Expressing a truncated SARS-COV-2 spike protein in mouse heart induces cardiac hypertrophy

S. Negron, C. Kessinger, Z. Lin

Masonic Medical Research Laboratory, Utica, United States of America

Funding Acknowledgement: Type of funding sources: Other. Main funding source(s): Masonic Medical Research Institute

Cardiac injury is common in hospitalized and non-hospitalized COVID-19 patients, for which systemic inflammation stress is one of the causes (Topol, 2020). Although rare, COVID-19 cases that SARS-CoV-2 infecting cardiomyocytes (CMs) have been reported. In vitro, SARS-CoV-2 infection of human induced-pluripotent-cells derived CMs triggered innate immune responses and induced apoptosis (Bojkova et al., 2020; Chen et al., 2020). Therefore, the current literature indicates that the heart is attacked by SARS-CoV-2 directly or indirectly; however, the underlying mechanism remains largely unknown. Involved in the pathogenesis of heart diseases, Toll-like receptors (TLR) are a family of pattern recognition receptors that sense the pathogenic stimuli and signal the cardiac residential cells to cope with harsh conditions (Yu and Feng, 2018). Among the best characterized TLR signaling pathways is TLR4/NF-kB axis (Lu et al., 2008), in which TLR4 convey the danger signals through its down stream kinases, such as TAK1 and TBK1, to activate NF-kB. SARS-CoV-2 Spike protein is well known for its role of mediating virus entry into host cells, but its immunogenic role has not been clearly defined. Recently, we have found that SARS-CoV-2 Spike protein directly interacts with TLR4 and activates NF-kB transcriptional activity. Pharmaceutically blocking either TBK1 or TAK1 attenuates Spike protein's immunogenic activity. To pinpoint Spike protein's role in the heart, we generated an AAV to specifically express a truncated Spike protein (S1-TM) in the CMs. Our data show that expressing S1-TM in CMs induces cardiac hypertrophy and decreases heart systolic function in mice. On the molecular level, Spike protein increases RelA (p65 subunit of the NF-kB complex) and activates the expression of pro-inflammatory cytokine genes. In summary, our study suggests that Spike protein directly interacts with TLR4 to trigger innate immune signaling, and that Spike protein induced CM innate immune responses might be one of the underlying mechanisms of cardiac injury in COVID-19.