Responses to rhinovirus infection in human lung slices are reduced by Rupintrivir

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Introduction

Human rhinovirus (HRV) is a main cause of the common cold in humans, and for asthmatics a major risk factor for exacerbations. HRV targets the host epithelial cells in the airway mucosa and upon replication new virions are released without inducing a direct cytopathic effect (CPE). Infection of epithelial cells by HRV induces an innate immune response with secretion of cytokines to mediate the anti-viral host response.

The aim of the study was to establish a model of HRV1B infection in human PCLS including prevention of induced immune responses by intervention with 3C protease inhibitor Rupintrivir or capsid-binding agent Pleconaril.

Materials and Methods

Human PCLS containing cross-sectioned airways were prepared and inoculated with HRV1B, UV-inactivated HRV, medium or HRV in presence of Rupintrivir or Pleconaril for 2h at 33°C. PCLS were incubated for 1d and 3d. Viral load was titrated on HeLa cells and the CPE was analysed. Immunohistochemical staining for double-stranded RNA in infected and fixed tissue slices was performed. Tissue viability was determined using LIVE/DEAD® staining and measurement of lactate dehydrogenase. Pro-inflammatory and anti-viral cytokine regulation was determined by multiplex. Gene regulation was analysed using Affymetrix U133 Plus 2.0 chips.

Results

HRV1B infection did not induce an obvious cytopathic effect confirmed by maintenance of tissue vitality as indicated by LIVE/DEAD® staining of PCLS. However an increased release of LDH was observed after HRV infection in PCLS (Fig. 2).

Exposure of human lung tissue to HRV1B induced production of anti-viral and pro-inflammatory cytokines 24 h and 72 h post infection (Fig. 4). Single administration of 3C protease inhibitor Rupintrivir inhibited this effect after 24 h, which was statistical significant for IFN (Fig. 4A, B). Single dose treatment with Pleconaril reduced HRV induced immune response but did not reach statistic significance.

These data were supported by gene expression levels. Genes specific for anti-viral responses, pro-inflammatory chemokines and interferon pathways were upregulated after HRV1B infection in human PCLS as exemplary shown for i-tac and ifnλ1 (Fig. 6B).

Conclusions

The infection of ex vivo lung tissue with HRV1B induced pro-inflammatory and anti-viral immune responses. This response to HRV1B was inhibited by Rupintrivir. Future experiments will focus on the induction of an asthmatic phenotype in PCLS and a subsequent infection with HRV to investigate mechanisms of viral-induced asthma exacerbations.

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