Certain HLA-DR5 and -DR6 major histocompatibility complex class II alleles are associated with a CD8 lymphocytic host response to human immunodeficiency virus type 1 characterized by low lymphocyte viral strain heterogeneity and slow disease progression

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ABSTRACT Either of two structurally related major histocompatibility complex class II alleles, DRB1*1102, which encodes a DR5 specificity, or DRB1*1301, which encodes a DR6 specificity, was found in 67% of individuals responding to human immunodeficiency virus type 1 (HIV-1) infection with a syndrome characterized by persistent circulating and diffusely infiltrative CD8 lymphocytosis (DILS), slow progression to opportunistic infections, and delayed CD4 T-cell depletion. These alleles were present in only 28% of ethnically matched HIV-positive controls ($P = 0.001$). The frequency of DRB1*1301 was increased in both Blacks and Caucasians with this syndrome, while that of DRB1*1102 was increased only in Blacks, where 80% had either of these alleles. To investigate whether the host response associated with these alleles influences the evolutionary divergence of the HIV-1 genome, sequencing of the envelope V3 loop was performed. This revealed a significantly diminished lymphocyte viral heterogeneity compared with random HIV⁺ controls matched for CD4 T-cell levels. These results suggest that the immunogenetics of the host influence the nature of the immune response to HIV-1, which may lead to constrained evolution of HIV-1 gene products. Of possible relevance, the α -helical third diversity region common to both the DRB1*1102 and DRB1*1301 allelic products was noted to have homology with the C-terminal region of the HIV-1 envelope V3 loop at six of nine consecutive residues. This suggests the possibility that these alleles may bias the anti-HIV T-cell receptor repertoire through a mimicry mechanism.

A striking feature in human immunodeficiency virus type 1 (HIV-1) infection is the variation between individuals in the duration from initial infection to the appearance of a significantly compromised immune system (1). Some individuals progress slowly, with delayed appearance of CD4 T-cell depletion and opportunistic infections, while others progress very rapidly. Progression of HIV-1 infection is generally associated with increasing variability in the structure and function of infecting viral strains. HIV-1 strains isolated from infected persons at early stages of disease tend to replicate preferentially in monocyte lineage cells (M-tropic), whereas those isolated from individuals late in the course of infection with CD4 T-cell depletion and opportunistic infections are designated T-tropic because they grow more easily and at higher titers in T cells and exhibit greater cytopathic effects (2). Evidence has been presented that some of the M and T patterns of cellular tropism correlate with structural differences within the HIV-1 gp120 envelope, most notably the presence of particular charged amino acids within the principal neutralizing V3 domain (3–5), suggesting that the emergence of highly replicative T-tropic strains results, at least in part, from evolution of structural genes encoding the viral

envelope and other regions. These temporal changes in viral sequence have been considered to reflect the escape of the virus from successive constraints placed by the immune response on newly emerging variants (6, 7).

A subset of slowly progressing HIV-infected adults and children manifests an unusual host response to HIV-1 characterized by the development of persistent circulating CD8 lymphocytosis and infiltration of salivary glands and other viscera with CD8 T cells, a host response termed diffuse infiltrative lymphocytosis syndrome (DILS) (8, 9). For long periods of time these individuals maintain relatively well-preserved numbers of CD4 T cells and have low rates of opportunistic infections (10). The low frequency of culturable virus isolated from the circulating T cells of these persons and the demonstration of HIV-1 in their salivary gland macrophages (11) suggest that the syndrome may reflect a response to strains of HIV-1 that are at the M-tropic stage. Indeed, DILS clinically resembles the host response seen in some sheep to infection with visna Maedi virus, a lentivirus that is exclusively tropic for ovine monocytes (12, 13). The tissue infiltration in DILS has the characteristics of an antigen-driven reactive process in that the infiltrating CD8 T cells have a memory phenotype (11) and a T-cell receptor (TCR) β -chain repertoire characterized by both selective combinations of variable (V) and joining (J) region segments as well as distinct structural features of the VDJ joining region (D = diversity) (14). Moreover, there is often marked diminution in salivary gland size following zidovudine treatment (11), emphasizing the role of HIV-1 in driving this immune response.

A central issue is whether the immune response to HIV-1 present in persons with DILS is under control of the major histocompatibility complex (MHC). The MHC molecules function to both initiate an immune response by binding and presenting immunogenic peptides and, earlier in ontogeny, to shape the peripheral TCR repertoire by a process of positive and negative selection occurring in the thymus (15–18). Accordingly, HLA genotyping offers a clue to the existence of particular immune recognition events that may be present in different persons. In an earlier limited study, in which the syndrome was initially described and where most of the patients were Black, an increase in the frequency of the serologically defined MHC class II specificity HLA-DR5 was reported (19). However, HLA-DR5 has also been reported to be increased in HIV-infected Caucasians developing Kaposi sarcoma (20). This latter association may be due to a Caucasian haplotype, where HLA-DR5 is in linkage disequilibrium with the MHC class I specificity HLA-B35, which is also found at increased frequency among those with Kaposi sarcoma (21). Ethnic differences in the presence of such

haplotypes reflect differences in the ethnic distributions of various alleles that encode a particular serologic specificity. With respect to DR5, while the predominant allele in Caucasians is DRB1*1101, this subtype accounts for only about 50% of DR5 alleles found in Blacks (22, 23). Since the initial DR5 serologic association with DILS was made predominantly in Blacks, and HLA-B35 is found at very low frequency among all persons with DILS (10), at a molecular level the structure of the allelic product encoding the DR5 specificity in those with DILS is likely to differ from DRB1*1101.

In the present study, we sought to investigate whether certain MHC class II allelic structures might be enriched among individuals with the exuberant CD8 lymphocytosis syndrome, DILS. In addition, we sought to establish whether the presence of such structures results in an immune response that influences the evolution of HIV-1 gene products such as the V3 loop.

PATIENTS AND METHODS

Patients. Frequencies of different MHC class II alleles were compared in persons with DILS and in HIV-positive controls. Criteria for DILS consisted of (i) HIV positivity by ELISA and Western blot analysis, (ii) salivary gland enlargement persisting for at least 6 months in all adults and children, and (iii) salivary or lacrimal gland biopsy performed in all adults, but not children, demonstrating lymphocytic infiltration in the absence of granulomatous or neoplastic involvement. Serologic HLA frequencies were compared between 38 unrelated individuals with DILS (20 Black, 18 Caucasian) and 97 HIV-positive controls (51 Black, 46 Caucasians) from the same institutions in New York City. Of the HIV⁺ controls, 50 were asymptomatic and 47 had opportunistic infections. In the group with DILS, 30 were adults (16 Black, 14 Caucasian) and 8 were children (4 Black, 4 Caucasian). Molecular analysis of DRB1 alleles was performed on 21 of the patients with DILS and 102 controls. Individuals who considered themselves Hispanic were included with Caucasians. An HIV⁻ control panel consisted of 51 healthy Blacks and 81 healthy Caucasians.

Serological Analysis of MHC Class II Specificities. Conventional HLA typing was performed on enriched B-cell preparations by standard two-stage microcytotoxicity techniques, as described (24), using a panel of alloantisera to all of the well-defined HLA-DR and -DQ specificities. HLA-DR frequencies were recalculated after alternate exclusion of HLA-DR6 and HLA-DR5 persons. Statistical analyses used the Fisher exact method, with odds ratios (OR) calculated according to Haldane.

Molecular Analysis of DRB1 Alleles. In 15 individuals with DILS, total RNA was isolated from mononuclear cells by guanidine isothiocyanate extraction, and cDNA was synthesized using DRB1-specific oligonucleotide primers and reverse transcriptase. Following 30 cycles of amplification in a DNA thermal cycler using *Taq* polymerase (Perkin-Elmer/Cetus), the amplified product was size-selected on a low-melting agarose gel, cloned into pUC18 vector, and directly sequenced. To avoid PCR amplification artifacts, 10–20 clones were analyzed for each individual to confirm allelic sequence variations. In six patients with DILS and all HIV⁺ controls, DR alleles were determined by sequence-specific oligonucleotide (SSO) probes, according to methods established at the XIth Histocompatibility Workshop (25). 18-Mer SSO probes characteristic of particular DR allele motifs were 5' end-labeled with ³²P, hybridized at 54°C in 3 M tetramethylammonium chloride, and stringently washed at 57.5°C in 3 M tetramethylammonium chloride/1% SDS. Genomic DNA was amplified by 30 cycles of PCR using primers specific for the DRB1 second exon and dot blotted on the membrane

using a 96-well manifold. Signals were quantitated by a Betagen betascope.

Determination of HIV-1 V3 Domain Sequence. HIV-1 V3 loop sequences were determined in four individuals with DILS and in three controls, all with CD4 T-cell counts between 200 and 500 per mm³ and none of whom had ever had an opportunistic infection. DNA was extracted from 5 × 10⁶ uncultured peripheral blood mononuclear cells, and the HIV-1 V3 domain region was amplified by two rounds of amplification in a DNA thermal cycler using nested primers, different concentrations of MgCl₂, and *Taq* polymerase (Perkin-Elmer/Cetus). Each round of 30 cycles consisted of 30 sec of denaturation at 94°C, 60 sec of annealing at 55°C, and 90 sec of extension at 72°C. The first round of amplification was performed using sense and antisense primers, respectively, 5'-GAGCTCTACAATGTACACATGGAAT-3' and 5'-CTGCAGTTACAGTAGAAAAATTCTCC-3' in 3.0 mM MgCl₂. The second round used sense and antisense primers, respectively, 5'-GAGCTCAATGGCAGTCTAGCAGAA-GAAGA-3' and 5'-CTGCAGTTTCTGGGTCTCCTCCT-GAGG-3' in 1.5 mM MgCl₂. After directly ligating the amplified product into T/A vector (Invitrogen), 10–16 clones per person were sequenced using an automated DNA sequencer (Applied Biosystems). Evolutionary distances between nucleotide sequences of quasispecies present in each individual were determined using the two-parameter model of Kimura for pairwise comparisons (26).

RESULTS

Serological HLA Analysis: Increased Frequency of HLA-DR6 Among Blacks and Caucasians with DILS and of HLA-DR5 among Blacks Only. To address whether there might be an immunogenetic basis to the development of the host response in DILS the frequencies of different serologically defined MHC class II specificities were compared in 38 individuals with DILS and in 97 HIV⁺ controls. As shown in Table 1, those with DILS had a significantly increased frequency of HLA-DR6 compared with the controls (42% vs. 12%, OR = 5.0, *P* = 0.0003). The frequencies of two other specificities, HLA-DR4 and HLA-DR5, also exhibited increased odds ratios (2.1 and 1.7, respectively), neither reach-

Table 1. Ethnic divergence in serologically determined HLA-DR type and DILS risk susceptibility: Independent increase in the frequencies of HLA-DR6 and HLA-DR5 in Blacks, but of only HLA-DR6 in Caucasians

Selected HLA specificity	DILS, %	HIV ⁺ controls, %	OR	<i>P</i>
All ethnicities	(<i>n</i> = 38)	(<i>n</i> = 97)		
DR6	42	12	5.0	0.0003
DR5	47	35	1.7	0.13
DR5*	64	38	2.8	0.026
DR6 or DR5	79	45	4.3	0.0003
DR4	26	14	2.1	0.09
DR4*	27	17	1.9	0.19
DR1	11	18	0.6	0.23
DR2	21	36	0.5	0.07
DR3	18	22	0.8	0.44
DR7	18	19	1.0	0.60
Blacks	(<i>n</i> = 20)	(<i>n</i> = 51)		
DR5	65	37	3.0	0.032
DR6	40	16	3.5	0.032
Caucasians	(<i>n</i> = 18)	(<i>n</i> = 46)		
DR5	28	39	0.6	0.29
DR6	39	9	6.2	0.008

*Recalculated after exclusion of HLA-DR6 persons (DILS, *n* = 22; HIV⁺ controls, *n* = 85).

Table 2. Susceptibility to DILS is independently associated with two DRB1 alleles: Increased frequency of either DRB1*1301 or DRB1*1102 in Blacks and Caucasians

DRB1 allele	DILS, %	Controls, %	OR	P
All ethnicities	(n = 21)	(n = 103)		
DRB1*1101	10	12	1.0	0.56
DRB1*1102	29	9	3.7	0.029
DRB1*1301	38	19	2.6	0.062
DRB1*1102†	43	11	6.9	0.005
DRB1*1301‡	46	20	3.4	0.035
DRB1*1102 or DRB1*1301	67	28	4.9	0.001
Blacks	(n = 10)	(n = 38)		
DRB1*1101	10	8	1.6	0.62
DRB1*1102	40	8	6.4	0.034
DRB1*1301	40	21	2.5	0.20
DRB1*1102 or DRB1*1301	80	29	8.2	0.002
Caucasians	(n = 11)	(n = 64)		
DRB1*1101	9	14	0.6	0.55
DRB1*1102	18	11	2.0	0.39
DRB1*1301	36	17	2.8	0.15
DRB1*1102 or DRB1*1301	55	28	3.0	0.086

†Recalculated after alternate exclusion of persons with DRB1*1301 (DILS, *n* = 13; HIV⁺ controls, *n* = 84).

‡Recalculated after alternate exclusion of persons with DRB1*1102 (DILS, *n* = 15; HIV⁺ controls, *n* = 93).

ing statistical significance. After the exclusion of individuals with HLA-DR6, the frequency of HLA-DR5 was found to be significantly increased in the residual individuals with DILS (64% vs. 38%, OR = 2.8, *P* = 0.026). In contrast, the OR associated with HLA-DR4 decreased in this analysis, suggesting that HLA-DR5, but not HLA-DR4, acts as a second, independent risk factor for susceptibility to DILS.

Stratifying by ethnic background, different specificities were found to be associated with susceptibility to DILS in Blacks and in Caucasians. In Blacks with DILS, the frequencies of both HLA-DR5 and HLA-DR6 were significantly higher than in HIV⁺ controls (65% vs. 37%, *P* = 0.03, and 40% vs. 16%, *P* = 0.03, respectively). Indeed, 90% of Blacks with DILS had either HLA-DR5 or HLA-DR6 compared with 49% of HIV⁺ Black controls (OR = 13.5, *P* = 0.0002). Among Caucasians with DILS, the frequency of HLA-DR6 was also increased compared with HIV⁺ controls (39% vs. 9%, OR = 6.2, *P* = 0.008). However, the frequency of HLA-DR5 was not elevated in this group. No other DR specificity was increased in frequency among Caucasians with DILS after exclusion of persons with HLA-DR6.

Molecular HLA Analysis: Structurally Related MHC Class II Alleles DRB1*1102 and DRB1*1301 Are Increased in Frequency in DILS, Accounting for Ethnic Divergence in Serologic Associations. As shown in Table 2, in 21 individuals with DILS (10 Black, 11 Caucasian) whose DRB1 alleles were determined either by direct sequencing or oligonucleotide

probing, there was an increase in the frequencies of both the HLA-DR5 allele DRB1*1102 and of the HLA-DR6 allele DRB1*1301 compared with ethnically matched controls. After the alternate exclusion, respectively, of individuals with either DRB1*1301 or DRB1*1102, in the residual individuals with DILS there was a further increase in the frequencies of both DRB1*1102 (43% vs. 11%, OR = 6.9, *P* = 0.005) and DRB1*1301 (46% vs. 20%, OR = 4.9, *P* = 0.001), demonstrating that both DRB1*1301 and DRB1*1102 are independent risk factors for DILS. Fourteen of the 21 individuals with DILS (67%) had either DRB1*1102 or DRB1*1301, compared with only 28 of 102 controls (28%) (OR = 4.8, *P* = 0.001). DRB1*1301 was found at OR that were increased to a similar magnitude in both Blacks (2.5) and Caucasians (2.8) with DILS. In contrast, the OR for DRB1*1102 was much higher in Blacks with DILS (6.4) than in Caucasians (2.0). In both Blacks and Caucasians, the OR were higher for DILS being associated with either DRB1*1102 or DRB1*1301 than those with either allele alone, demonstrating that these alleles are acting as independent risk factors in both ethnic groups.

In the 21 DILS patients typed molecularly, DRB1*1301 was the DR6 allele identified in each of 8 patients who had been typed serologically as HLA-DR6, and DRB1*1102 was the DR5 allele identified in 7 of 8 patients who had been typed as HLA-DR5, including 2 DR5 Caucasians. Altogether, 13 of the 14 (93%) who had been typed serologically as DR5 or DR6 had either one or both DRB1*1102 or DRB1*1301 alleles. As shown in Table 3, DRB1*1102 encodes a very similar molecule to DRB1*1301, differing only at amino acid residues 32 and 37, where histidine and asparagine, respectively, are substituted for asparagine and tyrosine, and at residue 58, where glutamic acid is substituted for alanine. Since the DRB1*1102 allele is present in up to 45% of Black DR5 individuals but is found uncommonly in Caucasian populations (22, 23), these results likely explain the divergent DR5 serologic associations observed in Blacks and Caucasians with DILS.

HIV-1 V3 Domain Sequences: Low Evolutionary Divergence in DILS. To address whether there was evidence for a host-mediated effect on the evolution of HIV-1 structural genes in persons with DILS, V3 domain sequences from these persons were compared to those from HIV-infected controls matched for CD4 T-cell levels. Fig. 1 contrasts the distributions of pooled intrapatient nucleotide distances between pairs of sequences from the group of four persons with DILS and from the group of three controls. The distribution of intrapatient nucleotide distances in the group with DILS (204 comparisons) was narrower, with closer clustering about the mean than the distribution in the control group (224 comparisons). The mean intrapatient nucleotide distance between quasispecies present in the group with DILS was 2.9% ± 2.4% (mean ± SD). In contrast, the mean intrapatient nucleotide distance between species in the control group was 6.8% ± 4.9% (mean ± SD). The difference between the means of the two groups, 3.8%, was significant (*P* < 0.004).

Table 3. Major sites of polymorphism in HLA-DR5 and HLA-DR6 β-chain alleles illustrating regions of shared sequences between DRB1*1102 and DRB1*1301

DRB1 allele	Polymorphic residues in DR β-chain D regions															Serologic specificity
	First			Second					Third							
	9	11	13	26	28	30	32	37	57	58	67	70	71	74	86	
*1102	E	S	S	F	D	Y	N	Y	D	E	I	D	E	A	V	DR5 (11) (JVM)
*1301	—	—	—	—	—	—	H	N	—	A	—	—	—	—	—	DR6a (13) (Dw18)
*1101	—	—	—	—	—	—	—	—	—	—	F	—	R	—	G	DR5 (11) (Dw5)
*1401	—	—	—	—	—	—	H	F	A	A	L	R	E	E	—	DR6b (14) (Dw9)
*1402	—	—	—	—	E	—	H	N	—	A	L	Q	R	—	G	DR6 (14) (Dw16)
*0401	E	V	H	—	—	—	H	—	—	A	L	Q	K	—	G	DR4 (Dw4)

The amino acid sequence of DRB1*0401 is shown for comparison.

Fig. 1. Distributions of intrapatient nucleotide distances calculated from pairwise comparisons of 10–15 HIV-1 V3 sequences from each of four individuals with DILS and three HIV-1⁺ controls matched for CD4 T-cell levels: in DILS the mean intrapatient nucleotide distance between pairs of sequences is lower and there is closer clustering around the mean compared to controls.

DISCUSSION

The central point of this report is that the presence of either of two structurally related MHC class II alleles, DRB1*1102 and DRB1*1301, is associated with the development of the host response to HIV-1 infection characteristic of persons with DILS—i.e., persistent circulating and infiltrative CD8 lymphocytosis and retarded rate of progression to CD4 T-cell depletion and opportunistic infections. In persons having this response to HIV-1, there was a lower nucleotide evolutionary divergence of the HIV-1 principal neutralizing domain, the V3 loop, than was observed in viral strains from control subjects whose evolutionary divergence was within the range reported previously in the literature (7). These results suggest that particular alleles of the MHC enable the host to mount an immune response that prevents the divergence of HIV-1 quasiespecies and delays the emergence of cytopathic strains.

Although the operation of a linked gene cannot be excluded, the DRB1*1102 and DRB1*1301 alleles differ considerably in the elements at the DQA and DQB loci with which each is in linkage disequilibrium. Accordingly, the results suggest that a molecular motif encoded in common by these two DRB1 alleles might induce this host response. The DRB1*1102 and DRB1*1301 alleles are identical throughout the first and most of the second and third D regions, only differing at amino acid residues 32 and 37, where histidine and asparagine, respectively, are substituted for asparagine and tyrosine, and at residue 58, where glutamic acid is substituted for alanine, Table 3. In contrast, the predominant DR5 allele in Caucasians, DRB1*1101 (23), differs substantially from DRB1*1301 in the third D region, phenylalanine being substituted for isoleucine at position 67, arginine substituted for glutamic acid at position 71, and glycine substituted for valine at position 86.

Because of the lack of association between DRB1*1101 and DILS, this difference likely explains the lack of association with DR5 in Caucasians and implicates the third D region structures shared between the allelic products encoded by DRB1*1301, the predominant DR6 allele in both Caucasians and Blacks, and DRB1*1102, an allele found in up to 45% of Black DR5 individuals but rarely in Caucasians (22, 23), as the predisposing risk factor to developing DILS in both Blacks and Caucasians infected with HIV-1.

However, in contrast to the situation in rheumatoid arthritis where a β 1 chain third D region motif alone is sufficient for susceptibility (27), this does not appear to be the case in DILS since the DRB1*0402 and DRB1*0103 alleles, which have only this region in common with DRB1*1301/1102, were not found in any of eight DILS patients typed serologically as either DR4 or DR1. This suggests that the molecular basis of this response involves additional regions of the β 1 structure shared between DRB1*1301 and DRB1*1102. Because constrained viral evolutionary divergence has also been observed in individuals with DILS who do not have either DRB1*1102 or DRB1*1301, it is possible that in addition to the inheritance of these particular MHC class II alleles other factors may also be important in determining the clinical outcome of DILS. These could include additional MHC haplotypes, such as HLA-DR7/DQw2, which was increased, though not significantly, among Caucasians.

The narrower V3 loop diversity of viral strains observed in those with DILS compared with controls may reflect a more effective ability by the host to recognize and eliminate variants or to prevent their replication and release. More recently, using data from separated cell populations, we have determined that the HIV-1 sequences obtained from unfractionated mononuclear cells in this paper are primarily those of lymphocyte-derived strains and that V3 loop sequences from purified monocytes in DILS exhibit considerably more diversity. This may reflect the accumulation over time of mutants escaping host mechanisms of immune surveillance (6, 7, 28). These results should be contrasted with the narrow divergence of HIV-1 species reported in the subset of patients who progress very rapidly following initial infection (29). In that subset of rapid progressors, the immune response appears entirely incapable of constraining cytopathic strains that replicate highly and lead to rapid CD4 T-cell depletion.

The immune mechanisms by which individuals with DILS might be able to limit viral divergence remain conjectural. A role for non-MHC-restricted suppression of HIV-1 replication by CD8 T cells has been emphasized in infected, but otherwise healthy, individuals (30, 31). In DILS, however, the MHC class II associations presented in this report, together with the association of certain MHC class I alleles containing specific peptide binding motifs (32), suggest that MHC-restricted antigen-specific interactions are more likely. One potential mechanism would involve selective presentation of certain HIV-encoded peptides by DRB1*1102 or DRB1*1301 molecules on the surface of infected monocytes to CD4 T cells. The consequent proliferative response would result in an effective anti-HIV host response (33), possibly mediated by expanded MHC class I-restricted CD8 T cells capable of inhibiting HIV-1 replication (34).

An alternative mechanism, deriving from the “molecular mimicry” hypothesis of autoimmunity induced by an infectious agent (35), focuses on the effects of processed self-MHC fragments on the formation of the T-cell repertoire during early ontogeny (15–18). The possibility of such a mechanism is suggested by the observation that the third D region shared between the products encoded by DRB1*1102 and DRB1*1301 has considerable homology with the C-terminal region of the HIV-1 envelope V3 loop of monocyte tropic strains, as well as the North American V3 loop consensus sequence (5, 36) (Fig. 2).

HLA-DR β chain	42	66	70	76
DRB1*1301	SDVGEFRAVTELGRPDAEYWNQKD ILEDE RAAVD			
DRB1*1102	-----E-----			
HIV-1 V3 loop	1	25	35	
SC (M-tropic)	CTPRNNNTTSRIHIGPGAFYATGDIIGDIRQAHC			
North Amer. Cons.	-----RK-----T--E-----			
Homologous residues		DIL D R A		

FIG. 2. Homology between the α -helical third D region sequences of HLA-DR alleles associated with DILS susceptibility and the HIV-1 envelope V3 loop. Residues at positions 66, 67, 68, 70, 72, and 74 found in the DRB1 alleles *1102 and *1301 (shown in boldface type) are identical or homologous (Glu-Asp, Leu-Ileu) to those present at positions 25, 26, 27, 29, 31, and 33 in the V3 loop of HIV-1 strains tropic for monocytes as well as the North American consensus sequence. Residues 67, 70, and 74 of these DRB1 alleles (underlined) are polymorphic.

One way by which this mimicry could influence outcome is by deletion of self-reactive CD8 T cells, which would otherwise be injurious to the host by destroying HIV-infected CD4 T cells. However, the bias in the TCR repertoire of lymphocytes infiltrating the salivary glands in DILS suggests a positively selected antigen-driven response in those with DRB1*1102/1301 genotypes (14). Considerable evidence exists that T cells with reactivity to self-MHC peptides actually persist *in vivo*, by mechanisms involving either thymic selection or peripheral tolerance (17, 37, 38). It is possible that the introduction of the principal neutralizing V3 domain of the HIV-1 envelope into individuals with a TCR repertoire biased to recognize peptides of near-self DR could induce an enhanced proliferative and/or cytotoxic response to the region of homology. In support of this possibility, peptides encoded by either the third D region of the DR β molecule (18, 39) or the C-terminal half of the HIV-1 V3 loop (40) have been reported to induce T-cell-mediated responses. This potential mechanism could be one explanation for the observations by Schrier *et al.* (41) that in all HIV-infected persons with HLA-DR6, but only a minority of those with other DR types, there were high proliferative responses to peptides derived from the C-terminal region of the V3 loop. Should a mechanism involving DRB1-V3 loop mimicry be shown to exist, it would imply that HIV-1 vaccines using this region might induce different degrees of immunologic reactivity depending on the DRB1 genotype of the host.

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- Fauci, A. S. (1988) *Science* **239**, 617-622.
- Meltzer, M. S., Skillman, D. R., Gornatos, P. J., Kalter, D. C. & Gendelman, H. E. (1990) *Annu. Rev. Immunol.* **8**, 169-194.
- O'Brien, W. A., Koyanagi, Y., Namazie, A., Zhao, J. Q., Diagne, A., Idler, K., Zack, J. A. & Chen, I. S. (1990) *Nature (London)* **348**, 69-73.
- Shioda, T., Levy, J. A. & Cheng-Mayer, C. (1991) *Nature (London)* **349**, 167-169.
- Hwang, S. S., Boyle, T. J., Lyerly, H. K. & Cullen, B. R. (1991) *Science* **253**, 71-73.
- Wolfs, T. F., de Jong, J. J., Van den Berg, H., Tijnagel, J. M., Krone, W. J. & Goudsmit, J. (1990) *Proc. Natl. Acad. Sci. USA* **87**, 9938-9942.
- Simmonds, P. P., Zhang, L. Q., McOmish, F., Balfe, P., Ludlam, C. A. & Brown, A. J. L. (1992) *J. Virol.* **66**, 2577-2582.
- Itescu, S., Brancato, L. J. & Winchester, R. (1989) *Lancet* **ii**, 466-468.

- Itescu, S. & Winchester, R. (1992) *Rheum. Dis. Clin. North Am.* **18**, 683-697.
- Itescu, S., Mathur-Wagh, U., Skovron, M. L., Brancato, L. J., Marmor, M., Zeleniuch-Jacquotte, A. & Winchester, R. (1992) *J. AIDS* **5**, 37-45.
- Itescu, S., Dalton, J., Zhang, H. & Winchester, R. (1993) *J. Clin. Invest.* **91**, 2216-2225.
- Lairmore, M. D., Poulson, J. M., Adducci, T. A. & DeMartini, J. C. (1988) *Am. J. Pathol.* **130**, 80-90.
- Kennedy-Stoskopf, S., Zink, C. & Narayan, O. (1989) *Clin. Immunol. Immunopathol.* **52**, 323-330.
- Dwyer, E., Itescu, S. & Winchester, R. (1993) *J. Clin. Invest.* **92**, 495-502.
- Schwartz, R. H. (1989) *Cell* **57**, 1073-1076.
- Nikolic Zucic, J. & Bevan, M. J. (1990) *Nature (London)* **344**, 65-67.
- Benichou, G., Takizawa, P. A., Ho, P. T., Killion, C. C., Olson, C. A., McMillan, M. & Sercarz, E. E. (1990) *J. Exp. Med.* **172**, 1341-1346.
- Rosloniec, E. F., Vitez, L. J., Buus, S. & Freed, J. H. (1990) *J. Exp. Med.* **171**, 1419-1430.
- Itescu, S., Brancato, L. J., Buxbaum, J., Gregersen, P. K., Rizk, C. C., Croxson, S., Solomon, G. & Winchester, R. (1990) *Ann. Intern. Med.* **112**, 3-10.
- Pollack, M. S., Satai, B. & Dupont, B. (1983) *Dis. Markers* **1**, 135-139.
- Pollack, M. S., Satai, B., Myskowski, P. L., Gold, J. W. M. & Dupont, B. (1983) *Tissue Antigens* **21**, 1-8.
- Johnson, A. H., Rosen-Bronson, S. & Hurley, C. K. (1989) *Transplant. Proc.* **21**, 3872-3873.
- Fernandez-Vina, M., Shumway, J. W. & Stastny, P. (1990) *Hum. Immunol.* **28**, 51-64.
- Matsuyama, T., Winchester, R., Lee, S., Shookster, L. & Nunez-Roldan, A. (1988) *J. Immunol.* **140**, 537-543.
- Moraes, M. E., Fernandez Vina, M. & Stastny, P. (1991) *Hum. Immunol.* **31**, 139-144.
- Kimura, M. (1980) *J. Mol. Evol.* **16**, 111-120.
- Gregersen, P. K., Silver, J. & Winchester, R. J. (1987) *Arthritis Rheum.* **30**, 1205-1213.
- Nowak, M. A., Anderson, R. M., McLean, A. R., Wolfs, T. F., Goudsmit, J. & May, R. M. (1991) *Science* **254**, 963-969.
- Ezzel, C. (1993) *J. NIH. Res.* **5**, 77.
- Walker, C. M., Moody, D. J., Stites, D. P. & Levy, J. A. (1986) *Science* **234**, 1563-1566.
- Mackewicz, C. E., Ortega, H. W. & Levy, J. A. (1991) *J. Clin. Invest.* **87**, 1462-1466.
- Itescu, S., Rose, S., Dwyer, E. & Winchester, R. J. (1994) *Hum. Immunol.*, in press.
- Clerici, M. & Shearer, G. M. (1993) *Immunol. Today* **14**, 107-111.
- Walker, B. D., Chakrabarti, S., Moss, B., Paradis, T. J., Flynn, T., Durno, A. G., Blumberg, R. S., Kaplan, J. C., Hirsch, M. S. & Schooley, R. T. (1987) *Nature (London)* **328**, 345-348.
- Oldstone, M. B. (1987) *Cell* **50**, 819-820.
- LaRosa, G. J., Davide, J. P., Weinhold, K., Waterbury, J. A., Profy, A. T., Lewis, J. A., Langlois, A. J., Dreesman, G. R., Boswell, R. N., Shadduck, P., Holley, L. H., Karplus, M., Bolognesi, D. P., Matthews, T. J., Emini, E. A. & Putney, S. D. (1990) *Science* **249**, 932-935.
- Gammon, G. & Sercarz, E. (1989) *Nature (London)* **342**, 183-185.
- Rudensky, A. Y., Rath, S., Preston-Hurlburt, P., Murphy, D. B. & Janeway, C. A., Jr. (1991) *Nature (London)* **353**, 660-662.
- Harris, P. E., Liu, Z. & Suci Foca, N. (1992) *J. Immunol.* **148**, 2169-2174.
- Takahashi, H., Merli, S., Putney, S. D., Houghten, R., Moss, B., Germain, R. N. & Berzofsky, J. A. (1989) *Science* **246**, 118-121.
- Schrier, R. D., Gnann, J. W., Jr., Landes, R., Lockshin, C., Richman, D., McCutchan, A., Kennedy, C., Oldstone, M. B. & Nelson, J. A. (1989) *J. Immunol.* **142**, 1166-1176.