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CELLULAR RESPONSE TO INFECTION

HIV-1 Epitope Variability Is Associated with T Cell Receptor Repertoire Instability and Breadth

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ABSTRACT Mutational escape of HIV-1 from HIV-1-specific CD8$^+$ T lymphocytes (CTLs) is a major barrier for effective immune control. Each epitope typically is targeted by multiple clones with distinct T cell receptors (TCRs). While the clonal repertoire may be important for containing epitope variation, determinants of its composition are poorly understood. We investigate the clonal repertoire of 29 CTL responses against 23 HIV-1 epitopes longitudinally in nine chronically infected untreated subjects with plasma viremia of <3,000 RNA copies/ml over 17 to 179 weeks. The composition of TCRs targeting each epitope varied considerably in stability over time, although clonal stability (Sorensen index) was not significantly time dependent within this interval. However, TCR stability inversely correlated with epitope variability in the Los Alamos HIV-1 Sequence Database, consistent with TCR evolution being driven by epitope variation. Finally, a robust inverse correlation of TCR breadth against each epitope versus epitope variability further suggested that this variability drives TCR repertoire diversification. In the context of studies demonstrating rapidly shifting HIV-1 sequences *in vivo*, our findings support a variably dynamic process of shifting CTL clonality lagging in tandem with viral evolution and suggest that preventing escape of HIV-1 may require coordinated direction of the CTL clonal repertoire to simultaneously block escape pathways.

IMPORTANCE Mutational escape of HIV-1 from HIV-1-specific CD8$^+$ T lymphocytes (CTLs) is a major barrier to effective immune control. The number of distinct CTL clones targeting each epitope is proposed to be an important factor, but the determinants are poorly understood. Here, we demonstrate that the clonal stability and number of clones for the CTL response against an epitope are inversely associated with the general variability of the epitope. These results show that CTLs constantly lag epitope mutation, suggesting that preventing HIV-1 escape may require coordinated direction of the CTL clonal repertoire to simultaneously block escape pathways.

KEYWORDS cytotoxic T lymphocytes, human immunodeficiency virus

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The major histocompatibility class I (MHC-I)-restricted CD8$^+$ T lymphocyte (CTL) response is a critical arm of immunity for clearance or chronic control of many viral infections. The central protective role of human immunodeficiency virus type 1 (HIV-1)-specific CTLs in the pathogenesis of HIV-1 infection is clear from studies such as *in vivo* CD8 depletion in the simian immunodeficiency virus (SIV)-macaque model (1–3) and the consistent observation that the MHC-I locus is the strongest correlate to immune control of HIV-1 infection in multiple genetic screening studies (4–6). However,

the CTL response fails to contain infection in the vast majority of infected persons, who eventually progress to severe immunodeficiency and death without treatment. The high mutation rate and genetic plasticity of HIV-1 likely are major contributors to this failure; viral adaptation to CTL responses is the major driver of viral sequence evolution in infected persons (7–9).

The CTL response against any given epitope is typically polyclonal, comprised of CTLs with distinct T cell receptors (TCRs). While these CTL clones have expanded in response to the same epitope, different TCRs may differ significantly in their recognition of different epitope sequence variants (10). Moreover, an epitope variant that escapes recognition by a CTL response can be recognized by a *de novo* variant-specific response that does not recognize the original epitope sequence (11). Clonal breadth has therefore been raised as a potentially important parameter for CTL containment of HIV-1 infection through broader coverage of epitope variation (12, 13). Although prior studies have suggested clonal stability (14) or shifting clonotypes (15) of HIV-1-specific CTL responses, the determinants of the clonal repertoire of CTL responses are poorly understood. Here, we examine the TCR repertoire over time for several HIV-1 epitopes in persons with chronic untreated infection who all maintained plasma viremia of <3,000 RNA copies/ml.

RESULTS

Quantitative spectratyping defines CTL clonal composition and breadth against HIV-1 epitopes longitudinally in persons with chronic HIV-1 infection. Quantitative spectratyping was utilized to assess the longitudinal clonal composition and breadth of 29 CTL responses against 23 epitopes in 9 chronically HIV-1-infected subjects, all of whom spontaneously maintained plasma viremia of <3,000 RNA copies/ml without receiving antiretroviral therapy during observation (Table 1). The time intervals of follow-up ranged from 17 to 179 weeks. Peripheral blood mononuclear cells (PBMCs) were cultured in the presence and absence of the epitopes of interest, followed by quantitative spectratyping as previously described (16) to identify epitope-specific clonal peak expansions within beta variable (BV) gene families (Fig. 1).

Clonal stability of CTL responses against HIV-1 epitopes varied independently of time over the period of observation. Examination of epitope-specific TCRs showed generally stable breadth over time (Fig. 2A). There was little variation in the number of clones targeting each epitope over time, and breadth and stability were similar between epitopes restricted by MHC-I A and B versus C types (Fig. 2B to D) or from different viral proteins (Fig. 2E to I). However, there were varying patterns of clonal dominance ranging from highly stable to shifting profiles. In some instances, the TCR clones targeting an epitope showed shifts in composition (Fig. 3A), whereas other responses showed stability (Fig. 3B) within the same person. To assess whether the varying degree of clonal stability between epitopes was due to variation in the duration of longitudinal observation, clonal similarity was compared to the duration between time points (Fig. 4A). This analysis showed that there was no significant relationship between the time elapsed and TCR clonal similarity between time points for the period of observation ranging from 17 to 176 weeks, suggesting that time was not a significant factor in the degree of clonal variation over the duration of observation.

TCR clonal stability inversely correlates with epitope variability. Because CTL persistence is driven by antigen recognition, epitope variability was compared to TCR clonal stability. Global epitope sequence diversity across all subtype B sequences in the Los Alamos HIV Sequence Database was calculated as a surrogate marker for epitope variability, given that most of the subjects had viremia below the limits of detection. This revealed a modest but statistically significant inverse correlation of TCR clonal stability and epitope variability (Fig. 4B). Of note, epitopes restricted by B*57, which is associated with superior immune containment of HIV-1 infection in some persons, spanned the range of epitope diversity and stability. Also, clonal stabilities were similar between epitopes restricted by MHC-I A and B versus C types and epitopes from different viral proteins (Fig. 5). Overall, these data suggested that the least variable

TABLE 1 HIV-1-infected participants and CTL responses evaluated longitudinally[a]

Participant	MHC class I			Duration of infection	Epitope						
	A	B	C		Sequence (abbreviated)	MHC- I type	Location	Diversity	Sampling interval (wk)	Similarity	Mean breadth
S00009	03	15	03	>14 yr	GLNKIVRMY (GY9)	B*15	Gag 269–277	0.06	114	0.73	7.0
	26	38	12		ALVEICTEMEK (AK11)	A*03	Pol 188–198	0.48	114	0.32	1.5
					AIFQSSMTK (AK9)	A*03	Pol 313–321	0.57	114	0.00	2.5
					IKLEPVHGVY (IY10)	B*15	Pol 464–473	0.44	114	0.72	4.5
S00016	03	18	02	>4 mo	KIRLRPGGK (KK9)	A*03	Gag 18–26	0.40	179	0.14	4.5
	32	40	07		RLRPGGKKKY (RY10-G)	A*03	Gag 20–29	0.60	179	0.35	2.5
					KELYPLASL (KL9-G)	B*40	Gag 481–489	0.83	179	0.39	4.0
					LEKHGAITS (LS9)	B*40	Nef 37–45	0.86	179	0.00	2.5
					KEKGGLEGL (KL9-N)	B*40	Nef 92–100	0.51	179	0.05	2.5
					RRQDILDLWIY (RY11)	C*07	Nef 105–115	0.83	179	0.47	4.5
S00024	02	13	06	>13 yr	RLRPGGKKKY (RY10-G)	B*15	Gag 20–29	0.60	76	0.25	1.5
		15	07		SLYNTVATL (SL9)	A*02	Gag 77–85	0.86	76	0.26	3.0
					GLNKIVRMY (GY9)	B*15	Gag 269–277	0.06	76	0.57	7.0
					RQANFLGKI (RI9)	B*13	Gag 429–437	0.24	76	0.22	4.5
					GQGQWTYQI (GI9)	B*13	Pol 488–496	0.74	76	0.17	1.5
S00031	02	13	03	>8 yr	RLRDLLLIV (RV9)	A*02	Env 770–778	0.69	132	0.00	3.0
		15	06								
S00036	02	39	06	>12 yr	SLYNTVATL (SL9)	A*02	Gag 77–85	0.86	111	0.00	1.0
	11	57	07		ISPRTLNAW (IW9-G)	B*57	Gag 147–155	0.47	176	0.52	3.7
					KAFSPEVIPMF (KF11)	B*57	Gag 162–172	0.14	64	0.43	3.5
					IVLPEKDSW (IW9-P)	B*57	Pol 399–407	0.73	176	0.00	0.7
					VLEWRFDSR (VR9)	A*02	Nef 180–188	0.91	111	0.00	2.0
S00039	31	13	04	>3 mo	RQANFLGKI (RI9)	B*13	Gag 429–437	0.24	43	0.55	6.0
	32	35	06		GQGQWTYQI (GI9)	B*13	Pol 488–496	0.74	43	0.00	1.0
S00052	01	18	06	>14 yr	KAFSPEVIPMF (KF11)	B*57	Gag 162–172	0.14	107	0.63	4.0
	25	57	12		AVRHFPRIW (AW9)	B*57	Vpr 30–38	0.86	161	0.68	2.0
					RTVRLIKLLY (RY10-R)	B*57	Rev 14–23	0.98	30	0.52	1.0
S00085	02	57	08	>15 yr	ILKEPVHGV (IV9)	A*02	Pol 464–472	0.43	17	0.91	2.5
	33	65	18								
S00096	01	08	07	>9 yr	YRLDQQLLGIWGC (YC13)	C*07	Env 586–598	0.70	20	0.56	1.0
	32	51	14		RRGWEALKY (RY9)	A*01	Env 787–796	0.81	20	0.61	1.0

[a]All the participants were men who did not receive antiretroviral therapy during the study duration. The MHC-I types, duration of infection at study onset, epitope sequence and restriction, epitope diversity across all HIV-1 subtype B sequences in the Los Alamos HIV Sequence Database, time intervals analyzed, Sorenson similarity index between time points, and mean clonal breadth as determined by spectratyping across time points are indicated.

epitopes were associated with greater TCR clonal stability and that this process is MHC-I independent.

TCR clonal breadth inversely correlates with epitope variability. Epitope variability, again reflected by the surrogate marker of epitope sequence diversity, was compared to TCR clonal breadth to investigate whether greater variability in epitope sequences might drive more clonal responses. Comparison of epitope diversity to TCR clonal breadth against each epitope revealed a robust inverse correlation (Fig. 6). Again, epitopes restricted by MHC-I B*57 spanned the spectrum of epitope diversity and clonal breadth and did not appear distinct from other epitope responses. These data in the context of the above-mentioned findings are consistent with a bidirectional interrelationship between epitope variability and the clonal composition of CTL responses against HIV-1 infection.

DISCUSSION

As adaptive immunity, CTL responses arise and are maintained by the presence of the epitopes that they recognize. As occurs physiologically when a viral infection is cleared and effector CTLs are no longer needed, HIV-1-specific CTL frequencies decay

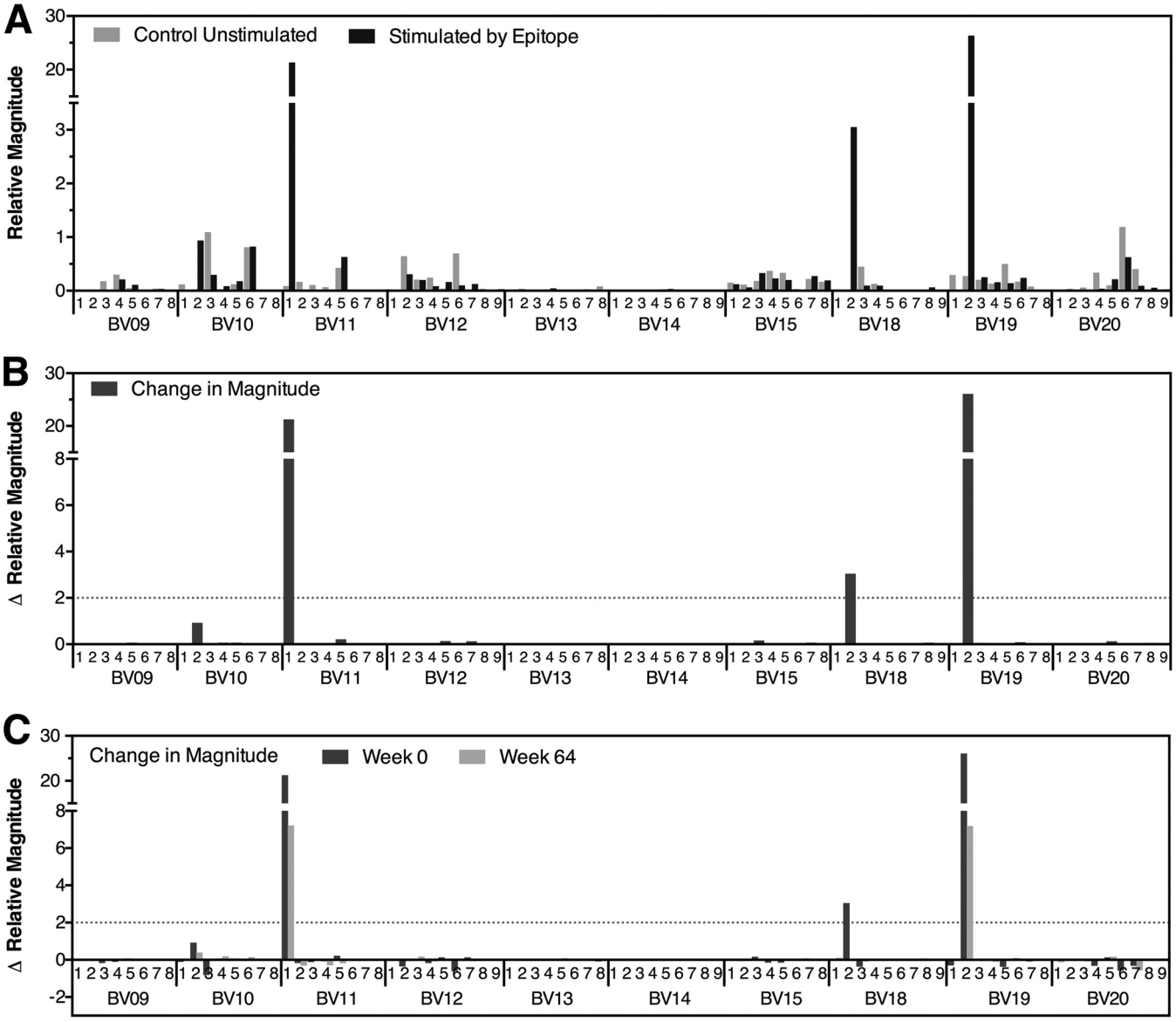

FIG 1 Delineation of the clonal profile of CTL responses targeting HIV-1 epitopes. An example of quantitative spectratyping is shown. PBMCs were cultured in the presence or absence of the epitope of interest, followed by spectratyping of 24 BV gene families within isolated $CD8^+$ T lymphocytes, using quantitative PCR to determine the copy numbers of each family. The relative concentration of each BV family was calculated as the ratio of its copy number to the median copy number across all families. The relative magnitude of each spectratype peak was calculated as the fraction of the peak area within the summed area of all peaks in its family multiplied by the relative concentration of the family. The last 10 of the 24 analyzed families are shown as representative examples, because they contained a mixture of families with and without epitope-specific responses. (A) Results are shown for unstimulated and peptide-stimulated peak profiles, demonstrating some families with epitope-specific expansions (BV11, BV18, and BV19). (B) The magnitude of change of each peak in response to epitope stimulation was calculated by subtracting the relative magnitude of unstimulated spectratypes from that of epitope-stimulated spectratypes. Results for the same 10 BV families are shown, quantifying the epitope-specific expansions (defined as increases of $\geq$2 units) in families BV11, BV18, and BV19 from panel A. (C) Results for the magnitude changes of each peak in response to epitope stimulation for the same 10 BV families for two different time points.

to low resting memory levels after virus replication is suppressed by antiretroviral drug treatment (17, 18). At the level of CTLs recognizing a single epitope, the same process occurs if a targeted epitope mutates to become a completely unrecognized variant (19, 20), indicating that the composition of the CTL response is driven by viral epitope sequence evolution. Conversely, however, the CTL response applies selective pressure that drives viral epitope evolution (7–9), individual clones within the response can select for different epitope escape variants (10), and HIV-1 tends to revert epitope mutations when a prior CTL response is absent (21).

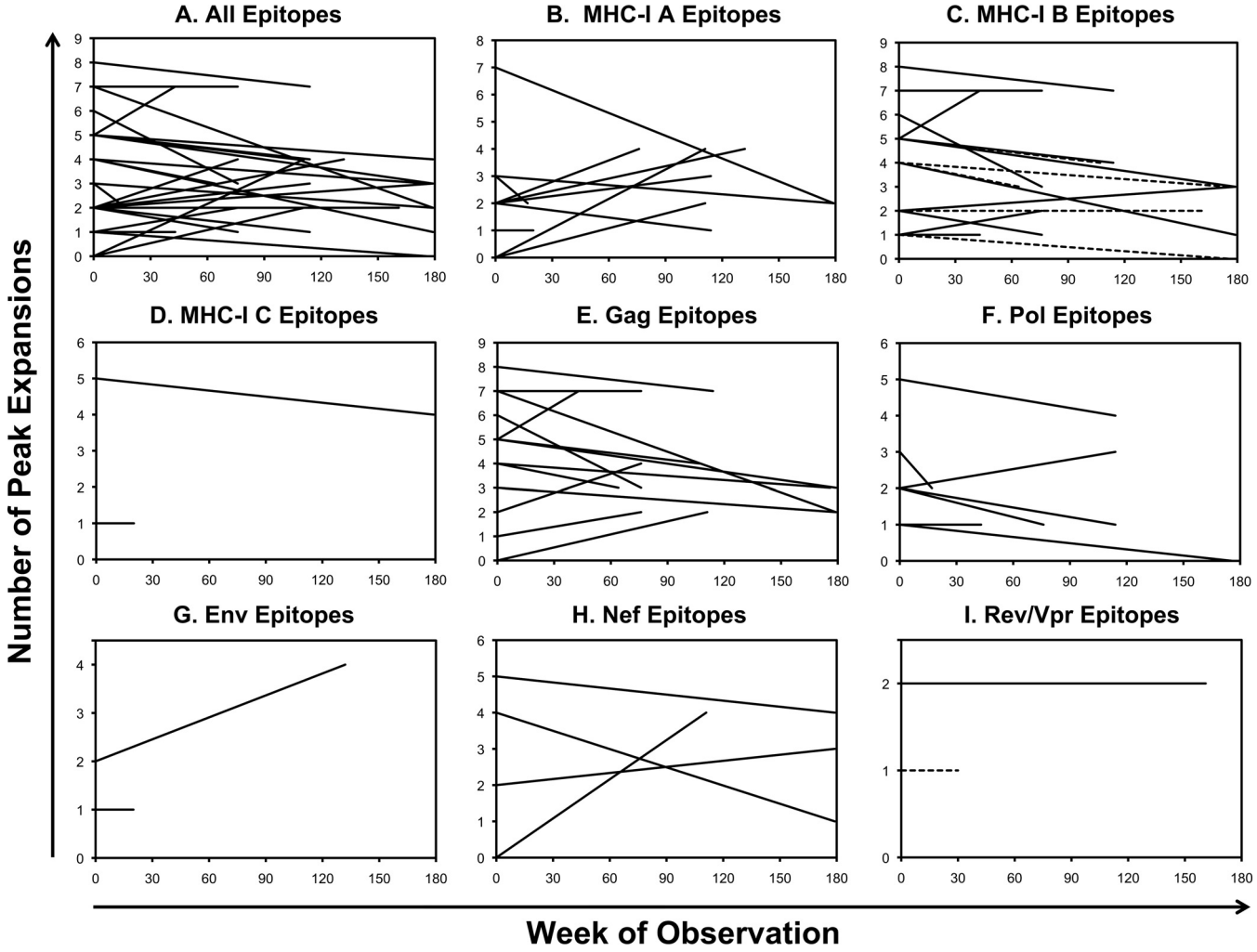

FIG 2 Generally stable clonal breadth of HIV-1 epitope-specific CTL responses over time. The clonal breadths of responses to the HIV-1 epitopes in Table 1 (as delineated in Fig. 1) are plotted over time for all epitopes (A), epitopes divided according to MHC-I restriction (B to D), and epitopes divided according to viral protein source (E to I). In panel C, the dashed lines indicate B*57-restricted responses. In panel I, the dashed line indicates a Rev epitope, while the solid line indicates a Vpr epitope.

Our data support the concept of a dynamic bidirectional interaction between the CTL response and HIV-1 sequence variation *in vivo*, and our prior observation of "partial escape" was demonstrated as persistence of viral epitopes with reduced fitness under CTL pressure *in vivo* (22). It has been demonstrated that the HIV-1 quasispecies *in vivo* has ongoing shifts in the frequency of individual CTL epitope mutants (23, 24). In the context of CTL expansion and contraction being driven by epitope recognition and nonrecognition, respectively, and differential recognition of epitope variants by different CTL clones recognizing the same epitope, the observed variation in CTL clonal frequencies over time is consistent with different clones expanding and contracting according to varying epitope variants within the quasispecies. In turn, the differential recognition of epitope variants that drives variation between frequencies of individual CTL clones also exerts differential antiviral pressure between different epitope variants, driving viral evolution. This process is analogous to the genetic coevolution of broadly neutralizing antibodies and HIV-1 Env *in vivo* (25), in which the neutralizing antibody response continuously lags behind viral evolution (26). This lag prevents the efficacy of antibodies in the infected persons in whom they arise, yet administration of a broadly neutralizing antibody to another person in whom HIV-1 has not coevolved can yield a potent antiviral effect (27–30), presumably by blocking escape pathways in advance of their evolution.

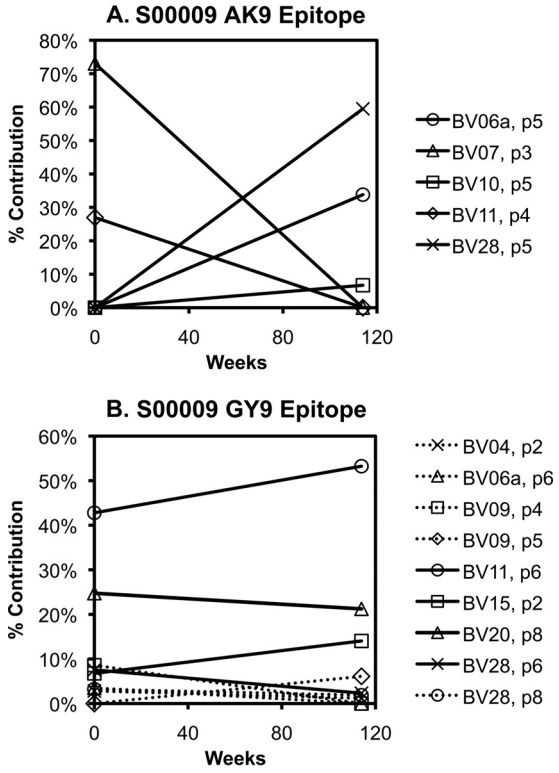

FIG 3 Varying clonal stability of CTL responses over time. An example of a CTL response exhibiting changing clonal composition over time is shown (A). The response to AK9 in subject S00009 was comprised of clonal expansions in BV7 (within peak 3) and BV11 (peak 4) at the baseline evaluation, but then clonal expansions in BV6a (peak 6), BV10 (peak 5), and BV28 (peak 5) 114 weeks later. (B) In contrast, another response (against the GY9 epitope) in the same person showed a relatively stable clonal composition over the same span of time.

Our results provide a likely explanation for varying prior observations of TCR clonotype stability (14) versus variability (15) in HIV-1-infected persons. HIV-1 CTL epitopes vary markedly in their sequence constraint, and thus in the breadth of their mutation landscape. Therefore, HIV-1 has more options for epitope variation in some epitopes than others, which consequently drives more options to escape CTL responses. The inverse correlation between CTL clonal stability and epitope diversity supports a scenario where greater epitope variability allows more dynamic shifting in

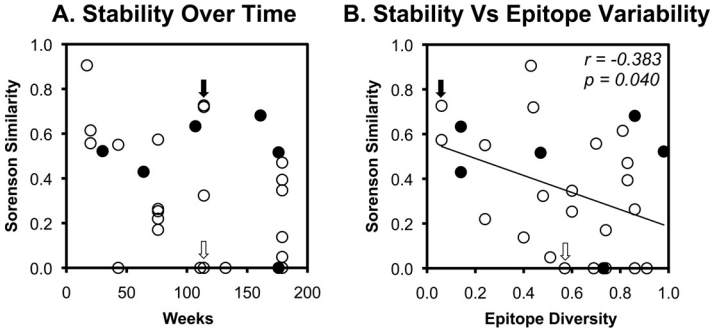

FIG 4 Correlates of clonal stability of CTL responses against HIV-1 epitopes. The clonal similarity of the CTL responses in Table 1 over time is plotted against time (A) and epitope variability (B) as approximated by sequence diversity among all subtype B sequences in the Los Alamos HIV Sequence Database. B*57-restricted epitopes are highlighted as filled circles. For reference, the examples in Fig. 3 are indicated by open (AK9 epitope) and solid (GY9 epitope) arrows. Correlations were evaluated using Spearman's rank test.

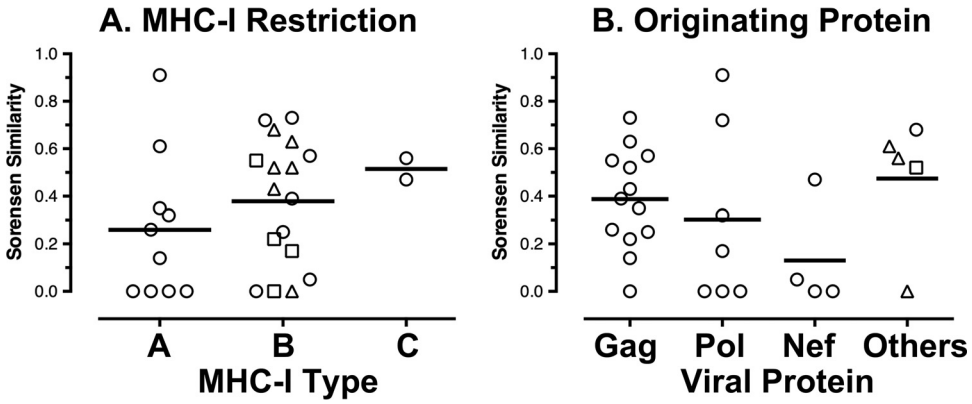

FIG 5 Clonal stability of CTL responses subdivided by MHC-I restriction and targeted HIV-1 proteins. The longitudinal similarity measurements plotted in Fig. 4 were divided according to MHC-I restriction (A) or targeted viral protein (B). (A) Triangles represent B*57, and squares represent B*13. (B) Triangles represent Env, circles represent Rev, and the square represents Vpr.

the population of epitope variants, followed by greater shifting in the CTL clones responding to the variants.

Finally, the robust inverse correlation between CTL clonal breadth and epitope diversity is novel evidence for an important determinant of the CTL response against HIV-1; we previously demonstrated that clonal breadth is not correlated with MHC-I restriction or the frequency of the response (16). Again, this is consistent with a bidirectional interaction of viral sequence evolution and the CTL response at the clonal level, in which greater epitope variability allows exposure of the CTL response to more epitope variants, driving greater CTL clonal breadth. This finding also suggests an explanation for the observation that "public TCR" clonotypes shared between multiple persons with a common MHC-I allele have mostly been observed for highly conserved epitopes, such as the B*57-restricted KF11 epitope in Gag (13, 31, 32). Additionally, it supports the rationale for using mixtures of sequences in vaccines to encompass diversity that drives greater recognition of epitope variation by CTL responses, such as the "mosaic" strategy (33, 34).

Although not a focus of this report, it is interesting that the "protective" MHC-I type B*57 presents epitopes that span the observed range of variability in sequence diversity, stability of CTL responses, and clonal breadth of CTL responses. Although indirectly relevant, this finding is less consistent with the proposed mechanism of B*57 protection via thymic selection of more promiscuous TCRs (35) versus the concept that the protective contribution of CTL responses is epitope specific (36).

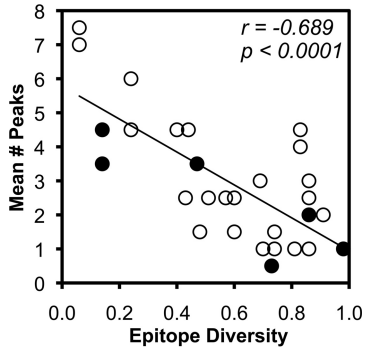

FIG 6 Inverse correlation of epitope variability and CTL clonal breadth. The average clonal breadth of each HIV-1 epitope-specific CTL response (shown in Fig. 2) is plotted against epitope variability as approximated by sequence diversity among all subtype B sequences in the Los Alamos HIV Sequence Database. B*57-restricted epitopes are highlighted as filled circles. Correlations were evaluated using Spearman's rank test.

There are inherent limitations to our findings. Epitope sequence diversity in the Los Alamos HIV Sequence Database is an indirect approximation of the mutational space available for epitope variation in a given person, which may be context dependent in terms of the strain of HIV-1 and host factors. Moreover, there are two major reasons for using this parameter as opposed to diversity within the participants' endogenous HIV-1 epitope sequences. First, the low levels of viremia in these persons is a significant technical barrier to ensuring acquisition of enough clonal sequences for accurate assessment of epitope diversity in their viral quasispecies. Second, and more important, the interaction of epitope sequences and CTLs is bidirectional. While the key parameter of interest is epitope plasticity, i.e., options for mutation, the observed diversity in each individual is the net outcome of the interaction, i.e., the options remaining after CTL targeting. Moreover, CTL responses against different epitopes likely vary significantly in their antiviral activity (37, 38), and thus, the selective pressure driving epitope diversity and resulting TCR diversity may not be uniform. Thus, while imperfect, sequence diversity in the Los Alamos HIV Sequence Database is a less biased indicator of epitope plasticity, reflecting the general variability of the epitope across all persons, most of whom do not have the CTL response studied here.

Finally, our methodology for defining epitope-specific TCRs depends on the capacity of CTLs to proliferate in response to an epitope, which could be biased by varying proliferative capacity or the use of a fixed epitope sequence, both factors that could underestimate clonal breadth. Because all our subjects were persons with stable controlled viremia off antiretroviral therapy, CTL functionality should have been relatively intact and similar between individuals.

In conclusion, we observed inverse correlations between epitope variability and CTL clonal stability over time and between epitope variability and CTL clonal breadth in persons with chronic stable untreated HIV-1 infection and plasma viremia of $<$3,000 RNA copies/ml. These findings provide evidence for a bidirectional interaction of the CTL response and HIV-1 sequence evolution where immunity lags virus sequence evolution. This suggests the potential of coordinating the CTL response in vaccine or immunotherapeutic approaches to block escape pathways in advance of viral evolution.

MATERIALS AND METHODS

Participants and peripheral blood mononuclear cells. The participants (Table 1) were persons with chronic HIV-1 infection who were not receiving antiretroviral treatment during the study period. All the participants were spontaneous "controllers" of infection with persistent maintenance of viremia at $<$3,000 HIV-1 RNA copies/ml plasma during observation. MHC-I typing was performed by the clinical immunogenetics laboratory at UCLA Medical Center. All participants provided informed consent under a UCLA Institutional Review Board-approved protocol. PBMCs were isolated by Ficoll-Hypaque gradient and viably cryopreserved until use.

Detection of HIV-1-specific CTL responses by IFN-γ ELISpot assay. CTL responses were identified by gamma interferon (IFN-γ) enzyme-linked immunosorbent spot (ELISpot) assay using polyclonally expanded CD8$^+$ T lymphocytes, as previously described (39–41). Screening was performed using previously described minimal epitopes for the MHC-I types of the individuals (42).

Delineation of the HIV-1 epitope-specific CTL clonal repertoires. For confirmed CTL responses against minimal epitopes, the clonal breadth of CTL clones recognizing selected HIV-1 epitopes was assessed by a quantitative spectratyping assay as previously described (16). In brief, PBMCs were cultured with the epitope to enrich the CTLs recognizing that epitope, with a parallel control cultured without the epitope. CD8$^+$ T lymphocytes were then purified for TCR analysis of cDNA using real-time PCR for each of 24 BV gene families. The relative concentration of each family was calculated as the ratio of its mean number of copies to the median number of copies across all families (relative units). For each family, capillary electrophoresis was performed on the real-time PCR product to resolve the size distributions of TCRs, and the concentration of each size population within a family was calculated using its percent contribution to the whole BV family. Epitope-specific TCRs were identified by comparing epitope-stimulated to control unstimulated spectratype profiles for peaks expanded by more than 2 relative units by epitope stimulation (an arbitrary cutoff based on control data showing that most nonspecific peak variations with this method are $<$1 unit).

TCR repertoire analyses. Comparison of epitope-specific TCR similarities between time points was performed using the abundance-based Sorensen Index (43): similarity $= 2UV/U + V$, where UV represents the summed magnitudes of shared spectratype peak expansions between time points and U and V represent the summed magnitudes of all expansions at each time point (thus, a value

of 1 indicates all identical expansions of the same magnitudes, whereas a value of 0 indicates no shared expansions).

Epitope sequence variability analyses. The variability of epitopes was assessed by calculating the Simpson diversity (D_s) index (44) using the set of all clade B sequences (excluding unresolved amino acids or deletions) returned by the QuickAlign tool at the Los Alamos National Laboratory HIV Sequence Database (http://www.hiv.lanl.gov) for each epitope, and diversity was calculated as follows: $D_s = 1 - \sum_{i=1}^{c} n_i(n_i - 1)/N(N - 1)$, where, *N* is the total number of sequences included for the analysis, *n* is the frequency of the *i*th epitope variant sequence, and *c* is the total number of epitope variants (thus, a value of 1 indicates an infinite number of different sequences, whereas a value of 0 indicates that all sequences are identical).

Statistical tests. For evaluation of correlations between two variables (Fig. 4 and 6), Spearman's rank test was utilized. For evaluation of differences between groups, the Mann-Whitney test was utilized (Fig. 5).

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