

Discovery of a conserved anti-SARS-CoV- potential therapeutic target in the heart of human and bat spike proteins

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The spike protein of SARS-CoV and SARS-CoV-2 can sequester physiological electrolytes (sodium, potassium and chloride ions) from the cellular environment in a fully conserved binding site. Credit: Enrico Margiotta, PhD

The spike glycoprotein of the human severe acute respiratory syndrome coronaviruses (hSARS-CoVs) represents an attractive target for the

design and development of biopharmaceuticals as well as small molecule drugs, desirable in terms of either preventing infection or effectively treating disease progression. Despite the effort spent in the development and large-scale production of vaccines to manage the actual COVID-19 pandemic, surges in SARS-CoV-related hospitalizations still represent a major risk for several countries. Nonetheless, first-line antiviral drugs are missing in clinical practice, especially for severely affected patients who may need a specific pharmacological treatment.

The spike protein funnel

As computational chemists, we decided to inspect available human SARS-CoV-2 spike-protein structures as recently solved by crystallographers, searching for any possible interesting site other than the ACE2-receptor binding domain (generally studied by scientists for the design of vaccines and spike-directed antibodies).

We were impressed by the elegant funnel shape assumed by the central helix domain in the state preceding fusion with the human cell. Our immediate question was "How important is this central motif?" After looking at the alpha-helix hydrogen bond path leading to the bottom of the protein funnel, in representative open and closed structures, it was clear that something structurally important was happening in that region. Both cryo-EM data and chemical intuition led us finally to the idea that ions could be bound in the latter.

The ion binding site of SARS-CoV spike glycoproteins

Interestingly, we found sequence conservation of the central helix residues to be 100% in human and bat SARS-like coronaviruses, suggesting an evolutionary role of this site. SARS-CoV-1 spike-protein structures, corresponding to the previous SARS-CoV epidemics of 2003,

were also available, and we now know that the same protein can effectively bind chloride ions after fusion with the cell membrane (see [Duquerroy et al, 2005](#)). So what about the pre-infection state? Is it also able to bind ions? Unfortunately, cryo-EM structures do not offer enough resolution to ion and water molecule visualization, but our DFT quantum-chemical calculations, recently published in [Computational and Theoretical Chemistry](#), overcome this limit and demonstrate that physiological electrolytes (sodium, potassium and chloride ions) can be easily bound by that central helix site, shared between SARS-like CoV spike proteins, especially sodium cation (Figure 2).

The funnel structure of the spike protein, extending from the human ACE2 receptor binding domain (in yellow ball-stick residue representation) to the central helix domain (in green). Credit: Enrico Margiotta, PhD

Conclusions and perspectives

The high conservation of the identified binding site indicates that it should have a substantial role in the spike-protein functions of any SARS-like coronavirus. Specifically, this aspect would be in line with the sequestration of electrolytes from the physiological solution, as probably a key result of the evolutionary adaptation to the mammalian cells' environment. Conservation of the site and also its general binding features suggest that small molecules may be specifically designed in order to interfere with the helix domain structure of either current or future SARS-CoVs, paving the way to new potential antiviral drugs for the clinical practice.

The ion binding site of the SARS-CoV-2 spike proteins as centrally bound to the sodium electrolyte and an axial coordinated water molecule (bond distances between sodium, water and protein are shown in angstroms). Credit: Enrico Margiotta, PhD

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More information: Stéphane Duquerroy et al, Central ions and lateral asparagine/glutamine zippers stabilize the post-fusion hairpin conformation of the SARS coronavirus spike glycoprotein, *Virology* (2005). [DOI: 10.1016/j.virol.2005.02.022](https://doi.org/10.1016/j.virol.2005.02.022)

Enrico Margiotta et al, SARS-CoV spike proteins can compete for electrolytes in physiological fluids according to structure-based quantum-chemical calculations, *Computational and Theoretical Chemistry* (2021). [DOI: 10.1016/j.comptc.2021.113392](https://doi.org/10.1016/j.comptc.2021.113392)

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