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Peer Review

Review of: "A Common Network of Residue-Residue Contacts Underlies Peptides' Interactions with MHC Class II Complex"

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The manuscript *"A Common Network of Residue–Residue Contacts Underlies Peptides' Interactions with MHC Class II Complex"* presents important structural insights that are often underexplored due to the mistaken perception that such analyses have limited methodological impact or relevance. I consider this kind of "anatomy" of molecular interactions and physicochemical features of ligands essential to stimulate new hypotheses and research directions in the field. The authors' effort to describe common contact networks and anchoring patterns is commendable.

It is clear, however, that the analysis would benefit from being expanded to a larger number of structures, ideally with a more explicit separation by alleles, to explore whether the observed interactions are consistent and whether more robust or allele-specific patterns can be detected. This could also help assess the generalizability of the proposed contact network.

Below, I highlight specific points that should be clarified or considered, either in this manuscript or in future work:

It would be valuable to incorporate molecular dynamics simulations in a future study to further investigate contact persistence and volume flexibility of the key residues identified in this work.

I suggest including other crystallographic structures involving CLIP to evaluate whether the observed contact patterns are broadly conserved or could be biased by stochastic crystallization artifacts.

In Table 2, when the authors indicate a peptide position (e.g., position 4) contacting a chain alpha residue (e.g., position 53), does that imply that in at least 9 structures this pair was consistently observed in contact? Please clarify the statistical criterion behind the threshold.

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Increasing the number of analyzed structures would be extremely valuable. One could consider using the current features (contact maps, volume, hydrophobicity, etc.) as input vectors for a neural network, aiming to predict peptide–MHC II binding. This could open interesting computational directions and comparative studies across alleles.

In Table 5, position 7 does not appear to exhibit 7 residues with high flexibility. This should be revised or clarified.

In the section “Contact Preference Scores for contacts between peptide and alpha/beta chain residues”, it would strengthen the analysis to include negative examples, i.e., peptides known not to bind to MHC II, to assess the discriminative power of these scores.

Finally, while the section “Can we use the knowledge of the common contact network to predict which peptides will bind to MHC II?” is conceptually interesting, it’s important to note that effective prediction models require capturing complex combinations of structural features that either enable or hinder binding. This usually demands machine learning approaches such as neural networks, similar to what is seen in sequence-based predictors, but now incorporating a much richer and multidimensional feature space.

Overall, the manuscript is valuable and offers solid contributions to our understanding of peptide–MHC II interactions. I encourage the authors to address the points above to enhance the robustness and applicability of their findings.

Declarations

Potential competing interests: No potential competing interests to declare.