# COVID-19: Viral shutdown of protein synthesis method found

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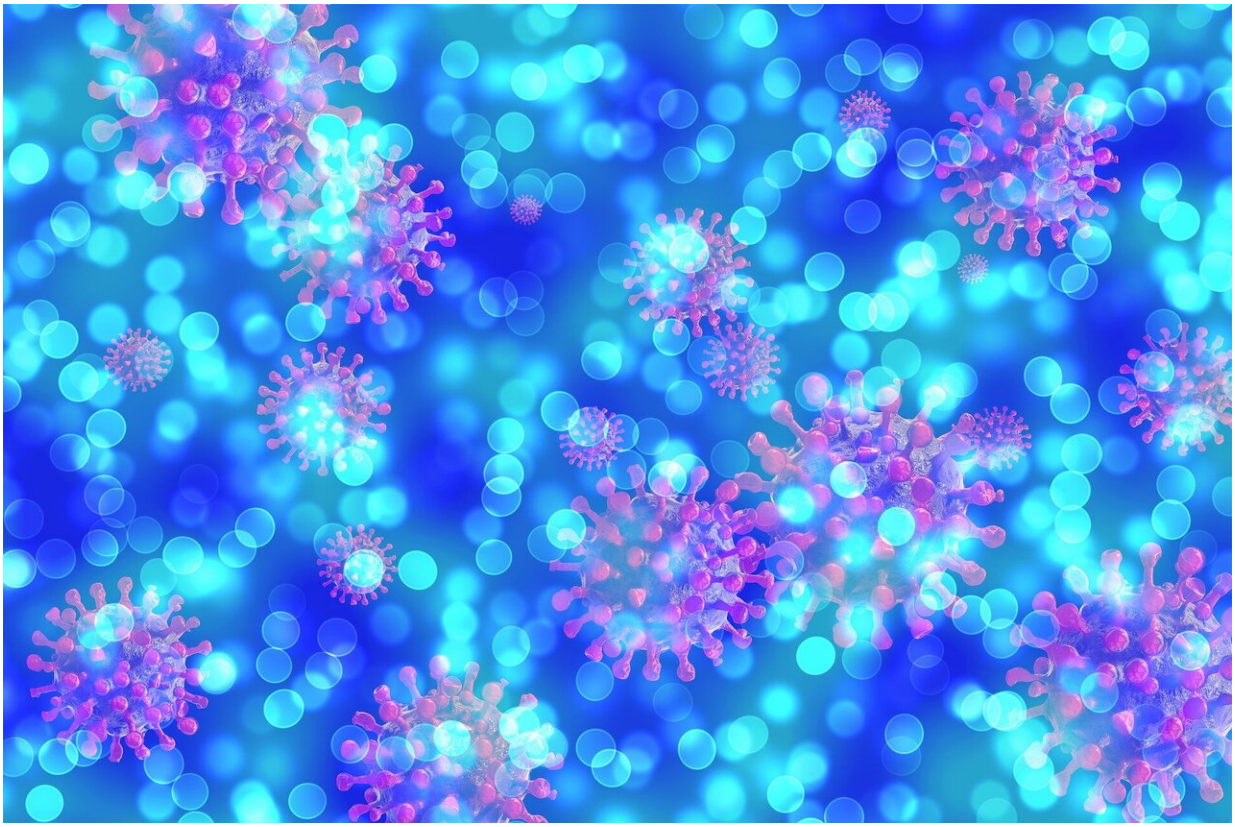

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Researchers from Munich and Ulm have determined how the pandemic coronavirus SARS-CoV-2 inhibits the synthesis of proteins in infected cells and shown that it effectively disarms the body's innate immune

system.

Although its name is relatively unspecific and indeed opaque, the Nonstructural Protein 1 (Nsp1) encoded by the coronavirus SARS-Cov-2, which is responsible for the current pandemic, has now been shown to have a devastating effect on host cells. Nsp1 is in fact one of the central weapons used by the virus to ensure its own replication and propagation in human hosts. Nsp1 was identified as a virulence factor following the outbreak of the related SARS coronavirus nearly 20 years ago, when it was shown to inhibit protein synthesis in infected cells. Now, researchers based at Ludwig-Maximilians-Universitaet (LMU) in Munich and Ulm University Hospital have discovered what makes Nsp1 so potent. In a paper which appears in the journal *Science*, they describe the protein's mode of action in detail.

In all biological cells, the task of synthesizing proteins is performed by complex molecular machines known as ribosomes. Ribosomes interact with messenger RNAs (mRNAs), which serve as blueprints for protein synthesis, and translate the nucleotide sequence of each mRNA into the amino-acid sequence of the corresponding protein. The amino-acid sequence in turn determines the shape and biological function of each individual protein. Ribosomes consist of two distinct subunits, and Nsp1 binds to the smaller one—the 40S subunit. The mRNA initially binds to the small subunit prior to the latter's interaction with the 60S subunit to form the cavity through which the mRNA is then threaded.

The new study shows that one end of the Nsp1 protein interacts with the 40S subunit in such a way that it prevents binding of the mRNA. With the aid of high-resolution cryo-electron microscopy, Professor Roland Beckmann and his colleagues at the LMU Gene Center have shown in three-dimensional detail how Nsp1 binds tightly to a specific pocket in the small ribosomal subunit and inhibits the formation of functional ribosomes. Further experiments revealed that Nsp1 can also interact with

specific configurational states of the fully assembled ribosome.

In addition, the team led by Konstantin Sparrer at Ulm University Hospital was able to show that the shutdown of protein synthesis leads to an almost complete collapse of one of the body's major lines of defense against the virus. Nsp1 inactivates the innate immune response by inhibiting a vital signaling cascade. The authors of the study hope that the insights gained will make it possible to find ways to neutralize the novel coronavirus, and thus mitigate the severity of the respiratory disease that it causes. One potential approach, they say, would be to develop a molecule that masks the viral protein's binding site. This should be feasible, since the Nsp1-binding pocket itself appears not to have an essential role in ribosomal function.

**More information:** Matthias Thoms et al. Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2, *Science* (2020). DOI: 10.1126/science.abc8665

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