
New Insights of the HIV-Neutralizing 2F5 Monoclonal Antibody Through Dynamic Force Spectroscopy

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Dynamic force spectroscopy has seen many applications in studying interactions in receptors and their ligand, oligonucleotides, and proteins. Elegant technological developments have been married to rigorous theoretical analysis. But has anything ‘new’ been discovered?

The gp41-specific human monoclonal antibody 2F5 is one of only a handful of antibodies capable of neutralising diverse primary isolates of the human immunodeficiency virus type 1 (HIV-1). Antibodies that recognise the 2F5 epitope (ELDKWAS) have been raised through immunisation, although none so far have possessed the primary isolate neutralising phenotype. Understanding the molecular features associated with this phenotype will help inform development of vaccines designed to elicit 2F5-like responses. Here, we performed dynamic force spectroscopy to dissect the force landscape of the interaction between 2F5 and a 12mer and a 25mer gp41 peptide containing its epitope. Analyses of the binding of a non-neutralising mouse serum, which was previously raised against the core 2F5 epitope, as well as a control HCV-specific antibody, to peptides containing their respective epitopes produced dissociation forces that were tightly distributed around their mode. By contrast, similar analyses using 2F5 Fab produced a much wider distribution that was composed of forces corresponding to single, double and triple interactions. Fitting models to the force data revealed that these were due to parallel loading and comparing data obtained when 2F5 Fab was immobilised on either the tip or the surface indicated that the multiple interactions were occurring between a single 2F5 Fab and more than one peptide.

Finally, analysis of the binding of the 12mer and 25mer peptides showed that residues beyond the core epitope are involved in antibody binding. The findings provide insight into important molecular features associated with 2F5-epitope interaction and the apparent ability of the neutralising antibody to bind multiple epitopes simultaneously that may be relevant to understanding its broadly neutralising phenotype.