

UNDER THE LENS

A spike with which to beat COVID-19?

Nawsad Alam and Matthew K. Higgins

This month's Under the Lens discusses how structural studies of the SARS-CoV-2 spike glycoprotein might guide a path towards a vaccine.

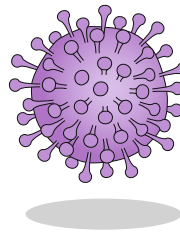
As SARS-CoV-2 (the cause of the COVID-19 pandemic) has swept across the globe, we have been reminded of what it is like to live with rampant infectious disease, without effective drugs or vaccines. Researchers have piled in to the quest to provide rational designs. The structural biology community are no exception, with structures of SARS-CoV-2 proteins emerging at unprecedented speed. One of their main focuses has been the viral spike glycoprotein that binds to the receptor angiotensin-converting enzyme 2 (ACE2), allowing virus entry. Here, we discuss some of these recent papers on structural characterization of the spike and highlight how they might guide structure-based approaches to develop an effective spike-based vaccine.

Coronavirus spikes are trimeric molecules that present their receptor-binding domains (RBDs) at their distal tips. These RBDs recognize receptors, allowing the virus to enter cells. During entry, the spike undergoes a large conformational rearrangement from its pre-fusion to post-fusion state, driving viral fusion with the cell membrane. Coronavirus spikes have been structurally characterized before, in particular for SARS-CoV and MERS-CoV, two related viruses that have caused epidemics of respiratory disease. A crucial question was whether SARS-CoV-2 resembled either of these related viruses. If it did, this would be exciting news, as years of study of these viruses could be applied to the quest for a SARS-CoV-2 vaccine.

Using cryo-electron microscopy, a number of studies, including Walls et al.¹, determined

structures of the spike. These resembled most closely the structure of the SARS-CoV spike. As seen for other coronaviruses, two conformations were visualized — a closed state, with the RBDs docked against the trimeric core, and an open conformation with a single RBD raised into its 'up' position¹. These studies also showed, just like SARS-CoV, that SARS-CoV-2 uses ACE2 for human cell entry¹. A crystal structure soon followed, showing how the RBD binds to ACE2 (REF.²). Shortly after this, the first structure of a neutralizing antibody bound to the RBD of the spike glycoprotein showed that SARS-CoV-reactive antibodies could neutralize the new virus³, and polyclonal antibody sera against SARS-CoV also proved effective¹. In many ways, these structural studies showed that the new virus resembles a virus that causes SARS; a true SARS-CoV-2.

So, what does this mean for design of a vaccine? Two spike-based vaccine-design strategies, developed for SARS-CoV, should be applicable. The first approach relies on stabilization of the spike. To generate the most effective neutralizing antibody responses, vaccinated individuals should generate antibodies to the pre-fusion spike, thus preventing ACE2 binding and cell entry. For this reason, structure-guided mutations have been designed that fix the SARS-CoV spike into this pre-fusion state⁴. Stabilized SARS-CoV-2 spikes, designed using this method, are therefore promising for a vaccine. But do we need the whole spike? A second approach is to design a vaccine that just contains the RBD. A number of studies



(reviewed in REF.⁵) suggest that the most effective neutralizing responses are

due to antibodies that target this small domain. Ensuring that we induce only the 'best' antibodies also reduces the risk of producing dangerous antibodies that help virus entry through antibody-dependent enhancement.

Whether the future holds stabilized spikes or RBDs, the new spike structures, which revealed that our knowledge of SARS-CoV is also applicable to SARS-CoV-2, are good news. Now we must all hope that the quest to design rational vaccines based on this knowledge is as quickly realized as those structural studies, as the research community work together to fight this global pandemic.

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Competing interests

The authors declare no competing interests.