Could Epstein Barr virus type 2 asymmetric circulation be explained with an Immunoinformatic approach?

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Epstein Barr virus geographic variation and evolution have been widely studied; however, South American isolates are still underrepresented. Uneven worldwide circulation of EBV1 and EBV2 is still unexplained and HLA allele frequencies also have geographic restrictions; hence, immune selection may act as a driving force for EBV-type asymmetric circulation. We aimed to study epitope variability in 4 selected EBV proteins from different geographies and HLA frequencies in these regions. Forty Argentinian isolates were NGS sequenced and 246 raw NGS data from other geographies were downloaded. Gp350, Zta, EBNA1 and LMP1 epitopes were searched in Immune Epitope Database (IEDB); those with confirmed binding to MHCI HLA alleles were chosen. Epitope variability and MHCI coverage in each region were assessed with IEDB tools. Phylogenetic trees were built with iqtree. In total 211 sequences were EBV1 and 75 EBV2, among Argentinians 29 were EBV1. In Gp350, two epitopes proved to be not conserved. Of these, FFNVEIPEF was not conserved in EBV2 from Africa, East Asia and Argentina but conserved in EBV1 worldwide. The HLA-A*24:02, which recognizes this epitope, is frequent in East Asia and Papua New Guinea (PNG) but not in Africa, where EBV2 is prevalent, and Argentina. A similar phenomenon was observed for GEDPGFFNV epitope and HLA-B*40:01. In Zta protein, 5 well HLA-covered (mainly HLA-A*02:01) epitopes (EECDSELEIKRYKNRVA, QLLQHYREVAA, VSTAPTGSWF, RAKFKQLL and FACPGANQGQQLADI) showed variability in EBV2. Of These, EECDSELEIKRYKNRVA was the only one variable exclusively in EBV2, while FACPGANQGQQLADI was variable in African and Argentinian EBV2, but not in Asian EBV2. Additionally, epitope VQTAAAVVF, which was variable mainly in African, Argentinian, and East Asian isolates, independent of EBV type, has poor HLA coverage by HLA-B*15:01 in Africa and Argentina, but high HLA-coverage in East Asia. EBV1 from Indonesia and Papua New Guinea (PNG) displayed variability in AYQAYAAPQLFPVSDITQ epitope, which is recognized by the frequent HLA-A*24:02 allele. Variability within EBNA1 epitopes was high, where the highest amount of variable epitopes occurred in African and Argentinian isolates and the lowest amount of variable epitopes occurred in Asian and Indonesian isolates. For all geographic regions, with the exception of PNG, EBNA1 epitopes were recognized by high frequency region-specific HLA alleles. Variability within LMP1 epitopes was high, but showed no clear pattern of distribution with viral type. Related to geography, only epitope ALLVLYSFALMLI, recognized by HLA-A*24:02, was variable mainly in Indonesia, PNG, Argentina and exclusively among African EBV2. Among the studied viral proteins, epitope variation in Zta and Gp350 was more related to EBV type and geographic origin, but not in EBNA1 and LMP1. Both Gp350 epitopes in African and Argentinian EBV2 were variable and poorly covered by HLA alleles; meanwhile, in East Asian EBV2, these variable epitopes presented a high population coverage by HLA alleles, suggesting that EBV2 Gp350 is under immune pressure in East Asia but not in Africa and Argentina, and that variability in this Asian epitopes could favor viral immune escape. Similarly, observed variation in Zta epitope FACPGANQGQQLADI in African and Argentinian EBV2, but not in Asian EBV2, all with good HLA coverage, suggests a way for EBV2 to evade immune selection in the former geographic regions. Conversely, lack of conservation in VQTAAAVVF and differences in HLA recognition, suggests immune evasion only in East Asia. Regarding disease, Zta displayed the greatest amount of variable epitopes statistically deferring between tumor and non-tumor samples (Fisher´s exact test: P=0.001; P=0.015; P=0.002; P=0.021 and P=0.007). These results, although limited to variable epitopes in 4 EBV proteins, demonstrated that EBV epitopes can be differentially subjected to immune pressure in the different geographic regions. Additionally, they could at least in part, shed some light on the higher prevalence of EBV2 in Africa and Argentina.

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