

SARS-CoV-2 protease cuts human proteins responsible for immune response

June 9 2021



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The SARS-CoV-2 papain-like protease (PLpro) plays an essential role in processing viral proteins needed for replication. In addition, the enzyme can cut and inactivate some human proteins important for an immune response. Now, researchers reporting in *ACS Infectious Diseases* have found other targets of PLpro in the human proteome, including proteins



involved in cardiovascular function, blood clotting and inflammation, suggesting a link between the inactivation of these proteins and COVID-19 symptoms.

Viruses like SARS-CoV-2 make multiple proteins as one long "polyprotein." Viral enzymes called proteases recognize specific amino acid sequences in this polyprotein and cut them to release individual proteins. However, some human proteins also contain these sequences (known as homologous host-pathogen sequences, or SSHHPS), including ones involved in generating the innate <u>immune response</u>, which could help protect the virus from the host. Patricia Legler and colleagues wanted to comprehensively identify human proteins that contain SSHHPS, examine their functions and see whether PLpro can cleave them in a test tube.

The researchers developed a computational method to search a database of all known human proteins for sequences similar or identical to the SARS-CoV-2 SSHHPS. The analysis revealed that the proteins with highest sequence identity were those that had cardiovascular, inflammatory, kidney, respiratory or blood-related functions. For example, two of the proteins containing SSHHPS were cardiac myosins, one was an anti-coagulant and another was an anti-inflammatory protein. Inactivation of these proteins by PLpro is consistent with COVID-19 symptoms of heart damage, blood clots and inflammation. The team confirmed that PLpro could cut these protein sequences in vitro. Performing the same analysis on SSHHPS for the Zika viral protease identified proteins associated with neurological development and disorders, consistent with Zika symptoms. These results suggest that the symptoms and virulence of viruses can be predicted directly from their genomic sequences, the researchers say.

More information: Nathanael D. Reynolds et al, The SARS-CoV-2 SSHHPS Recognized by the Papain-like Protease, *ACS Infectious*



Diseases (2021). DOI: 10.1021/acsinfecdis.0c00866

Provided by American Chemical Society

Citation: SARS-CoV-2 protease cuts human proteins responsible for immune response (2021, June 9) retrieved 27 April 2024 from <u>https://phys.org/news/2021-06-sars-cov-protease-human-proteins-responsible.html</u>

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