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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 title of the manuscript is interesting, but there are some issues to be addressed. For example, the majority of peptides that bind to MHC II are not structurally similar to CLIP because MHC II accommodates a diverse range of antigenic peptides with different binding motifs. Also, MHC II presents a wide range of antigenic peptides, including self and pathogen-derived sequences, which differ significantly from CLIP. Many antigenic peptides use strong anchor residues that enhance binding affinity, while CLIP primarily acts as a placeholder. I can add that the binding pocket of MHC II may adapt dynamically to different peptides, making structural similarity to CLIP unnecessary for stable interactions. On the other hand, peptides that resemble CLIP may bind with high affinity or low affinity to MHC II based on the structure of other (not similar) amino acids, as also mentioned in the manuscript.

To sum up, the low number of PDB structures analyzed for this network seems not to be enough for this conclusion or to fit all antigenic peptides available in different databases such as https://www.iedb.org/.

Declarations

Potential competing interests: No potential competing interests to declare.

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