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SPIKE PROTEIN FROM COVID-19 MAY HARM THE HEART

MMRI Finds Possible Reasons Why SARS-Cov-2 Damages the Heart

UTICA, NY — From the beginning, SARS-CoV-2 (COVID-19) has principally affected older patients or those with certain pre-existing conditions. Specifically, 20-25% of all COVID-19 related deaths have occurred in those with preexisting cardiovascular disease. More importantly, for those that have recovered from the virus, even those that suffered mild symptoms, a large number are now showing signs of long-term heart conditions as a consequence of the infection. Now, it is an urgent medical need to understand what causes these effects and how. Two recent publications by Dr. Zhiqiang Lin, Assistant Professor at the Masonic Medical Research Institute (MMRI), have helped establish a link of how SARS-CoV-2 harms the heart.

Even before the pandemic, the Lin Laboratory was investigating a group of pattern recognition receptor proteins, called Toll-Like Receptors (TLRs), which serve as antennas to detect invading pathogens. They found that the expression of most TLRs was low in neonatal mouse hearts and high in adult mice, and that several TLRs (including TLR4, which is harmful when activated) were increased in response to pathological cardiac stressors, such as high blood pressure and heart attack. They also demonstrated that activating TLR4 activity in a fraction of heart muscle cells makes the heart more vulnerable to a systemic inflammatory response. This work, entitled "YAP/TEAD1 Complex Is a Default Repressor of Cardiac Toll-Like Receptor Genes", was published on June 22, 2021, and can be found in the *International Journal of Molecular Science* (mdpi.com/1422-0067/22/13/6649).

In humans, SARS-CoV-2 infection relies on ACE2, a crucial enzyme that lowers blood pressure. During infection, SARS-CoV-2 spike protein, the component protruding out of the viral membrane, binds to host cell's ACE2 and facilitates virus entry. Therefore, one of the current leading hypotheses is that SARS-CoV-2 injured the heart by impairing ACE2 function. However, Dr. Lin sought to determine the existence of another possible pathological mechanism: the cardiac consequences of COVID-19 infection were at least partially due to TLR4 hyper-activation. His group confirmed that TLR4 recognized SARS-CoV-2 Spike protein, and his lab's data suggested that simple overexpression of SARS-CoV-2 Spike protein in the mouse heart was sufficient to induce heart dysfunction and inflammation. Since Spike protein interacts with murine TLR4, and not murine ACE2, taken together, Dr. Lin's data critically highlights the importance of TLR4 signaling in the pathogenesis of COVID-19-related cardiac injury. This group's study also unravels the reasons as to why cardiac injury perhaps occurs more frequently in COVID-19 patients with pre-existing cardiac diseases. This novel manuscript, titled

“Selectively expressing SARS-CoV-2 Spike protein S1 subunit in cardiomyocytes induces cardiac hypertrophy in mice,” was published in BioRxiv, on June 20, 2021 (biorxiv.org/content/10.1101/2021.06.20.448993v1).

BioRxiv makes manuscripts available before peer review to allow researchers the opportunity to comment on the timely nature of the work, prior to final publication. “Readers should be aware that articles on BioRxiv have not been finalized by authors, may contain errors, and could report information that has not yet been accepted or endorsed by the scientific or medical community” (BioRxiv.org). Additional co-authors on the manuscripts include, Dr. Chase Kessinger, Instructor at the MMRI, Dr. Bing Xu, Postdoctoral Fellow at the MMRI, and Dr. William T. Pu, Director of Basic and Translational Cardiovascular Research, Aldo R. Castaneda Professor of Pediatrics at Boston’s Children Hospital.

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