M7: HLA Epitope Electrostatics - a novel methodology to compare HLA epitope electrostatic potential and predict HLA-DQ immunogenicity

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Introduction: Structural and physicochemical comparison of HLA epitopes may enable greater understanding of immunogenicity and antigenicity in the transplant setting. Our previously developed Electrostatic Mismatch Score 3D (EMS3D) enables surface electrostatic potential (EP) comparisons of entire HLA molecules, but cannot be used to quantify EP differences at defined regions (epitopes) of the HLA molecular surface.

Methods: The EMS3D algorithm was adapted to compare EP at specific regions (epitopes) between HLA molecules. An experimental HLA sensitisation model (patients subjected to standardised donor lymphocyte injections, mismatched HLA-DQ n=230) was used to examine the relationship between donor HLA epitope electrostatics and donor-specific-antibody (DSA) formation (assessed using single-antigen-beads). Highly polymorphic residues within the extracellular HLA-DQ domain (genotypes identified in the BeTheMatch registry for all major ethnic groups) were identified (Shannon Entropy ≥1) and used to define 9 potential epitope regions on HLA-DQ with variable amino acids grouped together by mathematical proximity. Donor-Recipient EP differences were calculated for HLA-DQ regions and machine learning methods were utilised to identify epitope(s) features associated with DSA.

Results: HLA Epitope Electrostatics is a novel implementation of the EMS3D algorithm which can visualise and compare electrostatics on the HLA surface, enabling tertiary-level EP assessment of any region of interest. Four HLA-DQ regions/epitopes were highly associated with DSA development (AUC:0.75-0.78) indicating high potential immunogenicity of these regions. Following splitting the dataset into train:test parts (66%:33%, x10 repeats), machine learning models (Support Vector Machines, Gaussian Naïve Bayes, Linear Discriminant Analysis, Logistic Regression) identified combinations of EP differences in these epitopes that outperformed EMS3D whole-molecule scores alone (average accuracy: 0.77-0.79).

Discussion: We describe a novel methodology to investigate EP differences at the epitope level and demonstrate a clear relationship to HLA-DQ immunogenicity. This approach may enable improved identification of highly immunogenic, conserved epitopes across multiple HLA molecules.

Category: H&I (HLA typing - crossmatching - immunologically complex recipients)