「Global Study Identifies Common Vulnerabilities across Coronaviruses」

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In research published Oct. 15 in Science, an international team of almost 200 researchers from 14 leading institutions in six countries studied the three lethal coronaviruses SARS-CoV-2, SARS-CoV-1 and MERS-CoV in order to identify commonly hijacked cellular pathways and detect promising targets for broad coronavirus inhibition. [1, 2]

Using molecular insights gained from this multidisciplinary, systematic study of coronaviruses, the group analyzed medical records of approximately 740,000 patients with SARS-CoV-2, assessing clinical outcomes in these patients to uncover approved therapeutics with potential for rapid deployment. These results demonstrate how molecular information can be translated into real-world implications for the treatment of COVID-19, an approach that can ultimately be applied to other diseases in the future.

“This far-reaching international study elucidates for the first time commonalities and, importantly, vulnerabilities, across coronaviruses, including our current challenge with the SARS-CoV-2 pandemic,” said Nevan Krogan, the lead investigator of the study. “In unique and rapid fashion, we were able to bridge biological and functional insights with clinical outcomes, providing an exemplary model of a differentiated way to conduct research into any disease, rapidly identify promising treatments and advancing knowledge in the fields of both science and medicine. This body of work was only made possible through the collaborative efforts of senior scientific thought leaders and teams of next-generation researchers at premier institutions across the globe.” [3]

Building on previous work published in both Nature and Cell, [4, 5] the researchers leveraged a SARS-CoV-2 map, or “interactome,” documenting how SARS-CoV-2 proteins interact with their target human host cell proteins, the team built protein-protein interaction maps for SARS-CoV-1 and MERS-CoV, highlighting several key cellular processes that are shared across all three coronaviruses. These common pathways and protein targets represent high-priority targets for therapeutic interventions for this and future pandemics.

Using the three coronavirus interactomes as a guide, the team performed CRISPR and RNA interference (RNAi) knockouts of the putative host target proteins of each virus and studied how loss of these proteins altered the ability of SARS-CoV-2 to infect human cells. They determined that 73 of the proteins studied were important for the replication of this virus and used this list to prioritize evaluation of drug targets. Among these were the receptor for the inflammatory signaling molecule IL-17, which has been identified in numerous other studies as an important marker of COVID-19 disease severity; prostaglandin E

synthase 2 (PGES2), which functionally interacts with the Nsp7 protein in all three viruses; and sigma receptor 1, which interacts with Nsp6 in both SARS-CoV-1 and SARS-CoV-2.

Armed with this knowledge, the group performed a retrospective analysis of medical billing data from approximately 740,000 people who had tested positive for SARS-CoV-2 or were presumed to be positive. Pedro Beltrao, PhD, group leader at EMBL's European Bioinformatics Institute, said, "These analyses demonstrate how biological and molecular information are translated into real-world implications for the treatment of COVID-19 and other viral diseases. After more than a century of relatively harmless coronaviruses, in the last 20 years we have had three coronaviruses which have been deadly. By looking across the species, we have the capability to predict pan-coronavirus therapeutics that may be effective in treating the current pandemic, which we believe will also offer therapeutic promise for a future coronavirus as well." [2, 3]

Reference:

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2. 16 Oct, 2020. "International Team of Scientists Identifies Common Vulnerabilities Across Coronaviruses" *UCSF news*
3. 15 Oct, 2020. "Global study identifies common vulnerabilities across SARS-CoV-2, SARS-CoV-1 and MERS coronaviruses" *Georgia State University News Press*
4. David E. Gordon et al. 30 Apr, 2020. "A SARS-CoV-2 protein interaction map reveals targets for drug repurposing" *Nature;* 583, pages459-468
5. Mehdi Bouhaddou et al. 6 Aug, 2020. "The Global Phosphorylation Landscape of SARS-CoV-2 Infection" *Cell;* 182(3): 685-712.e19.