SARS-CoV-2 Spike Protein Interacts With the KCNA5 Potassium Channel: Potential Implications for Cardiac Ion Function and Arrhythmic Risk

Xu, Richard (School: New Hartford Senior High School)

COVID-19, caused by SARS-CoV-2, has been associated with a range of cardiovascular complications, including arrhythmias and cardiomyopathy. This study investigates how the SARS-CoV-2 spike protein affects cardiac ion channel function and protein–protein interactions. RNA-Seq analysis of mouse hearts expressing the spike protein revealed altered expression of several ion channels, although the core channels responsible for action potential generation remained largely unaffected. To identify potential direct interactions, AlphaFold3 was used to screen the spike protein against 25 key cardiac ion channels, identifying KCNA5, KCNQ1, and CACNA1C as top candidates. These predictions were validated in HEK293T cells using co-immunoprecipitation and colocalization imaging, which confirmed spike protein–KCNA5 interactions at the cell membrane. Electrophysiological recordings demonstrated that spike protein expression significantly increased KCNA5-mediated potassium currents, indicating functional modulation of the channel. In silico interaction analysis revealed distinct hydrogen-bonding patterns between the spike protein and KCNA5, suggesting that both Delta and Omicron variants interact with KCNA5. To explore therapeutic avenues, 308 E3 ubiquitin ligases were screened using AlphaFold3 and MARCHF2 was identified as a candidate capable of promoting degradation of the spike protein's S2 subunit. Collectively, these findings identify KCNA5 as a novel binding partner of the SARS-CoV-2 spike protein, with functional consequences that may contribute to the electrophysiological abnormalities observed in COVID-19-related cardiac dysfunction.

Awards Won: