In-silico prediction of HLA-DP and -DQ epitope content is poorly correlated with clinical immunogenicity of therapeutic proteins.

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Abstract

Purpose: Protein drug developers and immunogenicity screeners generally agree that HLA class II-restricted T helper cells can drive anti-drug antibody (ADA) responses to biologic therapeutics. The link between ADA and T cell responses has contributed to the proliferation of epitope prediction tools used by biologics developers. However, a consensus has yet to be reached regarding the set of HLA alleles most relevant for the prediction of clinical immunogenicity. The purpose of this commentary is to extend our previous analysis of the association between in silico predictions of HLA-DP and -DQ epitope content and observed immunogenicity by examining the contribution of HLA-DP and -DQ T cell epitope content to immunogenicity predictions.

Methods: To expand on our previous analysis, we employed HLA-DP, -DP and -DQ epitope prediction tools (available on the IEDB website) to measure the T cell epitope content of 20 licensed monoclonal antibodies (mAbs). Using linear regression analysis, “Hit” counts were then correlated with the percentages of treated patients who produced anti-drug antibodies.

Results: Consistent with our previous findings, HLA-DP and -DQ epitope content, as predicted using the IEDB Consensus model, did not predict observed immunogenicity. In order to establish a significant correlation it was necessary to adjust the IEDB Consensus model for the presence of regulatory T cell epitopes as predicted by our ISPRi immunogenicity screening system. Further, we found that HLA-DP and -DQ allele epitope content, as assessed by these available tools, did not correlate with published immunogenicity, nor did the inclusion of predicted HLA-DP and -DQ epitope content improve the accuracy of HLA-DP- and -DQ-based immunogenicity predictions. Finally, one model of HLA-DP restricted content was significantly negatively correlated with immunogenicity. This observation deserves further exploration.

Conclusions: Based on these findings, we suggest that, at least until available DP/DQ models can be correlated with observed immunogenicity, estimates of protein immunogenicity should be based on HLA-DP rather than DP/DQ epitope content. Furthermore, we underscore the importance of adjusting for regulatory T cell epitope content in the prediction of immunogenicity.

Background

In the expanding universe of therapeutic antibodies, it is critical to understand how antigenic determinants differ across species, how these differences impact immunogenicity, and how to deimmunize therapeutic antibodies.

Correlation of EpiMatrix Scores with Clinical Immunogenicity

Using Tregitope-adjusted Scores to Predict Immunogenicity

Protein T cell epitope content predicts immunogenic potential.

- Anti-therapeutic response mAbs were collected from studies performed by EpiVax.
- Protein sequences were collected from the EPIHIV database and parsed into overlapping 7-mer frames.
- EpiMatrix assesses binding potential of each 7-mer to 8 “SuperTrypt” Class II HLA-DR alleles.
- EpiMatrix Protein Immunogenicity Score reflects aggregate T cell epitope content (all scores are adjusted for the presence of Tregitopes).

These scores were highly correlated to observed immunogenicity using a polynomial regression (R² = 0.76).

- Without adjusting for Tregitope content, monoclonal antibody immunogenicity and raw EpiMatrix Protein Immunogenicity Scores are not well correlated (R²=0.17).

References / Acknowledgments