Identifying the cause and potential treatment for COVID-19-induced heart damage

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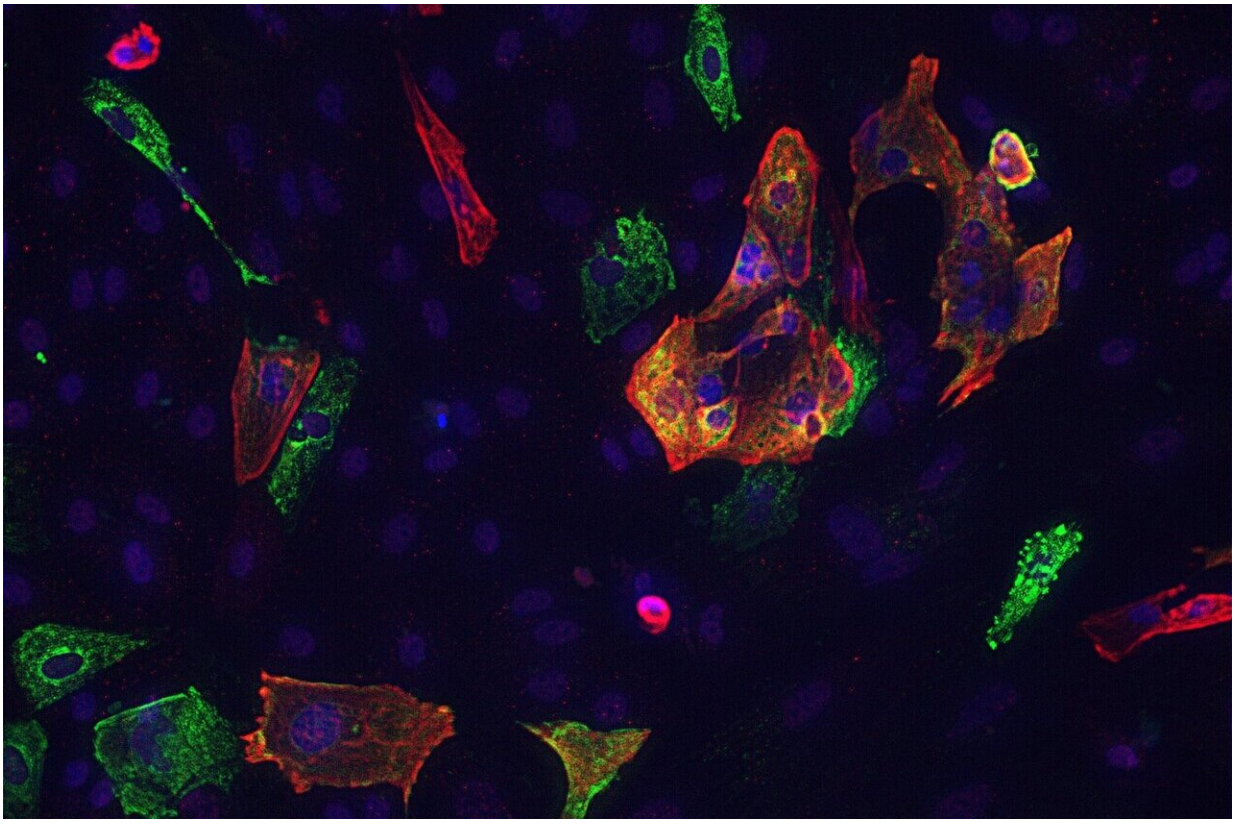

Credit: QIMR Berghofer Medical Research Institute

QIMR Berghofer researchers have discovered some of the ways COVID-19 damages the heart, and identified a class of drugs that could potentially protect or reverse this cardiac injury.

In severe cases of COVID-19, the immune system overreacts to the infection, releasing inflammatory molecules called cytokines into the bloodstream. This so-called 'cytokine storm' can damage multiple organs, including the heart.

Canadian company Resverlogix has used the QIMR Berghofer research findings as the basis for expanding its clinical trial of the drug, apabetalone, in COVID-19 patients.

Apabetalone belongs to a new class of drugs that has been in clinical trials for cardiovascular disease for more than five years. It has received breakthrough therapy designation from the US regulator, the Food and Drug Administration. Resverlogix initially planned to study apabetalone to improve clinical status in SARS-CoV-2 infected patients, but will now also examine if it can treat heart damage.

The head of QIMR Berghofer's Cardiac Bioengineering Research Group, Associate Professor James Hudson, said his team used thousands of lab-grown, miniature human heart organoids to understand how COVID-19 causes cardiac damage.

"We wanted to find out exactly how the cytokine storm causes cardiac damage by identifying the proteins responsible, and then try to repurpose existing drugs targeting those proteins," Associate Professor Hudson said.

"We thought understanding the biological basis of the heart damage was critical for identifying drugs with a much higher chance of success.

"We exposed the bioengineered, stem-cell-derived heart tissue to COVID-19 patient blood and found it caused dysfunction even when the virus didn't infect the tissue.

"These experiments revealed which inflammatory factors are potentially causing the cardiac problems. These factors activate bromodomain protein 4 in the heart, which we found was the key driver of cytokine storm damage.

"We then used our mini heart organoids to screen several existing drugs that inhibit this protein and found they can prevent and reverse the damage.

"One of these was apabetalone, which was also effective at blocking the inflammatory response. Because it is already in phase III clinical trials for treating cardiovascular disease, it could be available sooner to treat COVID-19 patients."

Associate Professor Hudson said the laboratory tests showed apabetalone also decreased the expression of the receptor protein ACE2, which is found on the cell surface and is used by the SARS-CoV-2 virus to infect cells.

"Inhibiting the expression of the ACE2 receptor with apabetalone also led to a lower viral infection, which in turn decreased heart damage in our lab experiments," he said.

"It's great to be working with Resverlogix to progress this research to a clinical trial to test if apabetalone can be safely used to prevent the terrible organ damage seen in COVID-19 patients around the world."

The President and CEO of Resverlogix, Donald McCaffrey, said it had been a pleasure to work with the QIMR Berghofer team.

"We are excited that we can finally share publicly some of the incredible early results of our collaborative COVID-19 research program," Mr McCaffrey said.

"Not only does apabetalone treatment reduce SARS-CoV-2 infection in cardiomyocytes, but it also prevents cardiac dysfunction induced by cytokine-storm.

"These findings showcase the unique dual-mechanism of apabetalone as a potential treatment for COVID-19 and provide strong support for human clinical trials.

"Collaborations such as this serve to quickly move our research forward for the benefit of patients."

The Australian Minister for Health, Greg Hunt, said it was gratifying to see that research funded through the Medical Research Future Fund (MRFF) was helping identify potential new treatments for COVID-19.

"We fast-tracked funding from the MRFF to support Australian researchers to help in the global effort against this disease," Mr Hunt said.

"It's wonderful to see this research contributing to the expansion of a clinical trial, which I hope will help prevent heart injury in COVID-19 patients."

Queensland's Health Minister, Yvette D'Ath, said the state has provided nearly $1 million dollars to Professor Hudson's team to continue their research to find new COVID-19 treatments.

"Professor Hudson's cardiac organoid research has been world leading, and provides a way to quickly test potential new drugs," Ms D'Ath said.

"We are lucky to have world leaders in this area of research working in our state, and the Queensland Government is proud to support this research."

A growing body of research suggests up to two-thirds of patients who have recovered from severe COVID-19 experienced some heart inflammation. About a quarter of patients hospitalized with severe COVID-19 sustained some form of cardiovascular injury.

Professor Hudson's research findings have been published on the pre-print server, *bioRxiv*, at the request of the reviewing scientific journal.

More information: *bioRxiv*, www.biorxiv.org/content/10.110 … /2020.08.23.258574v3

Provided by QIMR Berghofer Medical Research Institute