Synergistic Use of CryoEM and Mass Spectrometry to Study the Structure of a Highly Glycosylated Coronavirus Spike Protein

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Coronaviruses (CoVs) are major pathogens that are responsible for lethal diseases such as SARS and MERS. CoVs utilize their highly glycosylated surface spike proteins to recognize specific host (co)receptors thereby achieving viral entry and infection. Feline infectious peritonitis virus (FIPV) is an alphacoronavirus that causes nearly 100 % mortality rate without effective treatments. Here we report a 3.3 Å cryoEM structure of an FIPV spike protein that was produced recombinantly in a mammalian expression system to preserve its post-translational modification patterns. Mass spectrometry provided detailed information regarding the site-specific compositions of high-mannose and complex type *N*-glycans that account for 1/4 of the total molecular mass, most of which were directly visualized by cryoEM. The *N*-glycans that wedge between two galectin-like domains within the S1 subunit result in a unique propeller-like conformation for the FIPV spike protein compared to all known homologs of other CoVs. The structural insights derived from the synergistic use of cryoEM aand mass spectrometry provide a blueprint for a better molecular understanding of the pathogenesis of FIP.