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Exploring the polyreactivity of monoclonal antibodies using igome graphs

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Antibody repertoires are studied at the system level using two approaches: high throughput B cell receptor sequencing and high throughput binding experiments using phage display random peptide libraries (igome) or antigen arrays. While the latter can provide insights into the sequences recognized by a mixture of antibodies, such as serum antibodies, it does not reveal the contribution of individual antibodies to the overall reactivity. To bridge this gap, we first need to understand the footprints of single antibodies in the space of mimotopes.

Using the igome data from Ashkenazy et al. [1], we analyzed the structure of the repertoire of 4 different monoclonal antibodies: 3 anti-HIV antibodies and Herceptin. We constructed graphs where nodes represent 7-mer peptide mimotopes, and edges indicate shared subsequences of at least five amino acid residues. With the help of spectral embedding and the Leiden algorithm for graph clustering, we identified groups of highly similar peptides. Such clusters, summarized as sequence motifs, are hypothesized to correspond to different specificities of the antibody.

Our analysis reveals that each antibody has biologically relevant affinity to multiple different mimotope groups with distinct sequence motifs. This supports the idea that even highly specific antibodies can exhibit polyreactivity.

The reported approach provides a framework for dissecting individual antibody specificities and could be utilized to uncover their role in shaping the broader human antibody repertoire.

Keywords: antibody repertoire, graphs, bioinformatics

References

[1] H. Ashkenazy, O. Avram, A. Ryvkin, A. Roitburd-Berman, Y. Weiss-Ottolenghi, S. Hada-Neeman, J. M. Gershoni, T. Pupko, *Motifier*: An IgOme Profiler Based on Peptide Motifs Using Machine Learning, *Journal of Molecular Biology*, 433:167071, 2021.