New drug shows promise for fighting both COVID-19 and cancer

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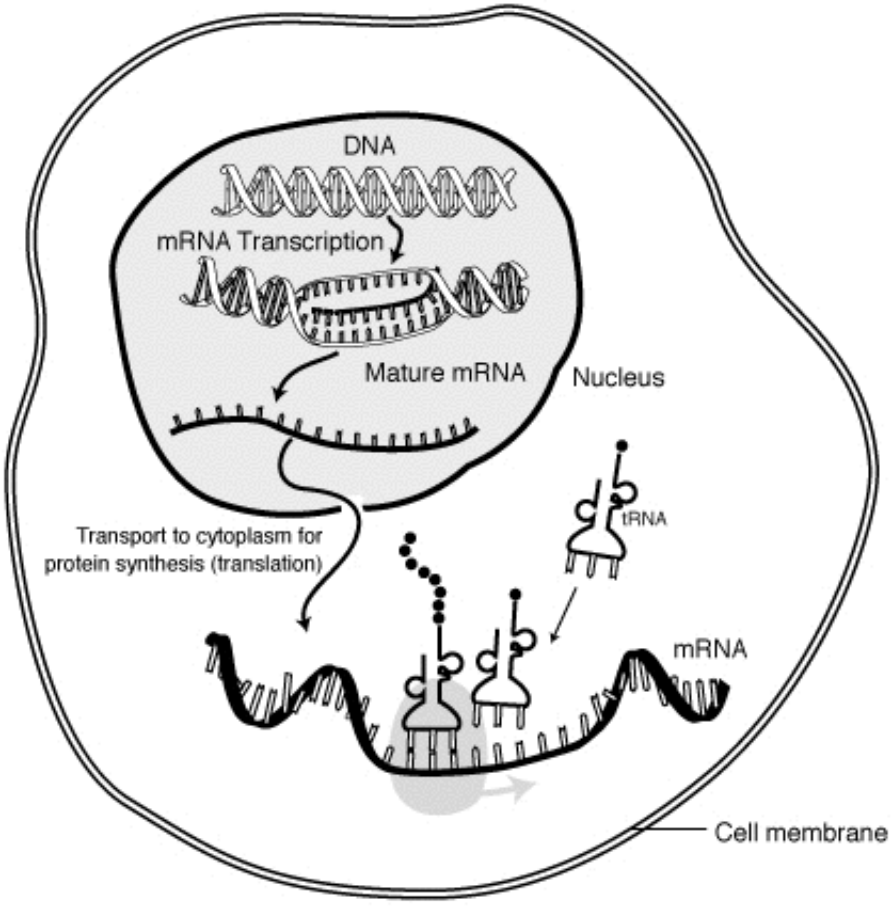

The "life cycle" of an mRNA in a eukaryotic cell. RNA is transcribed in the nucleus; processing, it is transported to the cytoplasm and translated by the ribosome. Finally, the mRNA is degraded. Credit: Public Domain

While vaccination can provide life-saving protection against COVID-19, scientists are still searching for ways to treat severe infections, including in people who cannot get vaccinated or in the event that dangerous new strains of the virus arise that could bypass vaccine protection.

Now, a new study from a team of researchers led by Amy S. Lee, Ph.D., professor of biochemistry and molecular medicine at the Keck School of Medicine of USC, shows that a chaperone protein known as GRP78, implicated in the spread of other viruses, plays an essential role in the spread of SARS-CoV-2, the virus that causes COVID-19. The study also shows that blocking the production of GRP78, or inhibiting its activity with a new targeted drug, greatly reduced the replication of SARS-CoV-2.

The research, just published in the journal *Nature Communications*, suggests this drug could potentially offer a new type of protection against COVID-19, one that might remain effective even as new strains develop.

"A major problem in fighting SARS-CoV-2 is that it is constantly mutating and adapting itself to more efficiently infect and multiply in its host cells," said Lee, also the Judy and Larry Freeman Chair in basic science research. "If we keep chasing the virus around, this could become quite challenging and unpredictable."

GRP78's role in the spread of viruses

Searching for a more stable way to combat COVID-19, Lee and her colleagues at the Keck School of Medicine of USC and the Cleveland Clinic Florida Research and Innovation Center began exploring the role of GRP78, a key cellular chaperone protein that helps regulate the folding of other cellular proteins. While healthy cells need a fraction of GRP78 to function normally, cells under stress need more GRP78 to

cope. The Keck School of Medicine researchers showed in a 2021 paper that when SARS-CoV-2 enters the scene, GRP78 is hijacked to work in tandem with other cellular receptors to bring the SARS-CoV-2 virus inside cells, where it can then reproduce and spread.

But questions remained about whether GRP78 is "necessary and essential" for SARS-CoV-2 replication inside human lung cells. Examining human lung epithelial cells infected with SARS-CoV-2, the research team observed that as the viral infection intensifies, the infected cells produce higher levels of GRP78.

The power of inhibiting GRP78

Then Lee and her team used a special messenger RNA tool to suppress production of the GRP78 protein in human lung epithelial cells in cell culture, without interrupting other cellular processes. When those cells were later infected with SARS-CoV-2, they produced a lower amount of the viral spike protein and released much less of the virus to infect other cells, proving that GRP78 was necessary and essential for viral replication and production.

"We now have direct evidence that GRP78 is a proviral protein that is essential for the virus to replicate," Lee said.

To further explore whether targeting GRP78 could work to treat COVID-19, the researchers tested a recently identified small molecule drug, known as HA15 on the infected lung cells. This drug, developed for use against cancer cells, specifically binds GRP78 and inhibits its activity.

"Lo and behold, we found that this drug was very effective in reducing the number and size of SARS-CoV-2 plaques produced in the infected cells, in safe doses which had no harmful effect on normal cells," Lee

said.

The researchers then tested HA15 in the body of mice that were genetically engineered to express a human SARS-CoV-2 receptor and infected with SARS-CoV-2, finding that the drug greatly reduced viral load in the lungs.

Drugs that target GRP78

Separately, Lee and her colleagues at the Keck School of Medicine are studying the efficacy of HA15 in cancer, as well as another GRP78 inhibitor, YUM70, in collaboration with researchers at the University of Michigan. They discovered that HA15 and YUM70 can suppress the production of mutant KRAS proteins—a common mutation that tends to resist drug treatment—and reduce the viability of cancer cells bearing such mutations in pancreatic, lung and colon cancer. Those findings, just published in the journal *Neoplasia*, suggest targeting GRP78 may help combat these deadly cancers.

These are basic proof of principle studies; further research, including clinical trials, is needed to establish that HA15 and YUM70 are safe and effective for use in humans. These and other GRP78 inhibitors are now being tested as treatments for both COVID-19 and cancer. These drugs may also prove useful for treating future coronaviruses that depend on GRP78 for entry and replication, Lee said.

In addition to Lee, the *Nature Communications* study's other authors are Dat Ha of the Department of Biochemistry & Molecular Medicine, Keck School of Medicine of USC; Keigo Machida of the Department of Molecular Microbiology and Immunology, Keck School of Medicine of USC; and Woo-Jin Shin of the Florida Research and Innovation Center, Cleveland Clinic.

More information: Shin, WJ., Ha, D.P., Machida, K. et al. The stress-inducible ER chaperone GRP78/BiP is upregulated during SARS-CoV-2 infection and acts as a pro-viral protein. *Nature Communications*, 13, 6551 (2022). doi.org/10.1038/s41467-022-34065-3