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Review

Viral infections in asthma and COPD

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ABSTRACT

Airway viral infections are associated with the pathogenesis of asthma and COPD. It has been argued that respiratory syncytial virus (RSV) infection in infancy is a probable causal factor in the development of pediatric asthma. RSV infections tend to induce Th2-biased immune responses in the host airways. RSV infection, atopy, and low pulmonary function in neonates may work synergistically toward the development of pediatric asthma. Human rhinovirus (HRV) is a representative virus associated with the exacerbation of asthma in both children and adults. Viral infections trigger innate immune responses including granulocytic inflammation and worsen the underlying inflammation due to asthma and COPD. The innate immune responses involve type-I and -III interferon (IFN) production, which plays an important role in anti-viral responses, and the airway epithelia of asthmatics reportedly exhibit defects in the virus-induced IFN responses, which renders these individuals more susceptible to viral infection. A similarly impaired IFN response is seen in COPD, and several investigators propose that latent adenoviral infection may be involved in COPD development. Persistent RSV infections were detected in a sub-population of patients with COPD and were associated with the accelerated decline of lung function. The virus-induced upregulation of co-inhibitory molecules in the airway epithelium partly accounts for the persistent infections. Experimental animal models for virus-asthma/COPD interactions have shed light on the underlying immune mechanisms and are expected to help develop novel approaches to treat respiratory diseases.

Abbreviations: RSV, respiratory syncytial virus; HRV, human rhinovirus; LAI, lower airway infection; AHR, airway hyperresponsiveness; TLR3, Toll-like receptor 3; RIG-I, retinoic acid-inducible gene I; MDA5, melanoma differentiation-associated gene 5; TRIF, Toll/IL-1R domain-containing adaptor-inducing IFN-β; IPS-1, IFN-β promoter stimulator 1; poly IC, polyinosinic-polycytidylic acid; D-GalN, D-galactosamine; PD-1, programmed death-1; PI3Kδ, phosphatidylinositol 3-kinase-delta; Nrf2, Nuclear erythroid 2 p45 related factor-2

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1. Introduction

All individuals are repeatedly subjected to airway viral infections in their lifetime. In a majority of subjects without chronic airway diseases, the infections are self-limited, and the symptoms resolve rapidly. In subjects with asthma or COPD, infections frequently lead to the exacerbation of underlying diseases, which remains a challenge for clinical practitioners. In addition, viral infections have long been regarded as one of the causal factors for asthma and COPD. In this study, we review the role of viral infections in the pathogenesis of asthma and COPD, particularly from an immunological standpoint.

2. Viral infections as causal factors for asthma

Respiratory syncytial virus (RSV) infection in infancy has long been argued to play a causal role in the development of pediatric asthma. RSV is an enveloped RNA virus that belongs to the Paramyxoviridae family; its genome is a non-segmented single-stranded (ss) RNA. Almost 100% of children suffer from RSV infection by 2 years of age. Repeated infection is common because it is not possible to acquire long-term immunity against RSV in humans. Infantile RSV infections result in 50–90% and 5–40% of hospitalizations due to bronchiolitis and pneumonia, respectively [1]. Generally, distinguishing RSV bronchiolitis from asthma at the onset of the disease is difficult, because both diseases show similar dyspnea with wheezing, and a long-term follow-up may be required to obtain a definitive diagnosis. In a previous study, the prevalence of asthma and sensitization to common aeroallergens at 13 years of age was significantly higher in children who had experienced hospitalization due to serious RSV infections in their infancy compared with children who suffered from RSV infections, but did not require hospitalization [2]. In another study, although the prevalence of recurrent wheezing after RSV bronchiolitis was significantly higher in children that had been hospitalized compared with children that had not been hospitalized, this difference disappeared as the children grew older [3]. In a cohort study that recruited children living in Tucson, Arizona, pulmonary function was assessed by measuring the expiratory flow rate at the level of functional residual capacity (FRC) within several months after birth and before the first RSV infection [4]. In this cohort, 45% and 7% of the children suffered from lower airway infections (LAI) and pneumonia, respectively, by 3 years of age, and 36% of the LAI- and pneumonia-affected children were found to be positive for RSV. At 6 years of age, the prevalence of asthma in children who had neither a history of LAI nor pneumonia was 5%, whereas the prevalence of asthma in the 6-year-old children who had either LAI or pneumonia was 10% or 14%, respectively. Notably, the pulmonary function in infancy was lower in the children with a history of pneumonia compared with the children who did not have a history of pneumonia [4,5]. These studies suggest that the low pulmonary function at birth might predispose infants to severe LAI and pneumonia due to RSV infections and the subsequent development of asthma.

3. Immunological aspects of viral infections in asthma development

A previous study showed an increased IL-4/IFN-γ ratio in the nasal secretion and the serum of children with RSV bronchiolitis compared with children with an upper airway infection, but not bronchiolitis due to RSV infection [6]. The IFN-γ/IL-10 ratio in the upper airway aspirates was revealed to be lower in the cases with RSV infection compared to the cases with other respiratory viral infections [7]. IL-10 is an anti-inflammatory cytokine that inhibits both Th1- and Th2-biased immune responses, whereas Th1 responses are more strongly inhibited by IL-10. Hence, a lower IFN-γ/IL-10 ratio implies the relative enhancement of Th2-biased responses. IL-13 is a unique cytokine capable of inducing eosinophilic airway inflammation, airway hyperresponsiveness (AHR), and airway remodeling—the cardinal phenotypes of asthma. Mice infected with RSV were reported to develop IL-13-mediated AHR [8]. G-protein, a secretory RSV protein, could augment the production of IL-5 and IL-13 and thus exacerbated eosinophilic inflammation in mice [9]. Multiple lines of evidence support the hypothesis that RSV contributes to the development of asthma due to its potential for inducing Th2-biased responses in hosts. Although the above hypothesis may be tempting to accept, it fails to explain why only a limited number of subjects with RSV infections develop asthma. Alternative explanations might be found in the