Atomic-Level Determinants Of SARS-Cov-2 Spike Trafficking During Infection and Vaccination

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The spike protein of coronaviruses demonstrates bidirectional trafficking between the endoplasmic reticulum (ER), the Golgi network, and the plasma membrane (PM). The retrograde trafficking pathway originating in the Golgi is one of the routes supplying the spike to the coronavirus assembly site in ER-Golgi intermediate compartment (ERGIC).
However, this serves as a barrier for spike export to the PM, which is the site of cell-cell fusion for coronavirus transmission and the interaction of the spike protein with the immune system upon genetic vaccination. Although the interaction of the spike with host coatomer complex is implicated in retrograde trafficking, the atomic-level determinants that govern the spike-coatomer interactions are poorly understood. Using functional analyses, here we show that spike association with virions is determined by coatomer-dependent spike delivery from the cis-Golgi and restricted by spike-coatomer dissociation. Although spike mimicry of the host coatomer-binding dibasic motif ensures retrograde trafficking to the ERGIC, avoidance of the host-like C-terminal acidic residue is critical for spike-coatomer dissociation as inferred from biophysical assays, X-ray crystallography, and NMR. This dissociation controls spike incorporation into virions and export to the PM for cell-cell fusion. Using single particle cryoEM, we elucidate key structural features of the spike protein retained in distinct states along this trafficking pathway. Overall, this research develops a platform to elucidate the modulation of spike trafficking, which is a critical determinant of coronavirus infectivity and of immunogenicity in spike-based genetic vaccines.

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