Likely molecular mechanisms of SARS-CoV-2 pathogenesis are revealed by network biology

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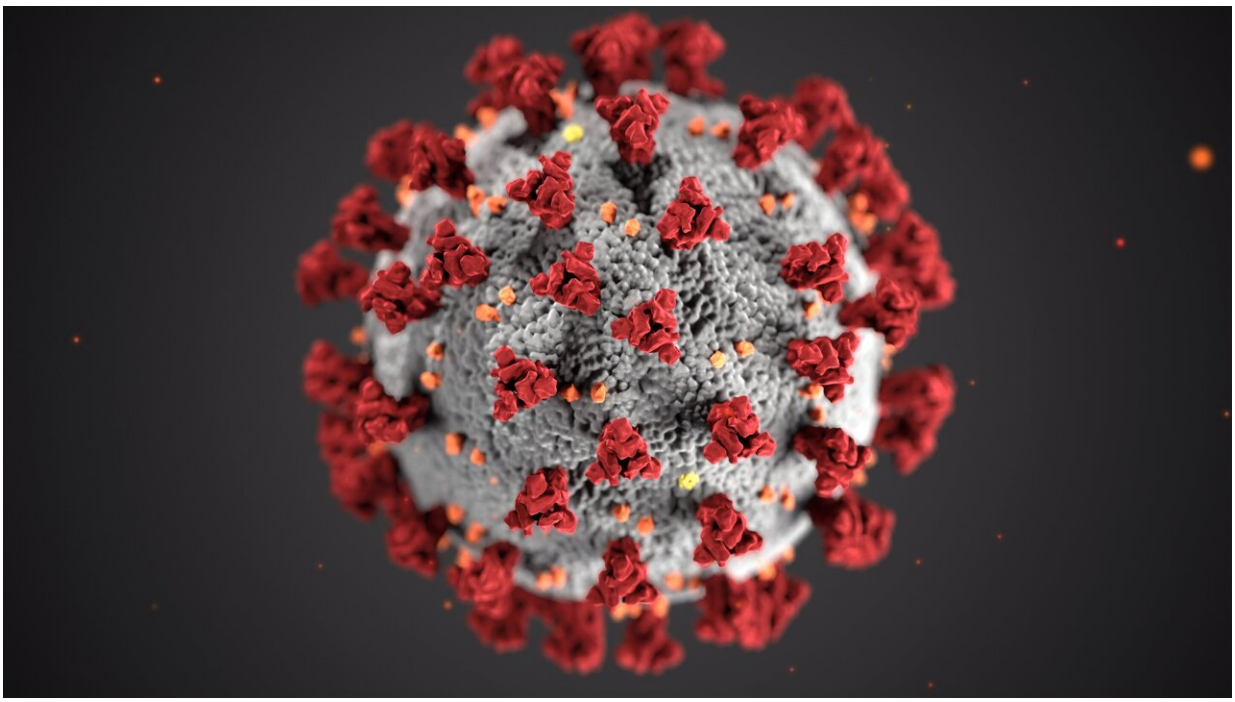

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Viral and bacterial pathogens wield pathogenic or virulent proteins that interact with high-value targets inside human cells, attacking what is known as the host interactome. The host interactome is the network map of all the protein-protein interactions inside cells.

Such networks have been studied in organisms as diverse as plants, humans and roundworms, and they show a similarity to social networks like Facebook or airline route maps. In Facebook, a few people will have a huge number of friend connections, some will have many, and a vast majority will have much fewer. Similarly, airlines have a few hubs that many passengers pass through on the way to their destinations.

Host interactomes show a limited number of high-powered hubs—where a protein has a large number of connections—and a limited number of important bottlenecks, which are sites with a large number of short paths to a node. These are key targets for pathogens as they seek to seize control of the infected cell, so it can rewire the cell's flow of information and cause disease.

University of Alabama at Birmingham researchers, led by Shahid Mukhtar, Ph.D., associate professor of biology in the UAB College of Arts and Sciences, have now built an interactome that includes the lung-epithelial cell host interactome integrated with a SARS-CoV-2 interactome. Applying network biology analysis tools to this human/SARS-CoV-2 interactome has revealed potential molecular mechanisms of pathogenesis for SARS-CoV-2, the virus responsible for the COVID-19 pandemic. The UAB research, published in the journal *iScience*, identified 33 high-value SARS-CoV-2 therapeutic targets, which are possibly involved in viral entry, proliferation and survival to establish infection and facilitate disease progression. These molecular insights may foster effective therapies, using combinations of existing drugs, for patients with COVID-19.

So far in 2019, the SARS-CoV-2 virus has killed nearly 1 million people worldwide and 200,000 in the United States.

The UAB researchers took many steps to generate the Calu-3-specific human-SARS-CoV-2 interactome, or CSI, that was the starting point for

their network biology analyses.

They began from a comprehensive human interactome of experimentally validated protein-protein interactions, posted online in 2015, and then manually curated other protein-protein interactions from four subsequent interactome studies. The resulting human interactome contained 18,906 nodes and 444,633 "edges"—the term for the links between protein nodes.

From two 2020 studies, the researchers compiled an exhaustive list of 394 host proteins that interact with the novel human coronavirus; these host proteins were called SARS-CoV-2 interacting proteins, or SIPs. The SIPs included 332 human proteins associated with the peptides of SARS-CoV-2 and 62 host proteins interacting with the viral factors of other human coronaviruses, including SARSCoV and MERS-CoV, the causes of SARS and MERS, which could also aid understanding the molecular pathogenesis of SARS-CoV-2.

By querying these 394 SIPs in the human interactome, they generated a subnetwork of 12,852 nodes and 84,100 edges that covered first and second neighbors of the 373 SIPs.

Finally, they filtered these interactions in the context of temporal changes during COVID-19 infection, using a high-resolution temporal transcriptome derived from cultured human airway epithelial cells, or Calu-3, treated with SARSCoV and SARS-CoV-2 over time. Integrating this Calu-3 expression data with the SIPs-derived protein-protein interaction subnetwork resulted in a Calu-3-specific human-SARS-CoV-2 interactome, or CSI, that contained 214 SIPs interacting with their first and second neighbors, and forming a network of 4,176 nodes and 18,630 edges.

The CSI had a power law degree distribution with a few nodes harboring

increased connectivity compared to a random network, and thus exhibited properties of a scale-free network, similar to the other, previously generated human-viral interactomes.

The robust, high-quality CSI was then further utilized for network-aided architectural and functional pathway analyses.

Topological clustering and pathway enrichment analysis showed that the SARS-CoV-2 virus attacks central nodes of the host-viral network that participate in core functional pathways. Network centrality analyses discovered 33 high-value SARS-CoV-2 targets for possible drug therapy; these targets are possibly involved in viral entry, proliferation and survival to establish infection and facilitate disease progression. A probabilistic modeling framework elucidated critical regulatory circuitry and molecular events pertinent to COVID-19, particularly the host modifying responses and cytokine storm.

"In summary," Mukhtar said, "our integrative network topology analyses led us to elucidate the underlying molecular mechanisms and pathways of SARS-CoV-2 pathogenesis." Mukhtar's lab continues to work on network medicine and artificial intelligence to battle COVID-19 and other human inflammatory diseases.

Co-first authors of the study, "Integrative network biology framework elucidates molecular mechanisms of SARS-CoV-2 pathogenesis," are graduate students Nilesh Kumar and Bharat Mishra, UAB Department of Biology.

More information: Nilesh Kumar et al. Integrative Network Biology Framework Elucidates Molecular Mechanisms of SARS-CoV-2 Pathogenesis, *iScience* (2020). DOI: 10.1016/j.isci.2020.101526