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Short Communication

Antigenic Structural Similarity as a Predictor for Antibody Cross-Reactivity

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ABSTRACT

Antibodies are an essential component of the adaptive immune system that function to neutralize foreign invaders, such as bacterial and parasitic pathogens. However, B-cell epitopes remain difficult to predict due to their general indistinguishability from other protein regions. Epitope prediction tools in the past have largely relied on amino acid sequence similarity; however, implementing three-dimensional protein structure analyses into the epitope prediction algorithms has been shown to increase detection accuracy. Furthermore, structural comparisons between antigenic proteins for their potential to bind cross-reactive antibodies have not been explored extensively in the literature. Recent studies have pointed to the utility of looking at shared epitope structures in predicting antibody cross-reactivity, which may shed light on cross-immunity between infectious pathogens and autoimmune diseases induced after infection. Thus, herein, the potential impact of including structural similarity comparisons in detecting shared epitopes is discussed. With the large amount of structural information being determined by three-dimensional computational protein modelling methods, the ability to perform these analyses is becoming more feasible.

Keywords: Antibody; Antigen; B-cell epitope; Structural similarity; Structural bioinformatics

DESCRIPTION

Antibodies are an essential component of the adaptive innate immune system [1]. In response to activation by upstream immune events, B-cells produce and secrete antibodies that can bind to antigens, such as cell surface proteins from infectious pathogens, in order to inhibit antigen activity directly or to target the antigen for recognition by phagocytic cells or the complement system [2]. The identification and prediction of antibody-binding motifs, or epitopes, is important for understanding immunogenicity of both pathogenic and endogenous biomolecules and, as a result, developing therapeutic antibodies or vaccines [3,4].

Antibody-antigen interfaces are treated as a specific type of protein-protein interaction and, thus, epitopes have been classified into two categories: contiguous amino acids in sequence that comprise a linear motif or discontinuous stretches of residues that fold together in three-dimensional space to create a structural motif [5]. Sun et al. reviewed antibody-antigen interfaces and found that linear and conformational motifs make-up 10% and 90% of B-cell epitopes, respectively [6]. Despite the interest in epitope identification, the computational prediction of B-cell epitopes has been proven somewhat difficult, since epitope and non-epitope regions on protein surfaces are generally indistinguishable from one another [7]. B-cell epitope prediction methods in the past have largely focused on sequence similarity; however, in order to more accurately predict conformational epitopes that comprise discontinuous regions of sequence, recent bioinformatics tools and pipelines have implemented structural information to optimize epitope detection [8]. Conformational epitope prediction tools and databases, such as Disco tope and CED, respectively, include parameters that account for protein domain solvent accessibility and flexibility, which have been shown to increase prediction accuracy [9,10]. Thus, more in-depth structural analysis may lend insights into B-cell epitope detection and characterization.

Although structural information has been shown as useful in predicting B-cell conformational epitopes, discussion of the comparisons of structures to elucidate epitopes shared between proteins is limited in the literature. Structural similarity has been demonstrated as an accurate predictor for protein-protein interactions; thus, it raises the question as to whether it can

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provide informative structural insights for epitope comparisons [11]. The antigenic similarity prediction algorithm and database, CE-BLAST, was developed based on defined antibody-antigen complexes in PDB [12,13]. Although successful in finding shared features between dengue virus and zika virus antigen structures, the database is limited by the relatively small number of structurally-defined epitopes and is missing information on post-translational modifications (e.g. glycosylation, palmitoylation). Comparing a broader diversity of antigenic structures may better inform shared conformational epitope prediction between proteins.

Recently, a comprehensive protein structure alignment screen was performed using the antigenic and accessible receptor-binding motifs of the spike proteins from highly pathogenic coronaviruses and found several structurally similar human proteins and antigenic proteins from viral, bacterial, and parasitic pathogens [14]. Interestingly, the receptor-binding motif from one of the studied coronaviruses, the Severe Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was found to be structurally similar to antigenic proteins from pathogens, such as *Plasmodium falciparum*, that have been found to be inversely correlated with SARS-CoV-2 infection [15,16]. Domains from human proteins, such as those found in coagulation cascades, were also found to be similar in structure, and this may partially explain autoimmune diseases arising in infected or vaccinated patients [17]. Further inspection of the structural alignments reveals that sequence identity can be low considering normal epitope-prediction methods, even though the prevalence of electrostatically similar amino acids was quite high. Although these observations require experimental validation, the widespread similarity of these epitopes to other proteins draws attention to the utility of high resolution structural similarity investigations of antigenic protein surface regions. Thus, the use of antigenic structural similarity may be a way to quickly and comprehensively scan for structural motifs that support recognition by similar antibodies.

The assessment of structural similarity in epitope prediction algorithms, after refinement using parameters like solvent accessibility, may help delineate cross-immunity between different pathogens as well as human proteins and proteins from pathogens giving rise to autoimmune-induced diseases. One of the primary setbacks thus far in using structure-based methods to predict epitopes has been the lack of available structural templates in the PDB, due to the time it takes to generate an experimentally-defined structure. However, as large-scale human and pathogen protein databases are becoming more frequently created using homology and ab initio computational three-dimensional modelling approaches, as exemplified in the proteome-wide modeled databases of *Mycobacterium* and *Plasmodium* species, more structural features are becoming known that can be used for structural comparisons [18-24].

CONCLUSION

The inclusion of additional annotations, such as transmembrane domains, post-translational modifications, and protomer surfaces involved in oligomerization, will be helpful to create biologically-relevant models that can be used for more accurate structural comparisons. The use of structural similarity to predict antibody-antigen interactions may further the understanding of antibody specificity and cross-reactivity.

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