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Structural landscape of SARS-CoV-2 entry and activation of spike glycoprotein by engaging unique host factors & potential interventions

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The ongoing COVID19 pandemic caused by SARS-CoV-2 with lower respiratory tract infections, is an enduring public health concern [1]. Emergence of new immune evading variants are challenging the current effective vaccines and several antiviral treatments are being clinically evaluated to fill the "therapeutic gap" in treating infected people [3]. Understanding the entire repertoire of diverse host factors engaged by SARS-CoV-2 for entry and pathogenicity is required for long-lasting potential therapeutics or vaccines. Here, using a structural and molecular approach, we show multistage processing of SARS-CoV-2 spike-protein for virion activation, infection, and how mutations influence it. We solved the structures of spike protein in complex with different host cell factors (TMPRSS2, Furin, CD26, and NRP1) with functional activity, and these insights into uncovering how viral spike-protein engages and primed with these multiple host factors, in addition to ACE2, to hijack host cell entry [3-6]. Furthermore, our COVID19 patient genome sequencing reveals that allele in TMPRSS2 (V160M) [7], and Furin provided protection from COVID19 infection, and its structural mechanism is further addressed and potential drug clinical trials. Additionally, our large-scale retrospective cohort studies proved Arbidol and derivatives as potential therapies for COVID19, using structural studies, we demonstrated the mechanism of action of Arbidol in disrupting spike function [8,9]. These findings cognize the complete mechanism of viral spike-glycoprotein processing/priming that leads to cascading entry into the host cell, paving the door for future vaccine development and identifying key targets. Our comprehensive, multifaceted research reveals the complexity of the SARS-CoV-2 spike-protein and clinical studies aid in therapies.

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