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Immune Response to Human Rhinovirus C in Highly Differentiated Human Airway Epithelial Cells

Yu Jin[1,2*] and Xin-hui Yuan[1,2,3]

[1]*Medical School of Nanjing University, Nanjing 210093, P.R China*

[2]*Children's Hospital Affiliated to Nanjing Medical University, Nanjing 210008, P.R China*

[3]*The First Hospital of Lanzhou University, Lanzhou 730000, P.R China*

Abstract

Rhinovirus C (HRV-C) cannot be propagated in immortalized cells, and there is relatively little information on host cell responses to HRV-C infection. Human Bronchial Epithelial (HBE) cells are cultured at the Air-liquid Interface (ALI), which can form tight junctions, produce mucin, and differentiate to form cilia, representing an almost native cell system study HRV-C infections *in vitro*. In the present study, four strains of HRV-C from infectious clones and clinical specimens were infected with HBE-ALI cells. We found that they induced very similar immune responses, showing that the comparison basis was homogeneous.

Keywords: Rhinovirus C • Human bronchial epithelial (HBE) • *In vitro* • RSV

Introduction

Cytokines/chemokines play a critical role in regulating local inflammatory processes in the lung and subsequent tissue damage. Although we tested a variety of cytokines and chemokines associated with HRV-C infection according to previous data [1], only a few cytokines' levels significantly increased. A similar result was observed in Nakagome K, et al. [2] study. Souza demonstrated that undifferentiated cells showed increased expression of various inflammatory cytokines in response to HRV-A16 infection, but well-differentiated cells did not respond [3]. This phenomenon indicates well-differentiated cells are much more resistant to viral infection and its functional consequences than poorly differentiated cells from the same source. Furthermore, HRV-16 infects the highly differentiated HBE, and the infections are cleared without the need for immune cells, and the time to clearance does not depend on levels of IFNs [4]. Another study found that the cytokine increases induced by HRV-C appeared as two peaks in HBE 3D culture but only one peak in the medium 2D culture [5]. These data challenge several widely held paradigms generated from earlier studies in undifferentiated cells and emphasize the importance of appropriate cell context when performing experiments using HRV infections.

Literature Review

HRV and Respiratory Syncytial Virus (RSV) are two leading etiologies of acute respiratory diseases, and the epithelium of the airways is their main target [1]. Despite its lower cytotoxicity compared with RSV, HRV induces the activation of the airway cells with subsequent release of proinflammatory cytokines. Epidemiological studies suggest that RSV infection causes persistent wheezing and asthma [6]. At the same time, HRV is more frequently involved in wheezing exacerbations in later childhood [7] and seems less harmful to bronchial structures than RSV. Therefore, we wondered whether differences in induction of cytokines might accompany these differences in disease characteristics. In this study, HRV-C infection induced a weaker response than RSV, indicating that HRV-C causes minor cell damage and has lower cytotoxicity. Because of the production of cytokines such as IL-6 and IL-8, RANTES can lead to airway damage, neutrophil-mediated epithelial damage, and hyper bronchial responsiveness. It was also partly explained that the disease severity caused by HRV-C infection was lower than that of RSV.

Discussion

HRV-C can cause severe respiratory disease, particularly in asthmatics, and wasassociated with asthma exacerbations in children in a case-control study [8]. Children with HRV-C are more likely to require supplemental oxygen and wheezing than children with HRV-A [9]. CDHR3 is the only known receptor of HRV-C and highly expressed in the apical ciliated airway epithelial cells. A CDHR3 SNP (rs6967330) with G to A base change is associated with higher protein expression levels and correspondingly higher HRV-C replication [10], which supports previous clinical studies linked to severe exacerbations of asthma and increased susceptibility to HRV- C [11,12]. The rs6967330 SNP confers the risk of severe childhood asthma exacerbations. A recent study found that HRV-C15 infection augmented carbachol- induced airway narrowing and significantly increased the release of IP-10 and MIP1β[13]. Our study found that HRV-C induced high IL-8, IL6, CCL5, IP-10, IFN- β1, and MCP-1. An increase in neutrophil counts has been observed in the lower airways of infants with recurrent wheezing, and IL-8 production has been found in acute exacerbations of asthma induced by HRV [14]. RANTES is involved in the chemo attraction of eosinophils, monocytes, and T lymphocytes, and it is present in the respiratory secretions of patients with asthma [15].

HRV-A infection in human airway epithelial cells increases IP-10 protein in vitro and in vivo [16]. It may alter the host cytokine environment by leading to a persistent cytokine elevation, such as IP-10 gene expression [17]. As recently described in a paper by Sharif S, et al [18], recurrent HRV infections are a potent stimulus for airway remodelling through an increase in smooth muscle cell mass recruitment next to the epithelial cells, which CCL5, CXCL8 mediate, and IP-10 secreted during HRV infection. We found higher levels of IFN-β1 after HRV- C infection than after RSV infection. Previous studies have implicated that RSV pathogenesis and immune responses are determined by type I IFN, and RSV is a poor inducer of IFN [19,20]. Nevertheless, Miller KE, et al. [21] demonstrated that asthma exacerbation associated with HRV infection was mainly mediated by an increase in type III IFN response. These data might be useful to understand the dissimilarity of antiviral response to HRV-C infection and RSV infection. MCP-1 is a crucial mediator of monocyte chemotaxis and T-lymphocyte differentiation, with a critical role in the pathogenesis of several

***Address for Correspondence:** Yu Jin, Medical School of Nanjing University, Nanjing 210093, P.R China; Tel: +(86)025-83594532; E-mail: jinyu@nju.edu.cn.*

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conditions. In patients with asthma, an increased expression of MCP-1 has been reported to activate a dysregulated Th2 response [22]. Inhibition of MCP-1 expression significantly reduced airway reactivity in an experimental model of asthma [23]. Our study found that MCP-1 protein increased dramatically in both HRV-C and RSV infections, but HRV-C infection induced a lower level than RSV. These results support the clinical data that rhinovirus is responsible for 50% of asthma exacerbation and RSV has been associated with recurrent wheezing and asthma development [24].

Conclusion

Our study demonstrated that the HBE ALI culture system supported HRV-C infection and propagation. When compared with RSV, HRV-C induced relatively weaker cytokine expression in fully differentiated HBE cells. The analysis of the difference in immune response between the two viruses may be helpful for the development of therapies and preventive strategies.

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