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GPR183 antagonism reduces macrophage infiltration in influenza and SARS-CoV-2 infection

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Viral infections trigger oxysterol production in the lung, attracting macrophages *via* GPR183. Antagonising GPR183 reduced inflammation and disease severity in SARS-CoV-2 infection, making GPR183 a putative target for therapeutic intervention. https://bit.ly/3DXlJCY

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Abstract

Rationale Severe viral respiratory infections are often characterised by extensive myeloid cell infiltration and activation and persistent lung tissue injury. However, the immunological mechanisms driving excessive inflammation in the lung remain poorly understood.

Objectives To identify the mechanisms that drive immune cell recruitment in the lung during viral respiratory infections and identify novel drug targets to reduce inflammation and disease severity.

Methods Preclinical murine models of influenza A virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Results Oxidised cholesterols and the oxysterol-sensing receptor GPR183 were identified as drivers of monocyte/macrophage infiltration to the lung during influenza A virus (IAV) and SARS-CoV-2 infection. Both IAV and SARS-CoV-2 infection upregulated the enzymes cholesterol 25-hydroxylase (CH25H) and cytochrome P450 family 7 subfamily member B1 (CYP7B1) in the lung, resulting in local production of the oxidised cholesterols 25-hydroxycholesterol (25-OHC) and 7α,25-dihydroxycholesterol (7α,25-OHC). Loss-of-function mutation of Gpr183 or treatment with a GPR183 antagonist reduced macrophage infiltration and inflammatory cytokine production in the lungs of IAV- or SARS-CoV-2-infected mice. The GPR183 antagonist significantly attenuated the severity of SARS-CoV-2 infection and viral loads. Analysis of single-cell RNA-sequencing data on bronchoalveolar lavage samples from healthy controls and COVID-19 patients with moderate and severe disease revealed that *CH25H*, *CYP7B1* and *GPR183* are significantly upregulated in macrophages during COVID-19.

Conclusion This study demonstrates that oxysterols drive inflammation in the lung *via* GPR183 and provides the first preclinical evidence for the therapeutic benefit of targeting GPR183 during severe viral respiratory infections.