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HLA-Associated Viral Mutations Are Common in Human Immunodeficiency Virus Type 1 Elite Controllers[▽]

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Elite controllers (EC) of human immunodeficiency virus type 1 (HIV-1) maintain viremia below the limit of detection without antiretroviral treatment. Virus-specific cytotoxic CD8$^+$ T lymphocytes are believed to play a crucial role in viral containment, but the degree of immune imprinting and compensatory mutations in EC is unclear. We obtained plasma *gag*, *pol*, and *nef* sequences from HLA-diverse subjects and found that 30 to 40% of the predefined HLA-associated polymorphic sites show evidence of immune selection pressure in EC, compared to approximately 50% of the sites in chronic progressors. These data indicate ongoing viral replication and escape from cytotoxic T lymphocytes are present even in strictly controlled HIV-1 infection.

Human immunodeficiency virus type 1 (HIV-1)-infected persons who control viremia to below the limit of detection (<50 RNA copies/ml plasma) without therapy have been called elite controllers (EC) (3–5, 25, 28). Understanding the mechanisms responsible for successful viral control should contribute greatly to understanding HIV-1 pathogenesis and vaccine development.

Current evidence supports the notion that virus-specific cytotoxic T lymphocytes (CTLs) play a crucial role in controlling AIDS virus replication (1, 17, 18, 20, 27–32). Many studies have indicated that broad Gag-specific CTL responses are associated with lower plasma viral loads and better clinical outcomes (14, 19, 28, 33). However, viral escape from CTLs is commonly seen in AIDS virus infection (1, 10, 15, 21, 29). Recently, we reported that the replication capacity of chimeric viruses encoding *gag-protease* derived from EC was significantly reduced, associated with distinct HLA class I alleles in EC (26), suggesting that escape mutations from alleles enriched in EC diminish viral replicative fitness. However, to date, no population studies have examined the extent to which HLA-associated mutations, indicative of CTL escape mutations, are present in viruses from EC. In this study, we evaluated HLA-associated mutations in HIV-1 protein sequences (54 Gag, 41 reverse transcriptase [RT], and 39 Nef) derived from plasma viruses from EC and compared these to sequences obtained from untreated chronic progressors (CP) similarly obtained from North America (567 Gag, 392 RT, and 686 Nef) (7, 9). The median plasma viral load of CP was 120,000 (interquartile range, 42,000 to 310,000) RNA copies/ml. These studies were guided by a comprehensive list of HLA-associated polymorphisms in HIV-1 clade B defined in a cohort of more than 1,200 individuals by phylogenetically informed methods (7–9, 16). Our objective was to define the relative extent of polymorphisms in circulating plasma viruses from EC that could be attributed to HLA class I selection pressure, namely, putative CTL-driven mutations. Since there is bias in the distribution of HLA class I alleles between EC and CP (28), we report results in terms of the proportion of HLA-associated polymorphic sites within a given individual's autologous HIV sequence exhibiting the predefined specific HLA-associated polymorphisms. For each subject, the total number of predefined HLA-associated polymorphic sites in autologous viral sequences was determined and divided by the potential number in the context of their specific HLA class I allotype.

As shown in Fig. 1A, the proportion of putative CTL escape sites observed in EC was substantial in the Gag, RT, and Nef proteins (37.5%, 30.8%, and 42.1%, respectively) but still significantly lower than that observed in CP (0.375 versus 0.500 [$P < 0.0001$], 0.308 versus 0.400 [$P < 0.0001$], and 0.421 versus 0.533 [$P < 0.0001$], respectively). The proportion of HLA-associated mutations remained high in EC even after HLA-B57 subjects were removed (Fig. 1B).

We repeated the analysis limited to HLA-associated sites inside (within ±3 amino acids [aa]) published (Los Alamos National Database) or predicted (Epipred tool; Microsoft Research) CTL epitopes. Limiting the analysis to these sites has been used as an indication of mutations that are likely to directly affect escape from CTLs (9, 23), as opposed to compensatory mutations, which are usually observed more distant

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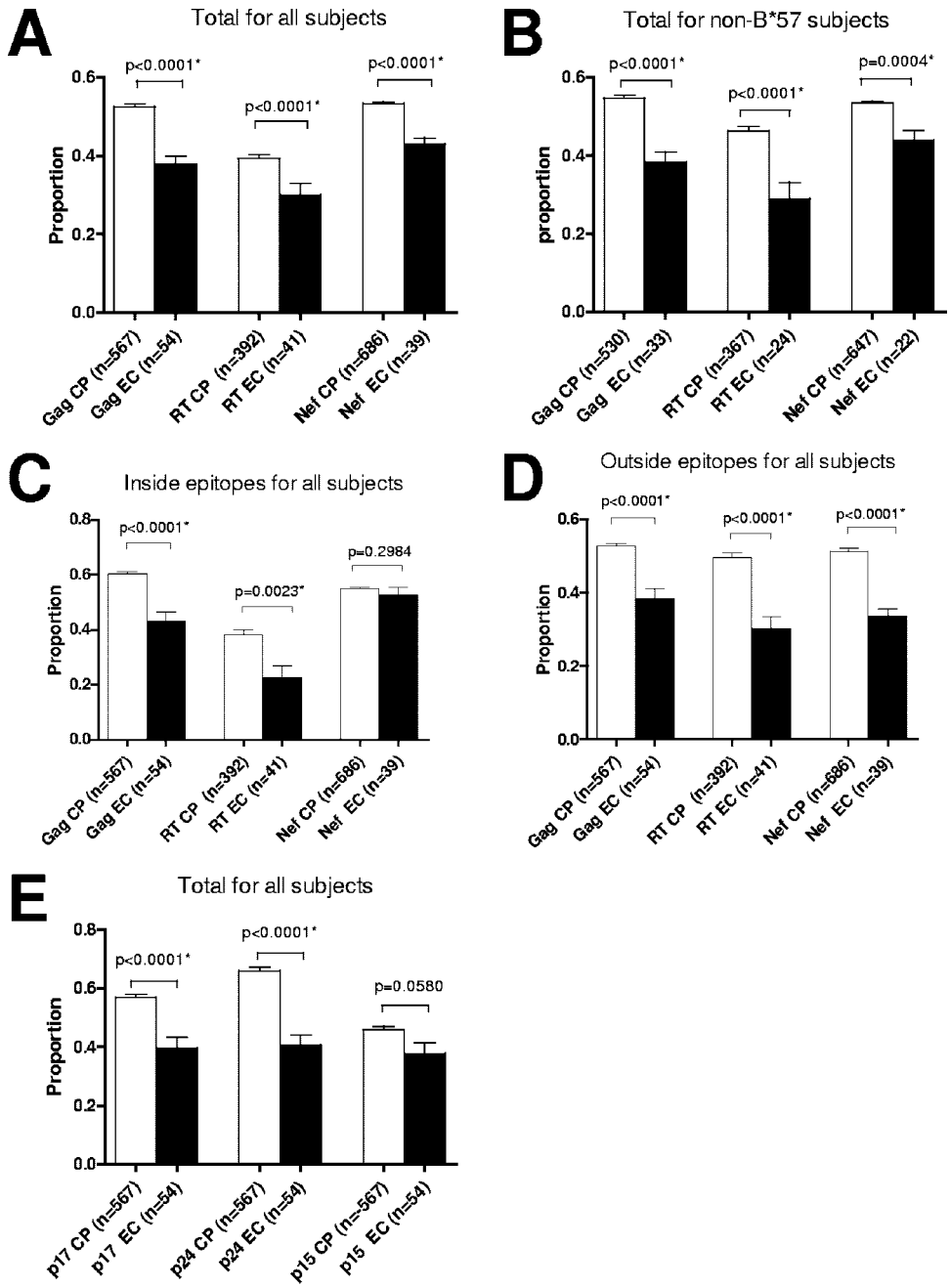

FIG. 1. Comparisons of the proportions of HLA-associated mutations between EC and CP. The mean and standard error of the proportion of sites with defined HLA-associated polymorphisms at which mutations were observed are shown. (A) Proportion of total HLA-associated sites at which mutations were observed in all of the subjects. (B) Proportion of total HLA-associated sites at which mutations were observed in non-B*57 subjects. (C) Proportion of HLA-associated sites falling within predicted CTL epitopes at which mutations were observed (inside epitopes and ± 3 aa) in all subjects. (D) Proportion of HLA-associated sites outside of predicted CTL epitopes (outside of predicted epitopes and ±3 aa) at which mutations were observed in all subjects. (E) Proportion of total HLA-associated sites at which mutations were observed in Gag subunits in all subjects.

from the epitope (6). In this analysis, the proportion of HLA-associated mutations remained high in EC (Fig. 1C).

Intriguingly, significant differences in HLA-associated polymorphisms between EC and CP were also evident in regions outside of CTL epitopes in all three proteins, with even stronger *P* values (Fig. 1D), which may suggest the presence of fewer compensatory mutations among EC. Thus, accumulation of compensatory mutations may also characterize disease progression (6). The high proportion of HLA-associated mutations in EC was seen regardless of the Gag subprotein (p17, p24, or p15) (Fig. 1E).

We next compared the proportion of HLA-associated polymorphisms present in the Gag and Nef proteins on an HLA-allele-specific basis. RT was excluded because of the small

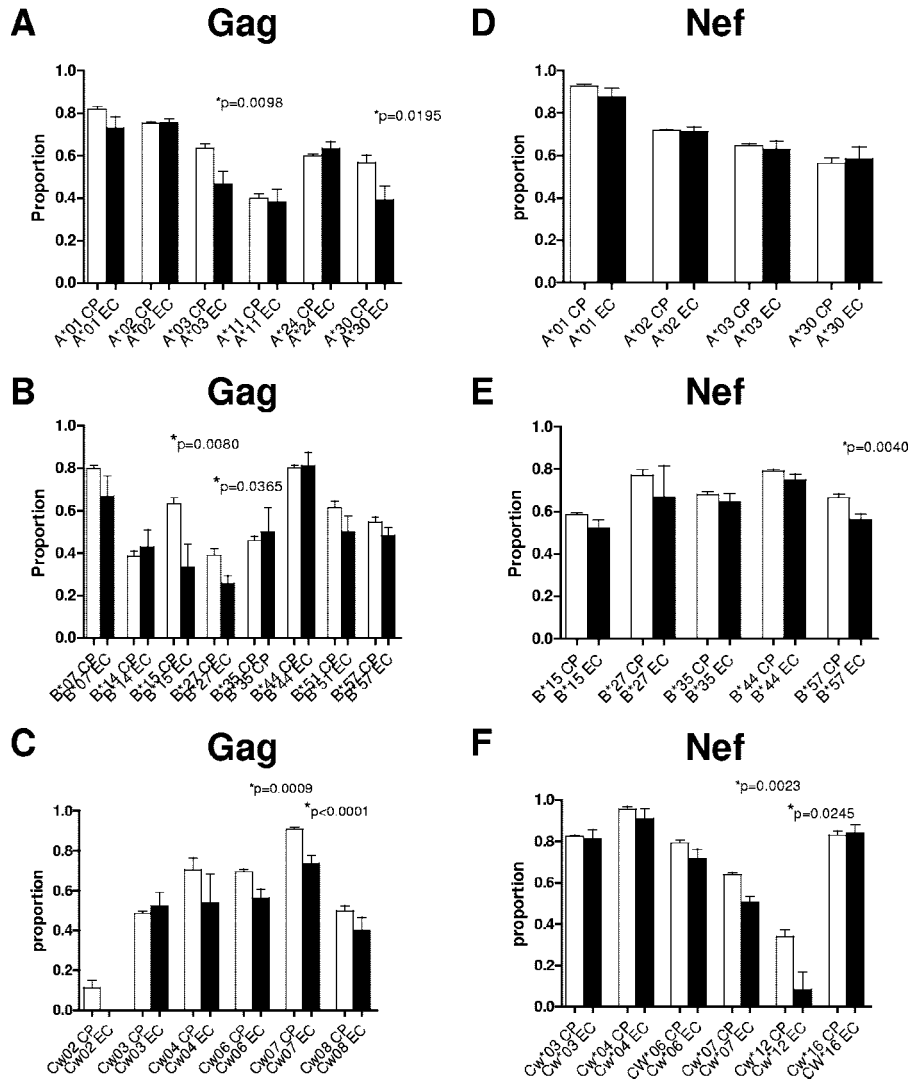

FIG. 2. Proportions of HLA-associated mutations in the Gag and Nef proteins by individual HLA class I alleles. The mean and standard error of the proportion of sites with defined HLA-associated polymorphisms at which mutations were observed are shown. HLA class I alleles present in more than four EC are shown. (A) HLA-A-associated mutations in the Gag protein. (B) HLA-B-associated mutations in the Gag protein. (C) HLA-C-associated mutations in the Gag protein. (D) HLA-A-associated mutations in the Nef protein. (E) HLA-B-associated mutations in the Nef protein. (F) HLA-C-associated mutations in the Nef protein.

numbers of HLA-associated polymorphisms identified. A high proportion of allele-specific mutations were observed in EC regardless of the HLA class I allele type in both the Gag and Nef proteins (Fig. 2). Of importance, for the majority of the alleles, EC viruses carried numbers of allele-specific mutations comparable to those of CP viruses. However, a significantly lower proportion of HLA-associated polymorphisms was observed in EC compared to CP for certain alleles, including HLA-A03, A30, B15, B27, Cw06, and Cw07 in Gag and for HLA-B57, Cw07, and Cw12 in Nef (Fig. 2A to F).

We next repeated this analysis for HLA-B57, which is overrepresented in EC and is associated with a large number of HLA allele-specific polymorphisms (28), allowing sufficient numbers to evaluate mutations inside and outside of epitopes separately (Fig. 3). B57 EC viruses tended to encode a smaller proportion of B57-associated changes inside predicted CTL epitopes in Gag than did B57 CP viruses; however, the difference did not reach statistical significance ($P = 0.0569$) (Fig. 3A). Such a trend was not seen for the Nef protein ($P = 0.3046$). As suggested by our earlier analyses, we observed significant differences in the frequency of B57-associated polymorphisms occurring outside of predicted CTL epitopes between EC and CP for both Gag and Nef ($P = 0.0029$ and $P = 0.0355$, respectively, Fig. 3B). Assuming that B57-associated changes outside of predicted CTL epitopes represent compensatory mutations, these data further indicate that the frequency of compensatory mutations may help to explain significant differences in the clinical disease course between B57 EC and B57 CP and may help explain why simple within-epitope sequence analysis has not shown any association (24). This model is consistent with recent results demonstrating the impact of escape and compensation on viral

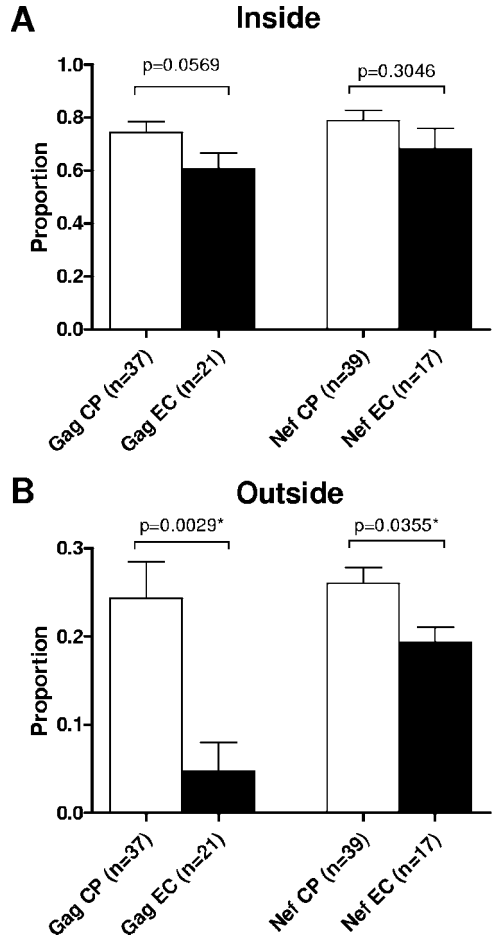

FIG. 3. Comparison of proportions of B*57-associated mutations between EC and CP. The mean and standard error of the proportion of HLA-associated sites at which mutations were observed are shown. (A) Proportion of B*57-associated sites falling within predicted B*57 CTL epitopes (inside epitopes and ± 3 aa) at which mutations were observed in the Gag and Nef proteins. (B) Proportion of B*57-associated sites outside of predicted B*57 CTL epitopes (outside of predicted epitopes and ±3 aa) at which mutations were observed in the Gag and Nef proteins.

replication capacity for the HLA-B57-restricted Gag epitope TW10 (6).

These results add considerably to currently available data (2, 4) in that they are based upon a substantially larger number of EC viral sequences and include multiple coding regions, they assess putative escape from CTLs in the context of multiple HLA class I alleles, they make direct comparison to CP viruses, and they use EC plasma viral sequences rather than proviral sequences, the latter of which do not represent actively replicating viruses in vivo in EC.

Why is it that escape from CTLs occurs in the context of such profound control of viremia? There are several feasible explanations. Firstly, CTLs targeting epitopes without escape may be contributing to the prevention of breakthrough viremia in EC. A few studies have suggested that subdominant CTL responses have an important role in controlling viremia (12, 13). Secondly, impaired viral pathogenicity due to CTL escape mutations may play a major role in controlling viremia. Recent studies demonstrating reduced viral replication capacity by HLA-B57 CTL escape mutations and recovery by putative compensatory mutations that occur outside of epitopes support this explanation (6, 22). As expected, we saw a stronger difference in the number of B57-associated mutations outside of predicted HLA-B57 epitopes than inside them. The role of compensatory mutations in HIV-1 disease progression remains unclear in non-B57 subjects. However, we also observed greater differences between EC and CP in the proportion of HLA-associated changes outside of CTL epitopes rather than within epitopes in B57-negative subjects (data not shown), suggesting that this mechanism might be applied to patterns of escape and disease progression for non-B57 alleles. Thirdly, de novo CTL responses targeting escape variants may contribute to the prevention of breakthrough viremia. Recognition of escape variants by HIV-specific CTLs has been reported (4, 11), yet the association with disease outcome is unknown. Finally, as observed in a different cohort in which individuals who subsequently achieved a low virus set point had experienced high viremia during the acute phase (our unpublished data), there is the possibility that a certain level of escape from CTLs is introduced during acute/early infection regardless of the subsequent viral set point. Similarly, there might be a concern that a longer duration of infection in EC than in CP increased the chance of viral evolution in EC regardless of the cause of viremia control. However, the important finding here is that, despite frequent evidence of escape from CTLs, viremia is still under control in EC. This suggests that escape per se is not necessarily detrimental, perhaps because of fitness constraints imposed.

There are limitations to the present study. HLA-associated polymorphisms outside of predicted CTL epitopes may represent false-positive associations, peptide processing mutations, or escape mutations in as-yet-undefined epitopes, so it will be important to investigate these mutations with larger cohorts and improved approaches to differentiate compensatory mutations from CTL escape mutations. Another limitation is that the list of HLA-associated polymorphisms used here was generated based upon viral sequences derived from chronic progressive infection and may have missed unique escape mutations present only in EC, if such mutations occur. Finally, the allele-specific mutations observed here are interpreted to be escape from CTLs, yet this has not been shown experimentally. Indeed, current assays using synthetic peptides to sensitize target cells in order to evaluate escape from CTLs are of limited value, since they do not assess potential impacts on antigen processing and presentation. Since these HLA allele-specific mutations are observed in plasma virus, the most likely interpretation is that they represent escape, but infection of cells with mutated viruses will be required to fully resolve this issue.

In conclusion, despite viral loads of <50 RNA copies/ml, EC plasma viruses display a substantial number of HLA-associated polymorphisms regardless of HLA class I allele types, indicating that viral escape from HIV-specific CTLs is common in EC. Further studies will be important to reveal the mechanisms of viremia control despite apparent escape from CTLs in persons who are able to maintain durable control of HIV infection.

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AUTHOR'S CORRECTION

HLA-Associated Viral Mutations Are Common in Human Immunodeficiency Virus Type 1 Elite Controllers

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Volume 83, no. 7, p. 3407–3412, 2009. GenBank accession numbers were erroneously omitted from the original publication. The GenBank accession numbers for the sequences derived from HIV elite controllers are EU517762 through EU517815 and EU517972 through EU518012 (as described in reference 25 of the original manuscript), EU873003 and EU873005 (as described in reference 26 of the original manuscript), and GU046566 through GU046604. The majority of the GenBank accession numbers for the sequences used to create the map of HLA-associated mutations appeared in references 7 and 9 of the original manuscript, and additional GenBank accession numbers are GQ303719 through GQ304249, GQ371216 through GQ372824, GQ398382 through GQ398387, and AY856956 through AY857186 (as described in a new publication [1]).

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