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Commentary

A Commentary on Fine Mapping of Antigen Antibody Interactions

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DESCRIPTION

A number of different methods are commonly used to map the fine details of the interaction between an antigen and an antibody. Undoubtedly the method that is now most commonly used to give details at the level of individual amino acids and atoms is X-ray crystallography. The feasibility of undertaking crystallographic studies has increased over recent years through the introduction of automation, miniaturization and high throughput processes. However, this still requires a high level of sophistication and expense and cannot be used when the antigen is not amenable to crystallization. Nuclear magnetic resonance spectroscopy offers a similar level of detail to crystallography but the technical hurdles are even higher such that it is rarely used in this context. Mutagenesis of either antigen or antibody offers the potential to give information at the amino acid level but suffers from the uncertainty of not knowing whether an effect is direct or indirect due to an effect on the folding of a protein. Other methods such as hydrogen deuterium exchange coupled to mass spectrometry and the use of short peptides coupled with ELISA-based approaches tend to give mapping information over a peptide region rather than at the level of individual amino acids. It is quite common to use more than one method because of the limitations and even with a crystal structure it can be useful to use mutagenesis to tease apart the contribution of individual amino acids to binding affinity.

Antibodies are a key biological molecule, with numerous applications in the fields of therapeutics, diagnostics and biological research. Within the field of therapeutics alone, antibodies represent one of the largest growing classes of molecule, with five of the top ten selling prescription drugs in 2012 being antibody-derived. Antibodies have evolved to bind with exquisite specificity to their target antigen to be able to potently neutralize 'non-self' intruders. Since their initial discovery, much study has focused on the precise nature of the binding between the antibody and the antigen.

The molecular structures within any given target antigen that make specific contacts with the antibody are referred to as antibody or B-cell epitopes and conversely, the molecular determinants within the antibody structure that make specific interactions with the antigen epitope are often termed paratopes.

Antibody paratopes are often composed primarily of the so-called complementarity-determining regions (CDRs), which can be classed in slightly different ways, based upon sequence variability or structural analyses, but often also contain other so-called 'framework' residues. Mapping the interactions between antibodies and antigens has a number of important uses, such as advancing our knowledge of the immune response and autoimmunity, predicting suitable antigens for use as vaccine components, gaining a greater understanding of a therapeutic antibody's mechanism of action, and securing and protecting intellectual property. Concurrent developments in the use and application of antibodies, the technologies available for antibody discovery engineering and the technologies for mapping antigen–antibody interactions have led to a rapid proliferation in publically available antibody epitope data, for example in the immune epitope database. Experimental methodologies for determining the molecular interactions of antibodies with their cognate antigens have evolved from simple ELISA-based approaches, such as the use of linear peptides representing small stretches of the antigen protein sequence, to more complex mutant screening approaches to determine structural, discontinuous epitopes; mass spectrometric methods, such as hydrogen deuterium exchange or protease protection, or, where possible, the use of nuclear magnetic resonance (NMR) or X-ray crystallography to precisely determine the interface between antibody and antigen. There has been much recent activity in developing in silico methods for predicting and determining antibody epitopes, but B-cell epitope predictions have been shown to be suboptimal, due to a preponderance of both false-positive and false-negative results. This review will therefore focus upon experimental methods for mapping antibody paratope and epitopes. The word 'epitope' can mean many things, e.g. the surface protein recognized on a virus, the individual protein bound in a protein complex, a domain of a particular protein, a small part of a protein and ultimately the contribution of individual amino acids and individual atoms.

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