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Human lungs show limited permissiveness for SARS-CoV-2 due to scarce ACE2 levels but virus-induced expansion of inflammatory macrophages

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Shareable abstract (@ERSpublications)
Scarce ACE2 expression limits alveolar permissiveness for SARS-CoV-2. Viral uptake by alveolar macrophages leads to a specific immune activation. COVID-19 ARDS is likely caused by secondary immunopathogenesis rather than direct alveolar viral damage. https://bit.ly/3ar4ei5

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Abstract

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Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) utilises the angiotensin-converting enzyme 2 (ACE2) transmembrane peptidase as cellular entry receptor. However, whether SARS-CoV-2 in the alveolar compartment is strictly ACE2-dependent and to what extent virus-induced tissue damage and/or direct immune activation determines early pathogenesis is still elusive.

Methods Spectral microscopy, single-cell/-nucleus RNA sequencing or ACE2 "gain-of-function" experiments were applied to infected human lung explants and adult stem cell derived human lung organoids to correlate ACE2 and related host factors with SARS-CoV-2 tropism, propagation, virulence and immune activation compared to SARS-CoV, influenza and Middle East respiratory syndrome coronavirus (MERS-CoV). Coronavirus disease 2019 (COVID-19) autopsy material was used to validate *ex vivo* results.

Results We provide evidence that alveolar ACE2 expression must be considered scarce, thereby limiting SARS-CoV-2 propagation and virus-induced tissue damage in the human alveolus. Instead, *ex vivo* infected human lungs and COVID-19 autopsy samples showed that alveolar macrophages were frequently positive for SARS-CoV-2. Single-cell/-nucleus transcriptomics further revealed nonproductive virus uptake and a related inflammatory and anti-viral activation, especially in "inflammatory alveolar macrophages", comparable to those induced by SARS-CoV and MERS-CoV, but different from NL63 or influenza virus infection.

Conclusions Collectively, our findings indicate that severe lung injury in COVID-19 probably results from a macrophage-triggered immune activation rather than direct viral damage of the alveolar compartment.