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A CRISPR study: What makes a cell coronavirus-resistant?

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Original title
Genetic Screens Identify Host Factors for SARS-CoV-2 and Common Cold Coronaviruses.[1]

Introduction
SARS-CoV-2, which caused the current pandemic, is part of a larger family of viruses called "Coronaviridae". All the viruses in this family cause some level of respiratory problems, from the common cold to the much more serious COVID-19, and as of now there are 7 that lack a vaccine. Identifying the mechanisms by which those viruses attack the cells is crucial to effectively fight them in the future.

A virus particle – called a virion – consists of a small piece of membrane wrapped around the blueprint for how it needs to reproduce. Viruses lack their own reproduction machinery, so they have to use the one of the human or animal that they infect instead. Upon attack, the virus blends its membrane with the membrane of a human or animal cell. Then the virus injects its blueprint or "genetic material", which is then amplified by the cell like if it was its own blueprint. Multiple new viruses are generated and released from the cell to attack even more cells.

All living organisms store their genetic information in the form of nucleic acid called DNA or RNA. Those are long strings of "letters" (bases) of the genetic code, which also form pairs with each other. Base pairing is very important for replication – producing identical copies of DNA or RNA. Specific fragments of the string form genes and their correct order is crucial for the correct gene to be formed. There are various techniques of modifying the genome by removing, adding or replacing single letters or fragments of the sequence. Such changes can be very precisely introduced using the CRISPR-Cas9 gene editing technique.

In this study, the authors used SARS-CoV-2 and two other related viruses to identify things in common for the whole family of coronaviruses involved in human cells infection. The scientists prepared human cells so that they could easily be infected by any of the three tested viruses. The human cells were then 1) grown in a laboratory, 2) mutated randomly using the CRISPR-Cas9 technique to switch off one gene at a time, and 3) infected with one of the three viruses. Cells that survived were analyzed to see which gene had been switched off in them. Then, mutations of the surviving cells were compared between the three types of viruses.

Findings
The study confirmed that all the tested viruses bind to membrane molecules called receptors to enter the cell. Some of those receptors were already known from other studies, which proves that the method works well. This work also describes which processes within the cell are important for the virus. Each of the three tested viruses binds to a different membrane receptor but all use similar parts of the cellular machinery once inside the cell. It is thus possible that all coronaviruses behave similarly inside the cell. Knowing which human genes help the virus to infect cells and reproduce, it may be possible to develop a therapy that switches them off and makes the cells less susceptible to the virus. Such strategy may possibly work well even against future mutations of the virus, which is advantageous over strain-specific therapies that need to be adjusted for every new variant.

The scientists used a computer approach called "network propagation" to show which of the identified genes work together. Using computer algorithms, the network was expanded over the whole genome to find even more genes, which

were not initially visualized by the screen, yet are also part of the same tasks.

Next, the scientists switched off the candidate genes in the cells and – as hoped for – the virus reproduced much slower than in cells without the mutation. And when the missing genes were re-introduced into the cells, the virus thrived. This experiment proved that the viral cycle relies on the identified genes, and so regulating their expression can be used to fight the infection. The scientists also showed that existing drugs that are designed for the candidate genes effectively fight the virus. Those findings point in new directions for potential coronavirus therapies.

Conclusions

This paper describes a genome-wide study of coronavirus resistance focused on strengthening host cells rather than attacking the virus. It discusses similarities in the virus-host relation between three representatives of the Coronaviridae family that potentially may be expanded over its other members. This way, studying common cold viruses can shed light on our understanding of the much more dangerous SARS-CoV-2. The scientists identified cellular genes that are important for the viral reproductive cycle and proved that they can be treated with known drugs to control the infection. The results may thus lead to additional treatment options for coronavirus infections.

Article info

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References

1. Wang, R. *et al.* Genetic Screens Identify Host Factors for SARS-CoV-2 and Common Cold Coronaviruses. (2021) doi:10.1016/j.cell.2020.12.004.