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IDENTIFICATION OF NOVEL HEPATITIS B VIRUS (HBV) T-CELL EPITOPES AND ESCAPE MUTATIONS IN ASIAN INDIVIDUALS WITH CHRONIC HBV INFECTION USING A POPULATION BASED APPROACH

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AIM: To identify HBV regions under putative in-vivo HLA-driven immune pressure by determining associations between HLA type and HBV sequence polymorphism in Asian individuals with chronic HBV infection. METHODS: High resolution 4-digit HLA class I and HLA class II typing together with full length HBV sequencing was undertaken in treatment-naïve patients with chronic HBV infection of Asian ethnicity prospectively recruited in Melbourne, Australia and Hong Kong, China (n=122). Associations between HLA and consensus amino acid (aa) with a Fisher's p-value <0.05 and a cluster-corrected Mantel-Haenszel p-value <0.1 to abrogate the influence of founder effect were selected as significant. Putative novel epitopes were screened using the BIMAS and SYFPEITHI databases of predictive algorithms of peptide/MHC interaction. The relationship between adaptation (defined as the number of residues at which the individual had non consensus aa and carried the relevant HLA allele) and clinical parameters was determined. RESULTS: Patients were infected with genotype B (n=64) or genotype C (n=58) and 63% were HBeAg+ve. The most frequent HLA types were HLA-A*1101 (42%), -B*4001 (29%), -Cw*0702 (42%) and -DRB1*1201 (41%). Two putative novel HLA alleles were found (one HLA B, one HLA C). Adaptation was significantly associated with HBeAg-ve status (p=0.007) and lower HBV viral load (VL) (r-squared=0.11 for logVL vs adaptation score r=-0.3 p=0.008). Significant associations between HLA type and HBV polymorphism were identified (n=48), and 18 (38%) were assessed for predicted peptide/MHC interaction. Significant HLA binding was demonstrated for 14/18 (78%) associations (including 4 within known HLA-matched epitopes). One further HLA class I and one HLA class II allele-specific polymorphism were not within but flanked CTL epitopes, possibly representing mutations that effect epitope processing rather than HLA class I or HLA class II binding. Novel possible epitopes involving the x-protein (-A*0201 aa 44-53, -A*1101 aa 135-143, and -DRB1*1501 aa 138-152), core (-B*4001 aa 105-113), preS1 (-A*1101 aa 210-218 and 335-343), and pol (-A*0201 aa 466-474, -A*1101 aa 261-269 and 671-679, and -DRB1*0701 aa 682-696) were defined. Aa polymorphisms associated with significantly lower predicted HLA binding was demonstrated in 9 known and novel epitopes, many involving anchor residues and escape mutants not previously described.CONCLUSIONS: We have demonstrated an association between viral adaptation and clinical parameters including HBeAg and HBV VL. This population based sequencing approach can be used to identify novel HBV epitopes and their escape mutations in various HLA types.

Disclosures:

George K. Lau - Consulting: Roche, Novartis

Stephen Locarnini - Advisory Committees or Review Panels: Gilead, Bristol-Myers Squibb; Board Membership: Evivar Medical; Consulting: Pharmasset

Paul V. Desmond - Advisory Committees or Review Panels: GlaxoSmithKline, Roche, Bristol-Myers Squibb; Speaking and Teaching: Roche, Schering-Plough, Giliad

Stuart K. Roberts - Advisory Committees or Review Panels: Roche; Consulting: Roche; Speaking and Teaching: Roche

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