Toward one drug to treat all coronaviruses

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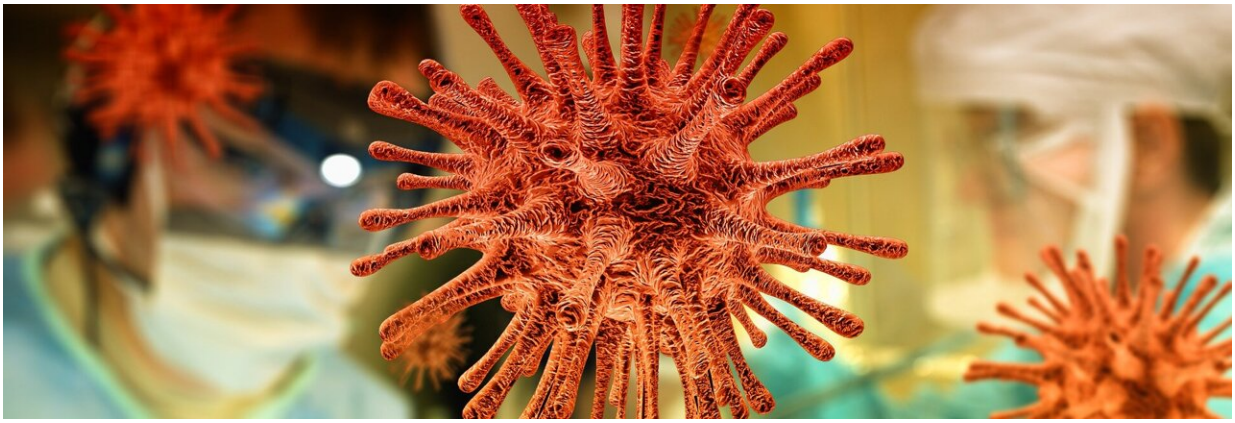

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Safe and effective vaccines offer hope for an end to the COVID-19 pandemic. However, the possible emergence of vaccine-resistant SARS-CoV-2 variants, as well as novel coronaviruses, make finding treatments that work against all coronaviruses as important as ever. Now, researchers reporting in ACS' *Journal of Proteome Research* have analyzed viral proteins across 27 coronavirus species and thousands of samples from COVID-19 patients, identifying highly conserved sequences that could make the best drug targets.

Drugs often bind inside "pockets" on proteins that hold the drug snugly, causing it to interfere with the protein's function. Scientists can identify potential drug-binding pockets from the 3D structures of viral proteins.

Over time, however, viruses can mutate their protein pockets so that drugs no longer fit. But some drug-binding pockets are so essential to the protein's function that they can't be mutated, and these sequences are generally conserved over time in the same and related viruses. Matthieu Schapira and colleagues wanted to find the most highly conserved drug-binding pockets in viral proteins from COVID-19 patient samples and from other coronaviruses, revealing the most promising targets for pan-coronavirus drugs.

The team used a computer algorithm to identify drug-binding pockets in the 3D structures of 15 SARS-CoV-2 proteins. The researchers then found corresponding proteins in 27 coronavirus species and compared their sequences in the drug-binding pockets. The two most conserved druggable sites were a pocket overlapping the RNA binding site of the helicase nsp13, and a binding pocket containing the catalytic site of the RNA-dependent RNA polymerase nsp12. Both of these proteins are involved in viral RNA replication and transcription. The drug-binding pocket on nsp13 was also the most highly conserved across thousands of SARS-CoV-2 samples taken from COVID-19 patients, with not a single mutation. The researchers say that novel antiviral drugs targeting the catalytic site of nsp12 are currently in phase II and III clinical trials for COVID-19, and that the RNA binding site of nsp13 is a previously underexplored target that should be a high priority for drug development.

More information: Setayesh Yazdani et al, Genetic Variability of the SARS-CoV-2 Pocketome, *Journal of Proteome Research* (2021). DOI: 10.1021/acs.jproteome.1c00206

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