O-15.5 Short talk

Oligomerisation-driven avidity correlates with SARS-CoV-2 cellular binding and inhibition

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Viral entry depends on efficient receptor engagement by viral surface proteins. Most proteins on the virus and cell surfaces are oligomeric, therefore their underlying molecular interactions offer great scope for both the virus and the immune system to leverage the thermodynamic benefits of multivalent interactions. For example, viral entry and inhibition in SARS-CoV-2 involve a trimeric spike surface protein, a dimeric ACE2 cell receptor and dimeric antibodies. While the importance of multivalency is widely recognised, its visualisation and quantification on membrane surfaces are challenging due to the resultant heterogeneity. Here, we developed a mass photometry and single-molecule tracking approach to observe and quantify receptor–ligand interactions at the single-molecule level, both in solution and confined to lipid bilayers. We reveal that multivalency and cooperativity govern SARS-CoV-2 infectivity, where more infectious variants, despite having weaker 1:1 affinity, enhance their cellular affinity by driving receptor clustering mediated by ACE2-spike oligomerisation. Furthermore, induced oligomerisation emerges as a fundamental mode of action of antibodies, operating on its own or combined with traditional receptor blocking. Our findings challenge 1:1 affinity-based potency predictions and highlight a broader role for induced oligomerisation in biomolecular interactions.