Antiviral CD8$^+$ T-cell immune responses are impaired by cigarette smoke and in COPD

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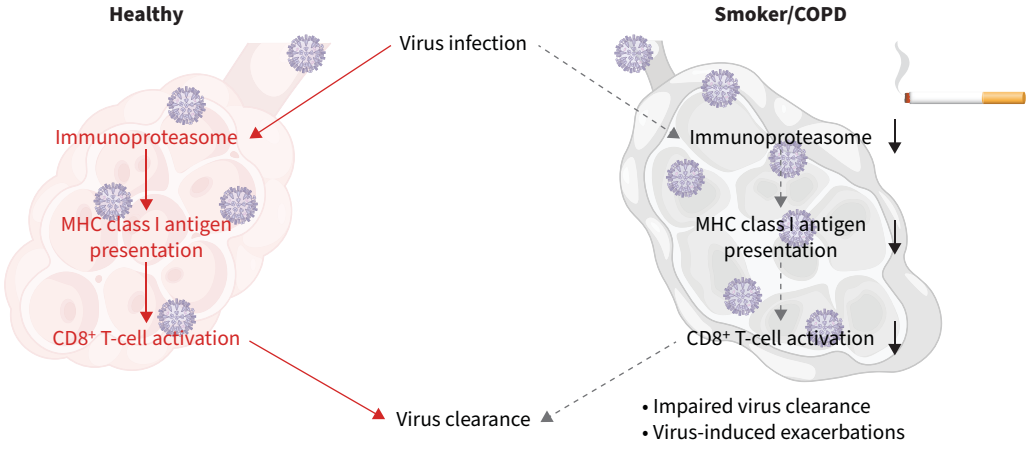

GRAPHICAL ABSTRACT Main findings of the study. Cigarette smoke impairs virus-induced upregulation of the major histocompatibility complex (MHC) class I antigen presentation machinery resulting in reduced activation of antiviral CD8$^+$ T-cells.

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Cigarette smoke impairs virus-induced upregulation of the MHC class I antigen presentation machinery resulting in reduced activation of antiviral CD8$^+$ T-cells. This may reduce viral clearance and increase susceptibility to viral exacerbations in COPD. https://bit.ly/43o0p3D

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Abstract

Background Virus infections drive COPD exacerbations and progression. Antiviral immunity centres on the activation of virus-specific CD8$^+$ T-cells by viral epitopes presented on major histocompatibility complex (MHC) class I molecules of infected cells. These epitopes are generated by the immunoproteasome, a specialised intracellular protein degradation machine, which is induced by antiviral cytokines in infected cells.

Methods We analysed the effects of cigarette smoke on cytokine- and virus-mediated induction of the immunoproteasome *in vitro*, *ex vivo* and *in vivo* using RNA and Western blot analyses. CD8$^+$ T-cell

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activation was determined in co-culture assays with cigarette smoke-exposed influenza A virus (IAV)-infected cells. Mass-spectrometry-based analysis of MHC class I-bound peptides uncovered the effects of cigarette smoke on inflammatory antigen presentation in lung cells. IAV-specific $CD8^+$ T-cell numbers were determined in patients' peripheral blood using tetramer technology.

Results Cigarette smoke impaired the induction of the immunoproteasome by cytokine signalling and viral infection in lung cells *in vitro*, *ex vivo* and *in vivo*. In addition, cigarette smoke altered the peptide repertoire of antigens presented on MHC class I molecules under inflammatory conditions. Importantly, MHC class I-mediated activation of IAV-specific $CD8^+$ T-cells was dampened by cigarette smoke. COPD patients exhibited reduced numbers of circulating IAV-specific $CD8^+$ T-cells compared to healthy controls and asthmatics.

Conclusion Our data indicate that cigarette smoke interferes with MHC class I antigen generation and presentation and thereby contributes to impaired activation of $CD8^+$ T-cells upon virus infection. This adds important mechanistic insight on how cigarette smoke mediates increased susceptibility of smokers and COPD patients to viral infections.