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Category: Postdoc
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Title: Receptor Binding Domain of SARS-CoV-2 is a functional αvβ3 integrin ligand that supports cellular adhesion and phosphotyrosine signaling
Abstract: Emma G Norris (1), Xuan Sabrina Pan (2), and Denise C Hocking (1,2) Departments of (1) Pharmacology and Physiology, and (2) Biomedical Engineering The extracellular matrix ECM protein, fibronectin (FN) is a key component of the airway wall, and is an essential regulator of epithelial morphogenesis, endothelial barrier maintenance, and tissue repair. FN-mimicking sequences have been identified across a broad spectrum of microbial pathogens. Among the novel mutations distinguishing SARS-CoV-2 from similar pathogenic respiratory coronaviruses is a K403R substitution in the receptor-binding domain (RBD) of the S1 subunit of the spike protein. This amino acid substitution appears near the cell attachment interface and gives rise to the canonical RGD motif of FN's integrin-binding domain. Thus, we hypothesized that in addition to its established role in mediating viral attachment via ACE2 ligation, S1-RBD possesses integrin-binding functionality. In the present study, we analyzed the ability of recombinant S1-RBD to serve as an adhesive ligand using both human small airway epithelial cells (SAECs) and FN-null mouse embryonic fibroblasts (FN-null MEFs). FN-null MEFs do not produce FN and are cultured under serum-free conditions, enabling characterization of cell adhesion events in the complete absence of cell-derived matrices. FN-null MEFs adhered to S1-RBD via a cation- and RGD-dependent interaction that was inhibited by anti-αV and –β3 integrin-blocking antibodies, but not by anti-α5 or -β1 integrin antibodies. Moreover, S1-RBD supported cell spreading, proliferation, focal adhesion formation, and triggered actin stress fiber formation as well as integrin-dependent phosphotyrosine signaling. Similarly, SAECs adhered to S1-RBD specifically, which triggered phosphorylation of focal adhesion kinase at Y397 and paxillin at Y118. These data indicate that the novel RGD motif of S1-RBD can bind to epithelial cells and fibroblasts via αv-containing integrins to trigger cell signaling pathways that control cell morphology and function.