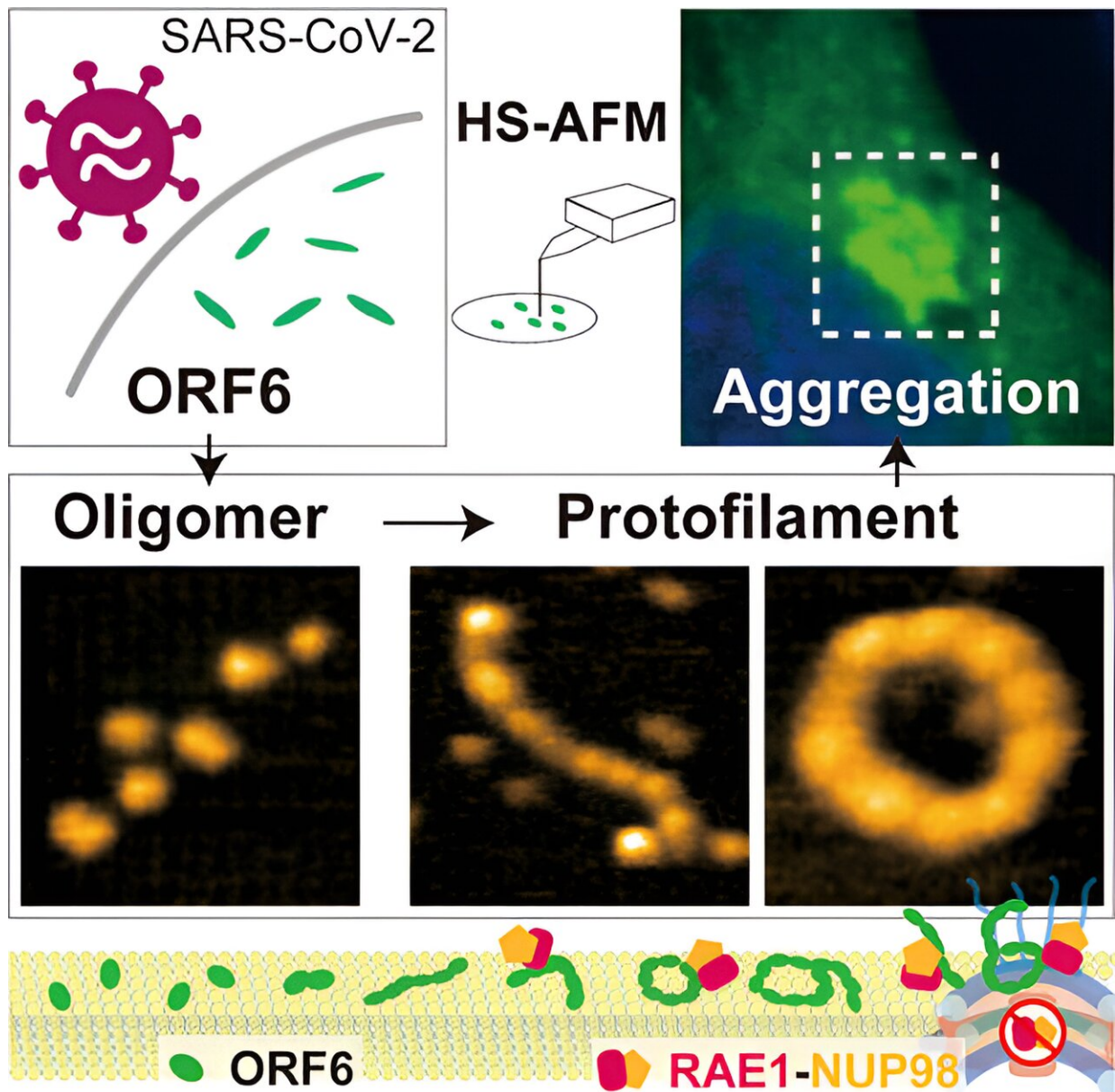


Researchers identify dynamic behavior of key SARS-CoV-2 accessory protein

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Observation of aggregation dynamics by COVID-19 severity factor ORF6 protein. Credit: *The Journal of Physical Chemistry Letters* (2023). DOI: 10.1021/acs.jpcelett.3c01440

Researchers at Kanazawa University [report](#) in the *Journal of Physical Chemistry Letters* high-speed atomic force microscopy studies that shed light on the possible role of the open reading frame 6 (ORF6) protein in COVID-19 symptoms.

While many countries across the world are experiencing a reprieve from the intense spread of SARS-CoV-2 infections that led to tragic levels of sickness and multiple national lockdowns at the start of the decade, cases of infection persist.

A better understanding of the mechanisms that sustain the virus in the body could help find more effective treatments against sickness caused by the disease, as well as arming against future outbreaks of similar infections. With this in mind, there has been a lot of interest in the accessory proteins that the virus produces to help it thrive in the body.

"Similar to other viruses, SARS-CoV-2 expresses an array of accessory proteins to re-program the host environment to favor its replication and survival," explain Richard Wong at Kanazawa University and Noritaka Nishida at Chiba University and their colleagues in this latest report. Among those accessory proteins is ORF6.

Previous studies have suggested that ORF6 interferes with the function of interferon 1 (IFN-I), a particular type of small protein used in the [immune system](#), which may explain the instances of asymptomatic infection with SARS-CoV2. There is also evidence that ORF6 causes the retention of certain proteins in the cytoplasm while disrupting mRNA

transport from the cell, which may be a means for inhibiting IFN-I signaling. However, the mechanism for this protein retention and transport disruption was not clear.

To shed light on these mechanisms, the researchers first looked into what clues various software programs might give as to the structure of ORF6. These indicated the likely presence of several intrinsically disordered regions. Nuclear magnetic resonance measurements also confirmed the presence of a very flexible disordered segment.

Although the machine learning algorithm AlphaFold2 has proved very useful for determining how proteins fold, the presence of these intrinsically disordered regions limits its use for establishing the structure of ORF6 so the researchers used high-speed [atomic force microscopy](#) (HS-AFM), which is able to identify structures by detecting the topography of samples the way a record player needle traverses the grooves in vinyl.

Using HS-AFM the researchers established that ORF 6 is primarily in the form of ellipsoidal filaments of oligomers—strings of repeating molecular units but shorter than polymers. The length and circumference of these filaments was greatest at 37°C and least at 4°C, so the presence of fever could be beneficial for producing larger filaments. Substrates made of lipids—fatty compounds—also encouraged the formation of larger oligomers.

Because HS-AFM captures images so quickly it was possible to grasp not just the structures but also some of the dynamics of the ORF6 behavior, including circular motion, protein assembly and flipping. In addition, further computer analysis also revealed that the filaments were prone to aggregate into amyloids as found in some neurodegenerative diseases, and which can lead to complications in COVID-19 symptoms. As the researchers point out this aggregation works "to effectively

sequester a vast numbers of host proteins, particularly transcription factors involved in IFN-I signaling."

Since these filaments break up in the presence of certain alcohols, urea, or sodium dodecyl sulfate Wong, Nishida and their colleagues conclude that the [protein](#) is largely held together by hydrophobic interactions. "Potential druggable candidates that dissociate ORF6 aggregates by disrupting [hydrophobic interactions](#) should be considered and tested in the near future to evaluate their therapeutic value in COVID-19 management and treatment," state the researchers.

More information: Goro Nishide et al, Nanoscopic Elucidation of Spontaneous Self-Assembly of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Open Reading Frame 6 (ORF6) Protein, *The Journal of Physical Chemistry Letters* (2023). [DOI: 10.1021/acs.jpcllett.3c01440](#)

Provided by Kanazawa University

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