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# Gene expression and *in situ* protein profiling of candidate SARS-CoV-2 receptors in human airway epithelial cells and lung tissue

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**ACE2 gene and protein expression is low to absent in airway and alveolar epithelial cells in human lungs. This study suggests the presence of a mechanism dynamically regulating ACE2 expression in human lung or other receptors for SARS-CoV-2.** https://bit.ly/3f85R1I

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ABSTRACT In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged, causing the coronavirus disease 2019 (COVID-19) pandemic. SARS-CoV, the agent responsible for the 2003 SARS outbreak, utilises angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) host molecules for viral entry. ACE2 and TMPRSS2 have recently been implicated in SARS-CoV-2 viral infection. Additional host molecules including ADAM17, cathepsin L, CD147 and GRP78 may also function as receptors for SARS-CoV-2.

To determine the expression and *in situ* localisation of candidate SARS-CoV-2 receptors in the respiratory mucosa, we analysed gene expression datasets from airway epithelial cells of 515 healthy subjects, gene promoter activity analysis using the FANTOM5 dataset containing 120 distinct sample

types, single cell RNA sequencing (scRNAseq) of 10 healthy subjects, proteomic datasets, immunoblots on multiple airway epithelial cell types, and immunohistochemistry on 98 human lung samples.

We demonstrate absent to low *ACE2* promoter activity in a variety of lung epithelial cell samples and low *ACE2* gene expression in both microarray and scRNAseq datasets of epithelial cell populations. Consistent with gene expression, rare ACE2 protein expression was observed in the airway epithelium and alveoli of human lung, confirmed with proteomics. We present confirmatory evidence for the presence of TMPRSS2, CD147 and GRP78 protein *in vitro* in airway epithelial cells and confirm broad *in situ* protein expression of CD147 and GRP78 in the respiratory mucosa.

Collectively, our data suggest the presence of a mechanism dynamically regulating ACE2 expression in human lung, perhaps in periods of SARS-CoV-2 infection, and also suggest that alternative receptors for SARS-CoV-2 exist to facilitate initial host cell infection.