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PRESS RELEASE

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The intrinsically disordered SARS-CoV-2 nucleoprotein in dynamic complex with its viral partner nsp3a

Scientists from the French Alternative Energies & Atomic Energy Commission (CEA), the University of Grenoble-Alpes (UGA), and the French National Centre for Scientific Research (CNRS) have combined forces with the European Synchrotron Radiation Facility (ESRF) to become the first to describe a key interaction between two SARS-CoV-2 proteins. This may lead to a new therapeutic strategy to treat Covid-19. The results of their study were published in Science Advances on 19 January 2022.

Whereas vaccines focus on introducing the SARS-CoV-2 spike protein into our body to elicit virus-neutralising antibodies, a joint CEA*, UGA, CNRS and ESRF team realised that it was just as interesting to target the virus's replication system to treat patients already infected with the virus.

With this in mind, the team chose to study the nucleocapsid protein (N) - one of the most abundant in SARS-CoV-2 - because it is a major component of the virus's replication-transcription complex (RTC). A function of the N protein is to protect the viral RNA genome of SARS-CoV-2 and thus evade the host's immune response.

This seemingly natural target for the development of an antiviral treatment contains long, dynamic disordered regions. This characteristic makes it a very flexible** protein, while also rendering it extremely complex to study. Experts in nuclear magnetic resonance (NMR) spectroscopy, the team was able to study very dynamic systems at an atomic-scale resolution. Thus far, they have been able to describe:

1. Structure and dynamics of the N protein
2. Interaction of the N protein with the nsp3a protein.

Interaction between these two proteins allows the N protein to bind to the viral RNA genome and thus replicate the virus. Responsible for genome packaging, the N protein envelopes nsp3a to form a compact molecular assembly that can regulate interactions between the N protein and the viral RNA.

This discovery brings the virus's replication mechanism to the fore, opening the way to new strategies to treat Covid-19, e.g. by inhibiting this key interaction in viral replication.

References: The intrinsically disordered SARS-CoV-2 nucleoprotein in a dynamic complex with its viral partner nsp3a, *Science Advances*, 19 January 2022

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** from the Interdisciplinary Research Institute of Grenoble (IRIG)*

*** Intrinsically disordered proteins lack a fixed 3D structure and function in a disordered state. Their high flexibility allows them to easily bind to the surface of their partners or to replicate during interactions. Though this level of flexibility is key to their biochemical action, it also led to the mutation responsible for the heightened severity of the Delta variant.*

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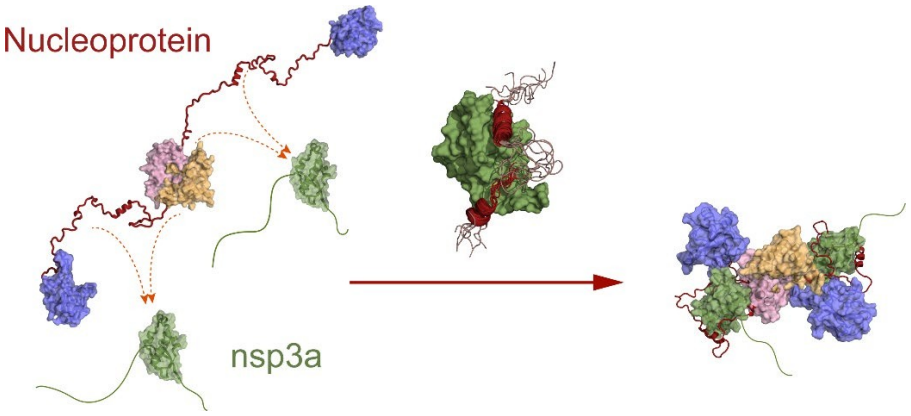

***Figure 1**: Interaction between the N and nsp3a proteins (CEA/CNRS/UGA/ESRF)*