SMBE 2017

Host-parasite coevolution

POB-318

Divergence of HPV16 variants reflects loci undergoing inter-host positive selection, potentially immunologic selection

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Abstract: Papillomaviruses are one of the most successful families of vertebrate DNA viruses. Among them, human papillomavirus type 16 (HPV16) is the most carcinogenic, causing approximately 50% of all cervical cancers. Unfortunately, no straightforward phylogenetic relationship or genetic variant(s) explains HPV oncogenicity, e.g., the second most carcinogenic type (HPV18, causing ~16% of cancers) is relatively distantly related to HPV16. Thus, the genetic and evolutionary mechanisms underlying HPV16's unique carcinogenicity remain unsolved. Mirabello et al. recently reported on viral genome data from 3,215 HPV positive specimens from women undergoing cervical cancer screening at Kaiser Permanente Northern California in the Persistence and Progression (PaP) cohort. Results demonstrated profound differences in disease risk by histologic subtype among the HPV16 sublineages (e.g., A1, A2, and D2), with over 100-fold risk differences. Here, we expanded this analysis to examine the genetic and evolutionary underpinnings of HPV16 carcinogenicity through an exhaustive analysis of viral nucleotide diversity.

The HPV16 genome displays significant evidence of purifying selection ($d_N/d_S = 0.267$; $P<0.001$). However, within the A1 and A2 sublineages, one of the two oncogenes (E6) does not differ from neutrality, while the other oncogene (E7) is significantly more constrained in cases ($d_N/d_S = 0.049$) than in controls ($d_N/d_S = 0.27$; $P<0.001$). Thus, benign viral infections exhibit less constraint, implying a nonsynonymous mutational burden. Using an unsupervised sliding window approach, we next identified genomic regions exhibiting strong evidence of inter-host positive selection. Among all of the sublineages, 26 regions displayed d_N/d_S values ranging from 1.28 – 33.52. A subset of these regions overlapped with phylogenetic sublineage-defining residues, therefore, we further analyzed individual sublineages to control for potential lineage fixation by genetic drift. Remarkably, 14 of these 26 regions were discovered independently in the A1 sublineage alone, with d_N/d_S values up to 59.44. Nine of these 14 regions match known HPV epitope sequences obtained from the Immune Epitope Database and/or the Human Papillomavirus T Cell Antigen Database. In particular, two regions of E6 were identified independently in cases and controls: codons 20-27 and codons 75-90, which include four sublineage-defining residues. Both overlap with experimentally verified HLA class I epitopes, and the second region also overlaps known antibody epitopes. Moreover, the 75-90 region exhibits a d_N/d_S ratio of 59.44 in cases and 28.05 in controls, shows substantial case vs. control divergence (between – within group d_N/d_S of 55.60), and includes a L83V variant that has been reported to contribute to persistence in European populations.

We conclude that diversifying positive selection likely played a key role in the historical divergence of HPV16 variants, possibly as the result of inter-host environmental heterogeneity based on host immune genotype. Moreover, since our data imply that positive selection is targeted to many of the same loci that are diagnostic as sublineage-defining residues, it is likely that similar evolutionary pressures have operated throughout the evolutionary diversification of HPV16. In particular, we suggest that host immune genotype (e.g., HLA) may play a key role in disease outcome, and must be prioritized in future studies of HPV evolution and its link to cervical cancer.

Disclosure of Interest: None Declared

Keywords: None