

Abstract

American Society for Histocompatibility and Immunogenetics

TITLE: Comprehensive class II HLA cross-reactivity profiling of single peptides across DR, DQ, and DP molecules

CURRENT CATEGORY: Basic/Translational Research: Immunotherapy

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ABSTRACT BODY:

Aim: Characterization of class II peptide binding is typically limited to a small number of alleles and does not capture cross-reactivity across the broader HLA class II repertoire. Here, we present a novel proof-of-concept mapping and validation platform using two model peptides to assess binding across an expanded panel of class II HLA molecules.

Methods: Biotinylated peptides with an Ahx linker were used to enable stable complex formation with soluble HLA class II molecules. Two peptides were evaluated: a well-characterized influenza hemagglutinin peptide and a CLIP control peptide. Binding was assessed across a library of more than 100 HLA class II molecules spanning DR, DQ, and DP. Peptide–HLA complexes were detected using a streptavidin-based ELISA platform. Signal intensities were quantified, and selected interactions were further evaluated using titration analysis to derive EC₅₀ values as a measure of binding potency.

Results: The platform confirmed expected high-affinity binding of the influenza hemagglutinin peptide to DRB1*01:01 and related DR alleles. In addition, broader DR cross-reactivity was observed across multiple alleles not previously characterized for this peptide. Limited or no binding was detected for most DQ and DP molecules, indicating class-restricted interaction patterns. The CLIP control peptide, derived from the class II–associated invariant chain, showed broad binding across class II molecules consistent with its role as a natural peptide-binding groove placeholder during antigen loading, while still exhibiting allele-dependent differences in interaction strength. Signal intensity trends correlated well with titration-derived potency, supporting internal consistency of the assay system. Together, the two-peptide model demonstrated feasibility of systematic class II cross-reactivity mapping and validation within a unified experimental framework.

Conclusion: This proof-of-concept study establishes a scalable mapping and validation approach for class II peptide–HLA interactions across a broad allele panel. Using two model peptides, we demonstrate the ability to resolve both expected and previously unrecognized cross-reactivity patterns. These findings support ongoing expansion of the platform toward systematic characterization of class II peptide binding landscapes for immunotherapy and immune monitoring applications.



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