecules restrict  $CD8^+$  cytotoxic T lymphocyte function and mediate immune responses against 'endogenous' antigens and virally infected targets, whereas HLA class II molecules are involved in the presentation of 'exogenous' antigens to T helper cells. The HLA class III region contains many genes encoding proteins that are unrelated to cell-mediated immunity but that nevertheless modulate or regulate immune responses in some way, including tumour necrosis factor (TNF), heat shock proteins (Hsps) and complement proteins (C2, C4) (**fig001nmn**).

the  $\alpha$  and  $\beta$  chains (encoded by the respective second exons).

### Function

The MHC class I and class II antigens are cell-surface glycoproteins that dictate the T-cell-mediated immune response and their prime function is antigen presentation to effector cells (reviewed in Ref. 15). HLA molecules interact with the antigen-specific TCR to provide a context for the recognition of antigens by T cells, thereby bringing about T-cell activation and resulting in an immune response. HLA class I-encoded molecules restrict  $CD8^+$  CTL function and mediate immune responses against 'endogenous' antigens and virally infected targets, and are present on the surface of almost all nucleated cells. By contrast, HLA class II molecules are involved in the presentation of 'exogenous' antigens to  $CD4^+$  T helper (Th) cells and are present on the surface of special immunocompetent cells called the antigen-presenting cells (APCs) such as macrophages/monocytes, dendritic cells,

activated T cells and B cells. The HLA class III region contains more than 75 genes encoding proteins that are unrelated to cell-mediated immunity but that nevertheless modulate or regulate immune responses in some way. These include tumour necrosis factor (TNF), heat shock proteins (Hsps) and complement proteins (Ref. 16). Since HLA molecules play a central role in mounting and regulating the immune response, they also play an important role in influencing resistance (protection) and susceptibility to disease.

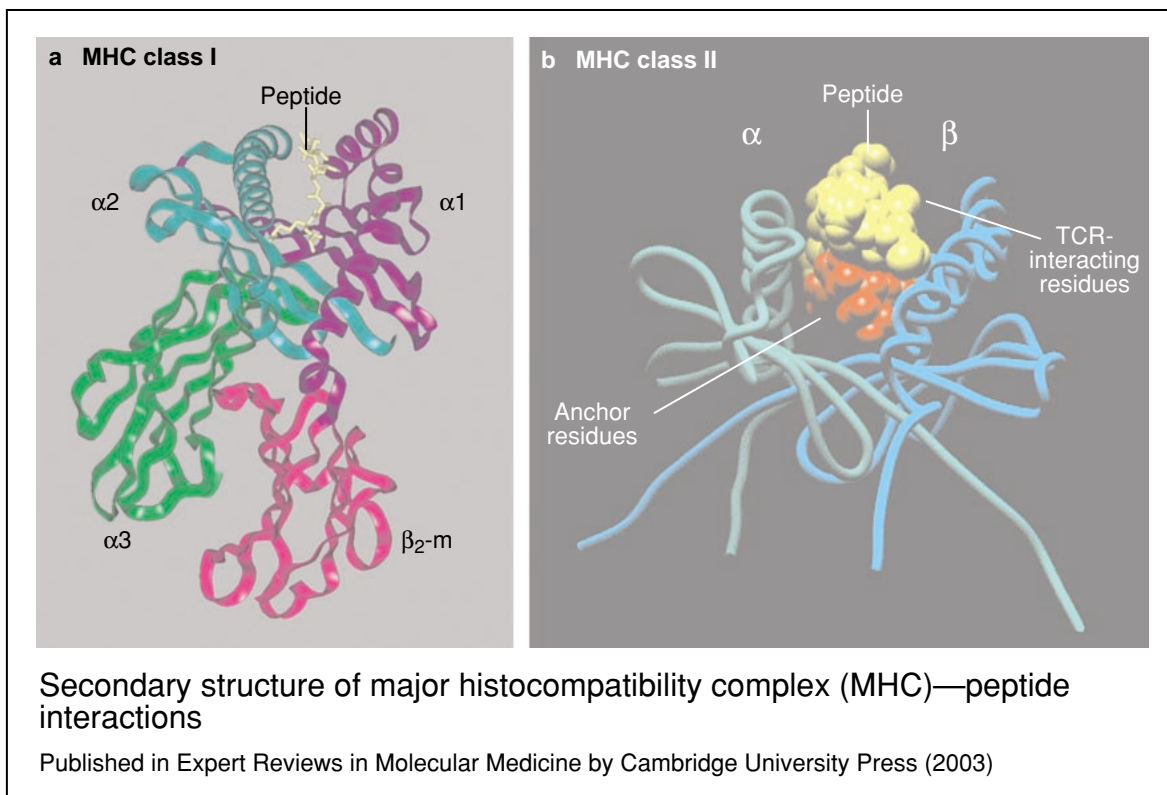
### MHC-peptide interactions: implications of genetic polymorphism

X-ray crystallography studies (Refs 17, 18) have helped significantly in understanding how peptides interact with, and anchor to, the peptide-binding pockets of MHC proteins (Fig. 2). All stable HLA molecules on the cell surface contain a tightly bound peptide 8–10 amino acids in length for class I molecules and 12–24 amino acids in length for class II molecules. The peptide

occupies a groove formed by the  $\alpha 1$  and  $\alpha 2$  domains at the membrane-distal surface of the class I molecule. Eight  $\beta$ -pleated sheets formed by the amino-terminal segment of the  $\alpha 1$  and  $\alpha 2$  domains form a platform bound by two helices (formed by the carboxyl-terminal ends of the two domains) that form the sides of the cleft. The floor and sides of the cleft interact principally with the peptide, whereas the top of the helices and areas adjacent to the peptide-binding groove interact

with the TCR. For class I, the sides of the peptide-binding groove restrict the bound peptide at its two ends and thus can only bind peptides of 8–10 residues.

Although a single MHC molecule can bind only a single peptide at one point in time, a single MHC allotype can bind a wide variety of MHC peptides (Ref. 19). However, there is also some specificity to its interaction. This is manifested in the preference of some MHC molecules for



**Figure 2. Secondary structure of major histocompatibility complex (MHC)—peptide interactions.** (a) Structure of an MHC class I molecule showing a bound peptide. Class I molecules comprise  $\alpha 1$ ,  $\alpha 2$  and  $\alpha 3$  domains complexed with  $\beta_2$ -microglobulin ( $\beta_2\text{-m}$ ). The peptide occupies a groove formed by the  $\alpha 1$  and  $\alpha 2$  domains at the membrane-distal surface of the class I molecule. Eight  $\beta$ -pleated sheets formed by the amino-terminal segment of the  $\alpha 1$  and  $\alpha 2$  domains form a platform bound by two helices that create the sides of a cleft. The floor and sides of the cleft interact principally with the peptide, whereas the top of the helices and areas adjacent to the peptide-binding groove interact with the T-cell receptor (TCR). For class I, the sides of the peptide-binding groove restrict the bound peptide at its two ends and thus can only bind peptides of 8–10 residues. Figure created by Dr John Coadwell (Bioinformatics Dept, The Babraham Institute, Cambridge, UK) using the PDB file 1HSA (see <http://www.ebi.ac.uk/msd/> for further details) and Insight II software (<http://www.accelrys.com/insight/>); reproduced with kind permission from John Coadwell and Birkbeck college (<http://www.cryst.bbk.ac.uk/pp97/assignments/projects/coadwell/004.htm>). (b) Structure of a peptide-binding groove of an MHC class II molecule showing a bound peptide. The peptide-binding site of class II molecules is much similar to that of class I, where the amino-terminal portions of the  $\alpha 1$  and  $\beta 1$  domains fold into  $\beta$ -pleated sheets and the carboxyl terminals form the helices. However, subtle changes in the helical regions produce a binding groove with open ends, which allows peptides to hang out of the groove at both ends and thus accommodate a larger peptide than the class I molecules. Reproduced with kind permission from Dr Peter Hjelmstrom (<http://depts.washington.edu/rhwlab/dq/3structure.html>) (**fig002nmn**).

binding peptides with specific amino acids in certain positions, depending upon the residues occupied in the peptide-binding site of that allotype. Indeed, most HLA polymorphisms are clustered in the cleft, in specific sites in the peptide-binding groove called the peptide-binding pockets that accommodate the peptide side chains (Ref. 20). The amino acid residues that form the pocket determine the size, shape and charge of the pocket and thus determine the antigen peptides that would be preferentially bound by the MHC allotype, accounting for the differential ability of different alleles to bind a variety of peptides. Thus, the peptide-binding groove of the MHC is essentially an exchange or shuffling of pockets between different allotypes. Most of the binding affinity of the peptides is provided by the hydrogen bonding at the end of the groove between the peptide and the conserved tyrosine residues. By contrast, the backbone of the peptide-binding groove is highly conserved, the root mean square deviation (RMSD) of the backbone atoms being 0.44Å for the  $\alpha$ 1- $\alpha$ 2 domains (Refs 21, 22).

For HLA class I, different pockets have variable effects on the binding of peptides. Among these, pockets B and F are the most crucial for binding of peptides to HLA-A and -B molecules (Refs 23, 24). These two pockets accommodate the side chains of the second residue (P2) and the carboxy-terminal end of the peptide, respectively, where most of the selectivity in peptide binding is exerted (Refs 25, 26). Almost 60% of known HLA class I motifs have P2 anchors. Pocket B is located between the  $\alpha$ 1 and  $\alpha$ 2 helix and the  $\beta$  sheet and is isolated from the rest of the peptide-binding groove. Its composition is thus a primary determinant of several allele-specific motifs. Residues in the middle of the bound peptide are not buried in the site and hence impose little or no restriction on peptide binding. However, a few MHC molecules such as HLA-A1 and HLA-B8 appear to have anchors interacting in the centre of the peptide-binding groove, in pockets C and D (Ref. 27). This flexibility in the various combinations of six pockets allows a broad spectrum of peptides to bind HLA class I molecules (Ref. 28).

The peptide-binding site of HLA class II molecules is similar to that of class I, where the amino-terminal portions of the  $\alpha$ 1 and  $\beta$ 1 domains fold into  $\beta$ -pleated sheets while the carboxy-

terminal portions form the helices. Subtle changes in the helical regions produce a binding groove with open ends, which allows peptides to hang out of the groove at both ends and thus accommodate a larger peptide than the class I molecules. Unlike HLA class I molecules, the peptide in the MHC class II molecule is held in the middle through hydrogen bonds formed at regular intervals throughout its length. Allotype-specific peptide binding is imposed by positions of polymorphism within the peptide-binding site. The most prominent pocket in the HLA class II groove is a large hydrophobic pocket at one end of the binding groove (pocket 1), formed by residues of both the  $\alpha$  and the  $\beta$  chain. The specificity of this pocket is mainly influenced by the first residue (P1) of the peptide. The presence of a glycine in this pocket dictates binding of large aromatic or aliphatic residues. By contrast, the presence of a larger valine residue in the same position reduces the size of the pocket and thus creates preference for smaller aliphatic residues (Ref. 29). Therefore, the constraints on peptide binding to class II molecules are less restrictive than those for class I molecules. This lower selectivity and potential for binding longer peptides enables promiscuous peptides to bind to different class II allotypes. An understanding of these fine details of molecular interactions between the epitope (on the foreign antigen) and the histope (on the HLA molecule) could assist in designing peptide-based universal vaccines.

#### Relevance to medicine and vaccine design

It seems likely that a major focus of medicine over the next two decades will be within the arenas of pharmacogenetics and pharmacogenomics, as a prelude to personalised molecular medicine. Since normal genetic variations in genes responsible for drug metabolism or receptors of various ligands become medically significant when drugs are applied, it becomes imperative to define the particular variations carried by each individual. This mammoth task of screening for potentially thousands of variations in the global population now appears achievable using advanced chip-based and mass-spectrometric approaches (reviewed in Refs 30, 31). Current focus is on the identification of single nucleotide polymorphisms (SNPs) representing points of variation between individuals. Empirical drug screening is being progressively abandoned and replaced by the logical design of small molecules interfering

with specific targets involved in receptor–ligand binding, pathogen recognition, signal transduction, transcription regulation, mitosis, apoptosis, angiogenesis and metastasis development (Ref. 32).

Modulation of the immunogenicity of antigenic determinants by their flanking residues is yet another dimension of induction of T-cell responses that are influenced by the HLA spatial matrices. A particular region within the native antigen might be pre-empted from binding to the MHC groove because of hindrance from flanking residues (Fig. 3). A ‘dominant’ determinant usually becomes readily available but what remains troublesome are the ‘recessive’ cryptic epitopes that remain shielded from immune attacks and yet might hinder and influence the outcome of the response. Thus, with respect to peptide vaccines, it is not certain whether such synthetic vaccines would be as capable as the naturally processed determinants from the native antigen of either binding to the appropriate MHC molecule (termed agretopic hindrance) or of interacting efficiently with the TCR (termed epitopic hindrance) (Ref. 33) (Fig. 3). Furthermore, for one particular MHC haplotype, certain amino acid residues of the peptide might act as a ‘hinderotope’, blocking binding of determinants from the pathogen, yet pose no interference for another MHC haplotype. Unlike hinderotopic hindrance, epitopic hindrance can be overcome by the presence of additional T cells with permissive receptor specificities. Nevertheless, a clear understanding of hindering agretopes or epitopes is vital for MHC-based vaccine engineering.

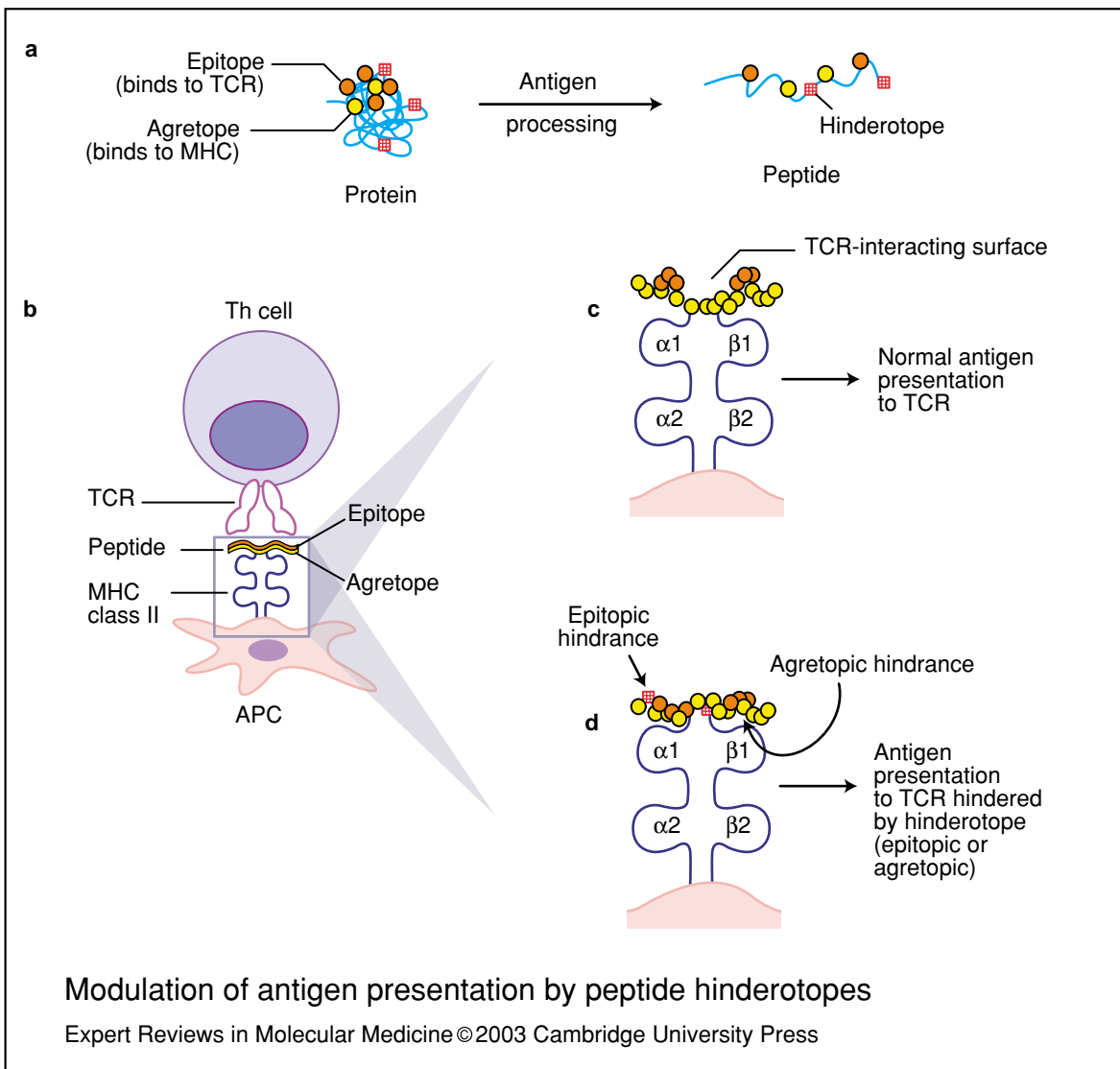
The MHC is not only relevant to vaccine design by modulating the immunogenicity of antigenic determinants, but is also relevant following the development of two new strategies, which will only briefly be mentioned here. In the first of these, a new concept of ‘cross-presentation’ has emerged where, under certain conditions, MHC class I molecules can be primed by peptides derived from extracellular sources (Ref. 34). It is worth mentioning here that high levels of antigen are critical for cross-presentation to CD8<sup>+</sup> T cells and that this mechanism is of prime importance in persistent bacterial or viral infections. It has also been suggested that, to limit self-reactivity, the cross-presentation system circumvents responses to self antigens by either ignoring low-dose antigens or deleting CD8<sup>+</sup> T cells specific for

antigens of higher doses (Ref. 35). The second strategy is based on the ‘veto’ effect, a naturally occurring mechanism that ‘reigns-in’ CTLs, such that they themselves are triggered to commit suicide, to prevent them from over-reacting when killing an invading cell (Ref. 36). The  $\alpha 3$  domain of MHC class I molecules and the CD8 $\alpha$  domain have been shown to participate in inducing cell death in T cells that are to be ‘vetoed’. This strategy is being extrapolated to non-CD8 cells using hybrid monoclonal antibodies (Ref. 37) and could serve as a modality to remove pathogen-laden/infected cells.

### Molecular diversity of HLA in the Asian Indian population

As we begin to elucidate the stringent yet dynamic interactions between crucial MHC peptide-binding pockets and their complementary peptides, we appreciate why nature bestowed the MHC with enormous genetic diversity. In addition, we appreciate how relevant it is for the antigen-presenting MHC molecules to possess extreme molecular diversity in order to provide adequate immune surveillance. A large number of peptides can theoretically be generated by foreign and self antigens. In addition, there are many different and often-changing pathogens as bacteria and viruses mutate extensively in an attempt to generate rare variants that can escape host immune surveillance mechanisms (Ref. 38). Thus, genetic polymorphism at the MHC is not only advantageous for an individual but also for the survival of the species. It is clear that microbial pressure is the main driving force that directs the evolutionary course of MHC polymorphism.

Population studies have gained immense importance in the post-genomic era, primarily with reference to molecular intervention by way of designing peptide-based vaccines. India is a vast genetic resource with a large population of more than 1 billion. The rich heritage includes extended families, more than 3000 communities, 325 functional languages and 25 scripts (Ref. 39). Recent studies have shown the existence of several ‘novel’ HLA alleles and ‘unique’ haplotypes in the Indian population, which could be a consequence of the racial admixture, gene conversion events or environmental influences associated with natural selection and best course to survival (Refs 40, 41, 42). These data indicate that the extensive diversity of HLA class I alleles and their uniqueness is a characteristic feature of the Indian



**Figure 3. Modulation of antigen presentation by peptide hinderotopes.** (a) Antigens derived either from intracellular or extracellular proteins are processed into shorter peptides inside the antigen-presenting cell (APC). (b) Peptides bind specifically to the peptide-binding cleft of MHC molecules at the cell surface for presentation to T-cell receptors (TCRs). The epitope (shown in orange) is defined as the peptide region recognised by the TCR; the agreptope (yellow) is defined as the peptide region that binds to the MHC molecule. MHC class II molecules are involved in the presentation of ‘exogenous’ antigens to T helper (Th) cells and are present on the surface of APCs such as macrophages/monocytes, dendritic cells, activated T cells and B cells. (c) Enlarged view of antigen presentation without any peptide hindrance. (d) Enlarged view of hindered antigen presentation. Adjoining amino acids in the peptide might act as hinderotopes (red boxes) that modulate the binding of a peptide. If the hinderotope alters binding of peptide residues to the TCR, it is referred to as epitopic hindrance; if the binding to MHC is hindered, it is referred to as agreptopic hindrance. Such hindrances vary among MHC haplotypes such that a hinderotope for a given peptide and MHC might in fact facilitate antigen presentation in another combination of MHC–peptide. Such interactions have significant implications for MHC-based vaccine design (**fig003nmn**).

population. The extent of these new allelic sequences and the appreciable heterozygosity observed in this population is discussed below.

#### Novel HLA alleles in Asian Indians

Studies on the distribution of HLA alleles and haplotypes in the population of northern India



indicate an appreciable Caucasoid as well as Oriental influence in the generation of allelic diversity in the MHC class I and class II regions (Ref. 43). On the basis of high-resolution studies, it is conceivable that subsequent selection might have favoured greater Oriental influence at the class I region and both Oriental and Caucasian influence at the class II region.

For HLA class I, analysis of commonly occurring alleles of the HLA-A2 and -A19 families has revealed high frequencies of typical Oriental alleles with negligible occurrence of common Caucasoid alleles. These results emphasise the uniqueness and high heterogeneity of the MHC repertoire in this population. In addition, a relatively rare subtype of HLA-A\*02 (A\*0211) was found to constitute 34% of the HLA-A2 repertoire in this population compared with an almost negligible occurrence of A\*0201, a Caucasian-specific allele that occurs in 96% of HLA-A2<sup>+</sup> Caucasians. Sequence analysis of HLA-A\*0211 indicates that it has a unique peptide-binding site with critical differences in the  $\alpha$ 1 domain, which suggests that A\*0211 might have originated from A\*0201 by interallelic gene conversion involving other donor genes. The increased incidence of HLA-A subtypes among northern Indians is significant and indicates a natural course of positive selection and their selective advantage.

For HLA class II, analysis has revealed allele frequency distributions more similar to those reported in Caucasians and other ethnic groups, with predominance of DRB1\*15/16 and DRB1\*07 (43% and 28.2%) along with their associated DQA1 and DQB1 alleles. Significant prevalence of Caucasoid alleles was observed in the DR\*15/16 and DR\*11/12 allele families. By contrast, the DR4 family displayed increased Oriental influence, with predominant prevalence of DRB1\*0403 and DRB1\*0405. Moreover, more than 10% of DR4 haplotypes occurred in typical Oriental combination with DQB1\*0401, the predominant association being with DQB1\*0302 (70%).

Asian Indians also manifest several disease-associated MHC haplotypes that are unique. For example, the extended haplotype that favours autoimmunity among western Caucasians, HLA-A1-B8-DR3-DQ2 (designated the AH8.1 haplotype), is rare in Indians and has been compensated by another related haplotype HLA-A26-Cw7-B8-DR3-DQ2 (AH8.2). Like the haplotype in Caucasians, the Asian haplotype is

strongly associated with susceptibility to coeliac disease (Ref. 44) and type I diabetes (Ref. 45) in Asian Indians and its impact on genetic predisposition is under investigation.

### Implications

Data obtained on the unique distribution pattern of several HLA alleles and their extended haplotypes in the Indian population with reference to global distributions suggest that: (1) the Asian Indians have an extreme diversity in HLA class I and II regions, with the occurrence of several novel alleles that could have arisen as a consequence of racial admixture; (2) the novel alleles in Indians might have also originated because of other factors such as natural selection, gene flow, single or multiple founding mutations or expansion or loss of other alleles owing to geophysical or socio-economic barriers; (3) Asian Indians share a parallel homology in molecular diversity of MHC class I more with Oriental populations than with Caucasian populations; (4) Asian Indians manifest several disease-associated MHC haplotypes (e.g. AH8.2) that are unique; and (5) Asian Indians have a unique repertoire of peptide-presenting molecules to combat pathogen-derived or autoreactive antigens.

As discussed earlier, the variable composition of the peptide-binding pockets and their cumulative combinations in a population confer the potential to bind a broad spectrum of peptides. With an insight into the stereo-chemical properties and solvation entropies of these molecules, it is now possible to predict the peptide-binding specificities of the peptide-binding groove using computer-based algorithms (Refs 21, 46) and extrapolate the findings to vaccine design strategies. Studies on the analysis of novel HLA alleles in Asian Indians highlight the point that extensive genetic admixture in the Indian subcontinent might prove to be a major hindrance in designing universal vaccines for diseases inflicting this large and very different population group because there is selective predominance of different HLA alleles and haplotypes in different populations. Therefore, a complete analysis of the genetic diversity of HLA genes in the Indian population and the functional differences in peptide-binding capabilities and CTL responses of the molecules they encode is imperative before assessing the efficacy of a vaccine designed and developed specifically in and for western populations.

### Predisposition to HIV infection and progression: a possible genetic basis

The AIDS epidemic is characterised by extreme heterogeneity in both the clinical course and in the incidence of HIV-1 infection among exposed individuals and between different ethnic populations. This is probably attributable to genetic variation both in HIV and in host genes such as those encoding HLA, chemokines, and cytokines and their receptors, as discussed below.

#### HLA association and HIV progression

Genes of the HLA complex regulate the immune response against HIV-1 (Ref. 12). Genetic polymorphism in these genes has been associated with effects on HIV pathogenesis (Ref. 47). An increased heterozygosity (or overdominant selection) at the HLA class I and class II region has been considered as an added selective advantage against several diseases including AIDS because a larger allelic diversity can present a diverse array of antigenic peptides to effector T cells, and therefore it takes longer for escape mutants to arise in heterozygous compared with homozygous individuals (Ref. 48). This also affirms the fact that infectious diseases play an important role in selection for heterozygosity within the species. Maximum HLA heterozygosity of class I loci (A, B and C) is reported to delay AIDS onset among patients infected with HIV-1, whereas individuals who are homozygous for one or more loci progress rapidly to AIDS and death (Ref. 48).

An exception to the advantage of HLA heterozygosity is found in HLA-Bw4-bearing B alleles, in which homozygosity has been associated with a significant advantage against HIV viraemia (Ref. 49). This can be directly extrapolated to natural killer (NK)-cell activity because HLA-Bw4, but not Bw6, motifs function as ligands for killer immunoglobulin-like receptors (KIRs) on NK cells. The loading of HIV-1 peptides onto HLA-Bw4 KIR ligands could potentially block the NK inhibitory receptor and thus favour the NK-cell-mediated elimination of HIV-1-infected autologous cells (Ref. 49). Alternatively, Bw4 molecules might fail to engage the inhibitory receptors and thus activate NK-mediated cell lysis. A recent report suggests that the activating KIR allele KIR3DS1, in combination with HLA-B alleles that encode molecules with isoleucine at position 80 (HLA-Bw4 Ile80), is associated with delayed progression to AIDS (Ref. 50). In the absence of KIR3DS1, the HLA-

Bw4 Ile80 allele was not associated with any of the AIDS outcomes. By contrast, in the absence of HLA-Bw4 Ile80 alleles, KIR3DS1 was significantly associated with more-rapid progression to AIDS. On the basis of these findings, a hypothetical model has been suggested that proposes an epistatic interaction between KIR3DS1 and HLA-B alleles as a mechanism that delays the progression to AIDS (Ref. 50). A similar study has shown a strong association of B\*5701 in HIV-1-infected LTNPs with normal CD4 counts and <50 copies ml<sup>-1</sup> in plasma (Ref. 86).

The HLA class I alleles B\*35 and Cw\*04 have been consistently associated with the rapid development of AIDS in Caucasians (Ref. 47). However, the failure of B\*35-Cw\*04 to protect against HIV might not reflect a simple inability to present HIV-derived epitopes to CTLs because significant HIV epitopes have been reported for both of these alleles. Interestingly, both HLA homozygosity and the B\*35-Cw\*04 haplotype have been shown to be associated with reduced NK-cell numbers and activity, respectively. Therefore, one mechanism to explain accelerated progression to AIDS in individuals with these HLA genotypes might involve inefficient NK-cell activity through interactions between NK cells and their ligands.

A recent study has shown the influence of HLA-B\*5301 and B\*35Px alleles compared with other alleles that differ in their peptide P9 preference in accelerating progression to AIDS (Ref. 51). The difference in peptide preference might influence the relative efficiency of HLA-B\*35Px and B\*35Py in presenting specific HIV-1 epitopes to CTLs and could therefore lead to either an ineffective immune response or a protective response, respectively. Other reports have shown a direct downregulation of HLA class I molecules and impaired class II antigen presentation owing to the HIV-1-encoded *nef* gene, and this might lead to shielding of the infected cells from CTL-mediated killing (Refs 52, 53). Nef acts by promoting an acceleration of MHC class I and CD4 endocytosis in clathrin-coated pits followed by their degradation.

Two extended haplotypes, HLA-A1-B8-DR3-DQ2 (AH8.1) and HLA-A11-Cw4-B35-DR1-DQ1 have been implicated in a faster rate of progression to AIDS (Refs 54, 55, 56). The underlying mechanism for the association of AH8.1 with fast disease progression and consequent loss of CD4<sup>+</sup> T cells remains obscure. As mentioned

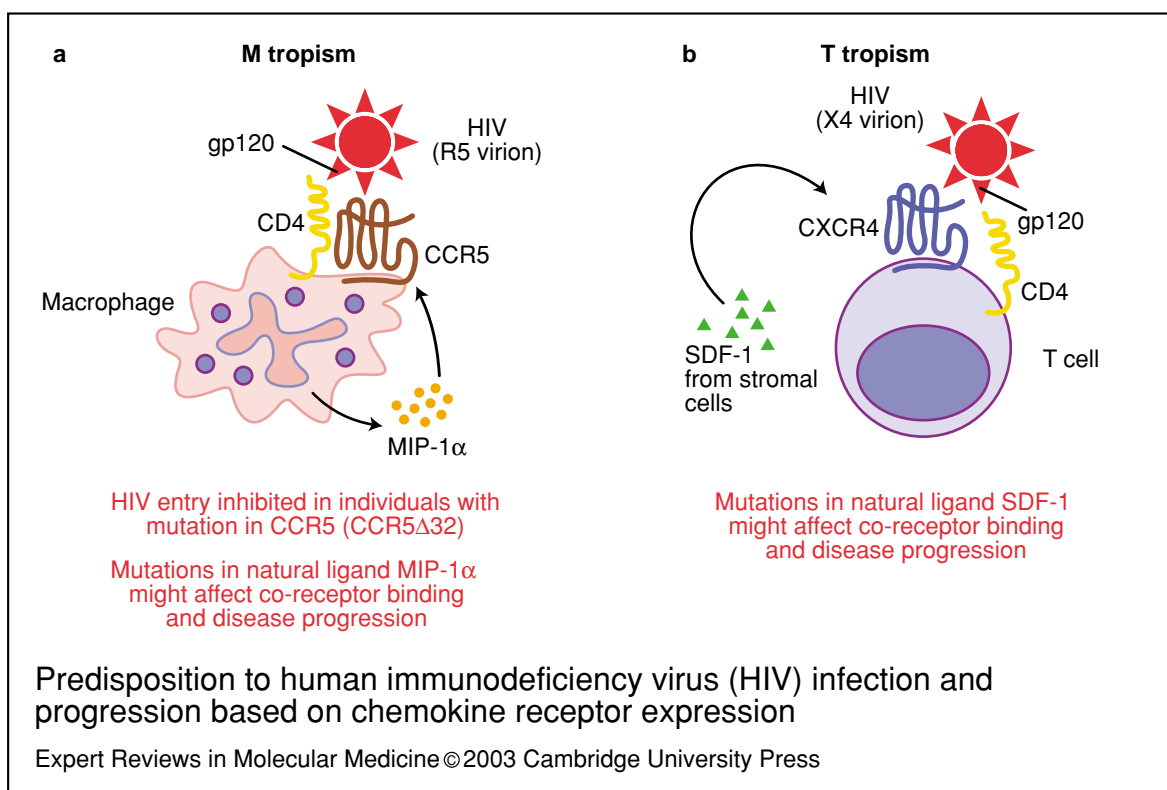
earlier, among Caucasians, this haplotype is well known to be associated with susceptibility to several autoimmune diseases, including type 1 diabetes, dermatitis herpetiformis, systemic lupus erythematosus, common variable immunodeficiency and IgA deficiency. Individuals carrying this haplotype can be considered as 'immunologically hyper-responsive' and it is possible that autoimmunity might be involved partly or wholly in the progressive immunodeficiency in AIDS. In Asian Indians, the AH8.1 haplotype is replaced by the HLA-A26-Cw7-B8-DR3-DQ2 (AH8.2) haplotype (see above); since these haplotypes only share the B\*0801 and DRB1\*0301 alleles, its association with susceptibility to HIV infection remains to be determined.

The genetic basis of natural resistance to HIV infection despite persistent exposure in cases of highly exposed persistently seronegative (HEPS) individuals is not fully understood. It could, however, be explained by factors such as: (1) epitope specificity of CD8<sup>+</sup> T cells that is different between HEPS and HIV-infected individuals (Refs 57, 58); (2) alloimmunisation to cellular antigens that impart crossreactive resistance to HIV; (3) cell-mediated immunity resulting from previous exposure to viral antigens at suboptimal chronic doses (Ref. 57); or (4) mutations in chemokine and chemokine receptor genes (see below). The possibility that allogeneic immune responses might confer a degree of protection against HIV infection is further supported by a recent study (Ref. 59), where it has been shown that the degree of concordance at HLA-A, -B and -DR loci differs significantly between transmitting and nontransmitting couples at risk of heterosexual HIV transmission. The study further showed a significantly higher frequency of DR5 among exposed uninfected individuals, relative to population controls. In another study, it was shown that transmission of HIV-1 from an infected woman to her offspring during gestation and delivery might be influenced by the infant's MHC class II DRB1 alleles (Ref. 60), especially the DRB1\*13, DRB1\*03 and DRB1\*15 subtypes. Furthermore, it has been suggested that the HIV-1 gp120 Env protein and *Mycoplasma genitalium* share an area of significant similarity with the CD4-binding site of the MHC class II proteins (Ref. 61). Interaction with this triad could contribute to T-cell dysfunction, T-cell depletion, changes in cytokine milieu, B-cell proliferation, hyperglobulinaemia and APC dysfunction.

### Chemokine receptor heterozygosity and HIV progression

HIV binds to the host cell-surface CD4 molecule via the HIV glycoprotein gp120 during the initial stage of infection, and then requires chemokine receptors as obligate accessory proteins for the virus to enter cells (Ref. 62). These so-called co-receptors are G-protein-coupled receptors with seven membrane-spanning domains and they normally bind to chemokines in order to direct leukocytes to migrate to sites of inflammation. Distinct members of the chemokine receptor family are used by macrophage (M)-tropic and T-cell (T)-tropic viruses: CCR5 for M-tropic HIV and CXCR4 for T-tropic HIV (Fig. 4) (Ref. 63). Although viruses usually start by using CCR5 preferentially, they tend to mutate to viruses that use CXCR4 around the time of the onset of clinical AIDS (called the 'R5 to X4 switch') (Ref. 64). HIV entry can be inhibited by downregulating the expression of the receptors or by blocking them with their ligands [e.g. for CCR5: RANTES, macrophage inflammatory protein 1 $\alpha$  (MIP-1 $\alpha$ ), MIP-1 $\beta$  and monocyte chemoattractant protein 2 (MCP-2); for CXCR4: stromal-cell-derived factor 1 (SDF-1)] (Refs 65, 66, 67).

A nonfunctional mutant allele of CCR5 with an internal deletion of 32 bp (CCR5 $\Delta$ 32) is found with high frequency in European and North American populations (Ref. 68). Heterozygosity for this allele is found in 10–15% and homozygosity in about 1% of the white population. An individual homozygous for this mutation is highly resistant to HIV (Ref. 69). By contrast, in a study of more than 100 healthy individuals both from north and south India, not even a single case of the CCR5 deletion genotype was found (in the equivalent number of Caucasian individuals, at least 10 heterozygotes would be expected) (Ref. 70). Studies conducted by others have also shown that: (1) the CCR5 deletion is indeed very rare (~1 in 145) in Indians (Refs 71, 72, 73), thus predisposing these individuals to M-tropic virions; and (2) insertions in the promoter region of MIP-1 $\alpha$  have been reported in 1 in 5 Indians (Ref. 74), and a guanine to adenine point mutation (3'UTR801G/A) in SDF-1 has been reported in 40% of healthy Indians, thus affecting ligand binding to the CCR5 and CXCR4 receptors, respectively (Ref. 75). Each of these differences might have disease-modifying effects and result in the prompt progression of



**Figure 4. Predisposition to human immunodeficiency virus (HIV) infection and progression based on chemokine receptor expression.** HIV enters cells by binding of the HIV glycoprotein gp120 to the host CD4 molecule; this process requires chemokine receptors as obligate accessory proteins or 'co-receptors'. Chemokine receptors are G-protein-coupled and have seven membrane-spanning domains. Chemokine receptors normally function by binding to chemokines in order to direct leukocytes to migrate to sites of inflammation. Distinct members of the chemokine receptor family are used by macrophage (M)-tropic and T-cell (T)-tropic viruses: CCR5 for M-tropic HIV and CXCR4 for T-tropic HIV. This entry can be inhibited by downregulating the expression of the co-receptors or by saturating them with their ligands. (a) M-tropic HIV. A nonfunctional mutant allele of CCR5 with an internal deletion of 32 bp (CCR5 $\Delta$ 32) is found with high frequency in European and North American populations, and this effectively protects individuals against M-tropic virions. This mutant allele is rarely found in Asian Indians. In addition, insertions in the promoter region of macrophage inflammatory protein 1 $\alpha$  (MIP-1 $\alpha$ ), a ligand for CCR5, have been reported in 1 in 5 Indians. (b) T-tropic HIV. A guanine to adenine point mutation (3'UTR801G/A) in stromal-cell-derived factor 1 (SDF-1), a ligand for CXCR4, has been reported in 40% of healthy Asian Indians. The possibility of such mutations in chemokine ligands that affect their binding to chemokine co-receptors remains to be determined (**fig004nmn**).

HIV infection in India. Knowledge about the genealogy of chemokine system gene variants would be advantageous in developing a greater understanding of the disease pathology and consequences.

In addition to SDF-1 3'A and CCR5 $\Delta$ 32, an allelic variant of CCR2 (CCR2-64I) has been associated with a significant delay of disease progression (Ref. 76). CCR2 acts as a receptor for the CC chemokines MCP-1–4 and, because CCR2 is rarely used as an entry co-receptor for HIV, the biological correlate of CCR2-64I remains undetermined, although linkage disequilibrium

between the CCR2-64I and a mutation in the CCR5 promoter has been described (Ref. 77).

The observed population-based differences in chemokines and their receptors considered together with their documented effects on susceptibility to HIV infection and rate of progression to AIDS have implications on the transmissibility of HIV and AIDS in the Indian population. Therapeutic modalities to inhibit HIV entry based on blocking co-receptor-mediated entry of HIV into the host cell are being devised (Refs 65, 66, 67). Other possibilities include enhancing ligand availability in order to

keep the co-receptor occupied, or inhibiting HIV gene expression (especially gp120, to block the entry of the virion) (Ref. 78) using ribozymes or DNazymes (Refs 79, 80).

### Designing a rational HIV-1 vaccine for use in India

HIV-1 is a highly variable virus that mutates readily, resulting in many different strains of HIV-1. These are classified according to groups and subtypes that differ in their genetic composition and are unevenly distributed throughout the world; for example, USA and the industrialised world has mostly subtype B, while South Africa and India have mostly subtype C (Ref. 81). Several strides are being undertaken worldwide to design a rational HIV-1 vaccine candidate based not only on the subtype B but also on non-subtype B HIV-1 strains including HIV-A to F, but to date most of the clinical trials have been conducted in countries where subtype B predominates. In addition to the fact that the HIV clade in India is mainly type C, and the fact that subtype C HIV in India is highly recombinogenic (Ref. 38), there are two other constraints with regard to vaccine development against HIV in India. First, there appears to be a very low degree of R5 to X4 co-receptor switch with disease progression, as shown by the finding that 39 out of 40 individuals in India utilised CCR5 exclusively irrespective of HIV disease status (Ref. 82). Second, the genetic basis of susceptibility to HIV pathogenesis (HLA and chemokine receptor polymorphism) favours the easy spread of AIDS in Indian populations (see above).

A potential way of overcoming the hypervariability of HIV is to develop vaccines using immunodominant viral epitopes that are well conserved within and between clades. For example, Africans infected with HIV clade A, C and G subtypes demonstrate cross-recognition of Gag, Pol and Nef proteins from clade B virus (Refs 83, 84). However, another major factor that determines the immunological breadth of the CTL response is the HLA class I haplotype of the host (see above). Multiple peptide vaccines might therefore have the best chance of effectively immunising diverse populations, although HLA-specific vaccines may need to be offered to certain groups. The best approach to overcome such limitations would be to exploit both the ability of certain degenerate antigenic peptides to bind multiple HLA class I molecules and the

promiscuous CTL recognition of cells presenting the same peptide in the context of different class I molecules. Recently, Threlkeld et al. (Ref. 85) reported that a variety of HIV-1 peptide epitopes, presented in the context of both HLA-A3 and A11, could elicit such degenerate and promiscuous CTL recognition.

### Conclusions

Predictive molecular medicine and immunobiology are encouraging new arenas of modern science. The MHC region is unique as it possesses an extreme degree of polymorphism whose functional importance lies in combating a whole range of pathogens by presenting them to the immune system. Information on HLA polymorphism in distinct racial groups is important for understanding the pattern of origin of HLA haplotype through superimposed effects of racial admixing and environmental pressures, and for subsequent utility in designing vaccines with global effectiveness. In particular, this knowledge should help progress towards HIV vaccine development. At present, little is known about the range and diversity of the genetic and ethnic background of HIV-1-infected individuals, or how genetics and ethnicity affect immune responsiveness to HIV. Furthermore, since HIV-1 is a highly variable virus, the viral epitopes that trigger a protective response might differ depending on the HLA type of the individual, the genetic subtype of the infectious virus, and the predominant virus that causes the HIV-1 epidemic in a certain geographical region. These facets highlight the need to study the molecular diversity of HLA molecules in HIV seropositive/negative populations. Construction of a poly-epitope, subtype-specific HIV-1 vaccine, including multiple copies of immunodominant CTL epitopes across the virion proteins as restricted by the prevailing HLA alleles, appears to be a logical approach in the design of a more-universal vaccine against AIDS.

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### Further reading, resources and contacts

The international ImMunoGeneTics (IMGT) database is an integrated information system specialising in immunoglobulins, T-cell receptors and major histocompatibility complex molecules of all vertebrate species. It consists of sequence databases, web resources and interactive tools:  
<http://www.ebi.ac.uk/imgt/index.html>

### Features associated with this article

Figure 1. Gene map of the human leukocyte antigen (HLA) region (fig001nmn)  
Figure 2. Secondary structure of major histocompatibility complex (MHC)–peptide interactions (fig002nmn)  
Figure 3. Modulation of antigen presentation by peptide hinderotopes (fig003nmn)  
Figure 4. Predisposition to human immunodeficiency virus (HIV) infection and progression based on chemokine receptor expression (fig004nmn)

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