Coronavirus: A map of Sars-CoV-2 activated proteins

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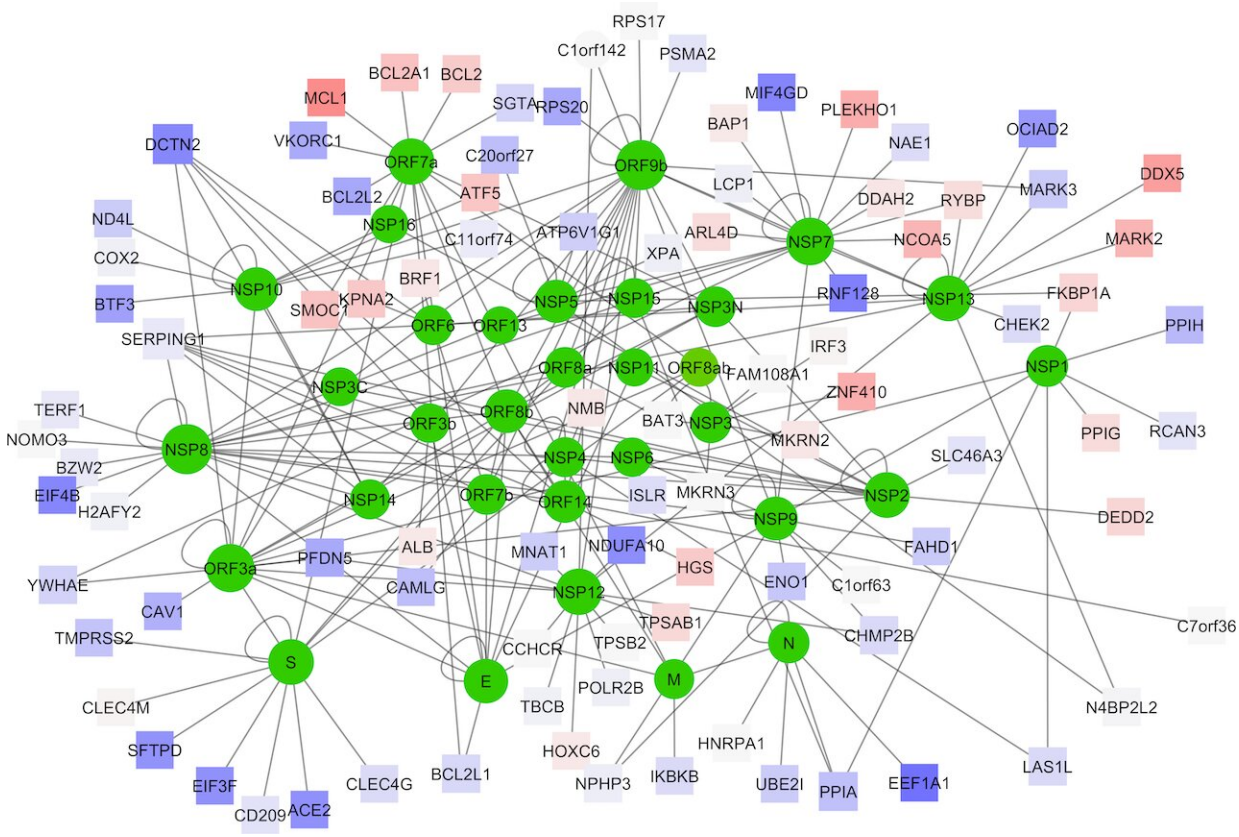

Representation of the predicted SARS-CoV-2/Human interactome [26] (available for download at http://korkinlab.org/wuhanDataset), containing 200 unique interactions among 125 proteins (nodes). SARS-CoV-2 proteins are depicted as green circles, while human proteins are represented as squares. The color of human protein nodes reflects the integrated effect of MERS and SARS infections on the node network (see Supplementary Table S2) as a Normalized Enrichment Score (NES). Network visualization was performed via Cytoscape [49]. Credit: Courtesy of Journal of Clinical Medicine

What happens when the pathogen responsible for the Covid-19 pandemic, the coronavirus Sars-CoV-2, makes contact with a human bronchial cell? A group of researchers from the Universities of Bologna and Catanzaro (Italy) mapped the interactions between the virus proteins and those of humans, showing which proteins are being "activated" and "de-activated" by Sars-CoV-2.

"Gaining knowledge about the molecular effects of Sars-CoV-2 on human proteins is fundamental to devise effective drug therapies," says Federico M. Giorgi, principal investigator of the study and a researcher at the University of Bologna. "Inhibiting the interactions that we mapped may represent an effective strategy for a therapy able to contain the disruptive force of Sars-CoV-2 and other coronaviruses on human cells."

This study was published on the *Journal of Clinical Medicine*. The researchers were able to identify human cell defense mechanisms, when the virus enters the body, for example, as well as how Sars-CoV-2 spreads in the human body, e.g., via proteins favoring its replication.

An integrated approach

Beta-coronaviruses, a sub-family of coronaviruses, mainly cause respiratory and intestinal diseases. To date, we are aware of seven strains of beta-coronavirus that affect humans. Three of them are particularly dangerous: Sars-CoV, causing Sars, Mers-CoV, causing Mers, and the new Sars-CoV-2, causing Covid-19, the illness that has already infected over 1 million people around the globe.

We know that Sars-CoV-2 has a lot in common with its beta-coronavirus "cousins," and with Sars-CoV in particular. Nevertheless, a detailed description of how this virus attacks human cells is still missing. To shed

some light on this issue, researchers compared the interactome (the set of interactions between proteins) deriving from the encounter between Sars-CoV-2 and a human cell with the available information on the behavior of Sars-CoV and Mers-CoV viruses.

"This integrated approach draws from our knowledge of other beta-coronaviruses and from what we have learned about this new coronavirus so far. Crucially, it allowed to identify the main factors behind the action of Sars-Cov-2," explains Giorgi. "As a result, we were able to create a map showing which proteins are activated, thus increasing their production, and which are deactivated, consequently decreasing their quantity, when the virus attacks a cell of the human breathing system."

Attack and defense

This analysis revealed proteins that play a relevant role when the new coronavirus encounters a human cell. One of these proteins (MCL1) regulates the process of apoptosis (programmed cell death), an anti-viral defense mechanism, setting in motion a series of reactions that eventually cause cells to trigger their own death in order to stop the attack of the virus. Other proteins are instead limited in their scope once they come into contact with the coronavirus. The deactivation of protein EEF1A1, for example, hinders the replicating ability of the virus.

The downside, however, is that Sars-CoV-2 also exploits other mechanisms in order to spread throughout the body. Indeed, researchers came to three main conclusions. Firstly, they found out that the virus is able to hinder the activity of mitochondria (the organelles in charge of cell respiration); secondly, they discovered that some specific viral proteins (NSP7 and NSP13) are able to deactivate some cell defense mechanisms; and thirdly, they observed the increase of some proteins that favur RNA metabolism, and as a consequence, the action and replication of the virus (whose genome is a single RNA strand).

Then the protein ACE2 interacts with the "spikes" of the coronavirus, allowing it to enter the cells. The analysis shows that the cells fight the virus attack, decreasing the presence of ACE2. Researchers also observed that a lower presence of this protein may damage lung tissues, thus favoring the spread of the virus anyway.

"This valuable information about the effects of the new coronavirus on the proteins of human cells may prove to be fundamental in redirecting the development of drug therapies, since common antiviral treatments seem to be unsuccessful," says Federico M. Giorgi. "Recent advances in pharmaceutical science allow for the quick development of new molecules, which may prove to be very effective to counteract the action of the virus proteins and to improve the response of human cells."

Finally, the researchers analyzed the presence of ACE2 to shed some light on the animal origin of the Sars-CoV-2 coronavirus, which was initially ascribed to bats and then also to pangolins. This study brought to the fore a closer similarity between ACE2 proteins of human cells and those of pangolins. This result supports the hypothesis that this small mammal might have been the first host of Sars-CoV-2, or at least an intermediate one between bats and humans.

The title of the study is "Master Regulator Analysis of the SARS-CoV-2/Human Interactome." The researchers are Federico M. Giorgi, Daniele Mercatelli and Carmine Ceraolo from the Department of Pharmacy and Biotechnology of the University of Bologna and Pietro H. Guzzi from the Magna Græcia University of Catanzaro.

More information: Pietro H. Guzzi et al. Master Regulator Analysis of the SARS-CoV-2/Human Interactome, *Journal of Clinical Medicine* (2020). DOI: 10.3390/jcm9040982

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