Pulmonary infection by SARS-CoV-2 induces senescence accompanied by an inflammatory phenotype in severe COVID-19: possible implications for viral mutagenesis

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Shareable abstract (@ERSpublications)
In severe COVID-19, alveolar type 2 (AT2) cells infected by SARS-CoV-2 exhibit senescence accompanied by a proinflammatory phenotype, a molecular mechanism that may be important in persistence of disease (post-acute sequelae of COVID-19) and mutagenesis https://bit.ly/3fnopg9

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Abstract

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of the respiratory system can progress to a multisystemic disease with aberrant inflammatory response. Cellular senescence promotes chronic inflammation, named senescence-associated secretory phenotype (SASP). We investigated whether coronavirus disease 2019 (COVID-19) is associated with cellular senescence and SASP.

Methods Autopsy lung tissue samples from 11 COVID-19 patients and 43 age-matched non-COVID-19 controls with similar comorbidities were analysed by immunohistochemistry for SARS-CoV-2, markers of senescence and key SASP cytokines. Virally induced senescence was functionally recapitulated *in vitro*, by infecting epithelial Vero-E6 cells and a three-dimensional alveosphere system of alveolar type 2 (AT2) cells with SARS-CoV-2 strains isolated from COVID-19 patients.

Results SARS-CoV-2 was detected by immunocytochemistry and electron microscopy predominantly in AT2 cells. Infected AT2 cells expressed angiotensin-converting enzyme 2 and exhibited increased senescence ($p16^{INK4A}$ and SenTraGor positivity) and interleukin (IL)-1β and IL-6 expression. *In vitro*, infection of Vero-E6 cells with SARS-CoV-2 induced senescence (SenTraGor), DNA damage (γ-H2AX) and increased cytokine (IL-1β, IL-6, CXCL8) and apolipoprotein B mRNA-editing (APOBEC) enzyme

expression. Next-generation sequencing analysis of progenies obtained from infected/senescent Vero-E6 cells demonstrated APOBEC-mediated SARS-CoV-2 mutations. Dissemination of the SARS-CoV-2-infection and senescence was confirmed in extrapulmonary sites (kidney and liver) of a COVID-19 patient.

Conclusions We demonstrate that in severe COVID-19, AT2 cells infected by SARS-CoV-2 exhibit senescence and a proinflammatory phenotype. *In vitro*, SARS-CoV-2 infection induces senescence and inflammation. Importantly, infected senescent cells may act as a source of SARS-CoV-2 mutagenesis mediated by APOBEC enzymes. Therefore, SARS-CoV-2-induced senescence may be an important molecular mechanism of severe COVID-19, disease persistence and mutagenesis.