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Review Article

Dysregulated Epithelial Innate Immune Response Puts Asthmatics at Risk for Susceptibility to Respiratory Virus Infection

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Abstract

Airway epithelium not only functions as a physical barrier but also expresses innate immune response to virus infection. Rhinovirus (RV) infection is most often detected virus type during asthma exacerbation according to epidemiological studies. In normal subjects, once activated by virus through innate immune pattern recognition receptors, airway epithelial cells primarily and readily release type I interferon (IFN) particularly IFN-β and IFN-λ to limit viral replication and prevent viral spreading into adjacent epithelial cells, leading to promoting viral infection recovery. In contrast, this innate immune response of asthmatic respiratory epithelium to RV infection is impaired in a delayed and deficient manner. The impairment of epithelial innate immune response in asthma is mediated through suppressor of cytokine signaling (SOCS)1-and transforming growth factor-β-suppressed IFN transcription. In addition, RV infection exacerbates type 2 immune response through the induction of epithelial-derived mediators (IL-25 and IL-33) and therefore potentiates the severity of asthma exacerbation. All mediators involved in RV-exacerbated asthma are likely to be novel pharmacological targets for the development of new therapies to prevent virus-induced asthma exacerbations.

Keywords: *Innate Immune Response; Asthmatics; Virus Infection*

Introduction

Airway epithelium is a physical barrier and constitutes the interface between the environment and the host. In asthma, airway epithelium fails to orchestrate proper innate antiviral immune responses, as well as augmentation of a pro-Th2 response to maintain the Th2 cytokine response to respiratory viral infection during exacerbation [1]. Lower respiratory symptoms of virus-induced exacerbations in asthmatics are more severe and prolonged, with greater changes in airway physiology than do those without asthma. This may due to the balance between protective antiviral responses and inflammatory responses being skewed individuals with asthma that is likely to be the explanation for the differences in symptom duration and severity.

The majority of experimental studies on epithelial responses in asthma has paid attention on rhinovirus infections because of being the most commonly detected virus type during exacerbations in epidemiological data [2,3]. Rhinoviruses can be classified as rhinovirus (RV)-A, -B, and -C on the basis of genetic similarity [4]. The RV-A and RV-B are most often associated with wheezing illnesses whereas the RV-C subtype causes more severe respiratory illnesses including pneumonia or severe asthma exacerbation. RV-C exacerbates clinically severe lower respiratory illness, at least in part its possession of the functional binding receptor cadherin-related family member 3 that facilitates cell entry and enhance its clinical severity [5]. Airway epithelial immune and inflammatory responses are triggered when rhinoviruses enter and replicate in epithelial cells that serve as the major host cell for viral replication [6]. Synthesized viral RNA, a product of

viral replication, is recognized by innate immune pattern recognition receptors. These receptors include the cytosolic RNA helicases, retinoic acid inducible gene I, melanoma differentiation-associated protein-5, double-stranded RNA/protein kinase receptor, and the toll-like receptors (TLR)-3, -7, and -8 [7-10]. The binding of viral ligand to cognate receptors triggers a signaling cascade, leading to the activation of transcription factors including IFN regulatory factors-3 and -7, nuclear factor-kB, p65/p50, activating transcription factor 2, and c-Jun [11-13]. Following activation, the transcription factors translocate to the nucleus of airway epithelial cells to induce transcription of type I and type III IFNs (IFN-α/-β and IFN-λ1, 2, and 3, respectively) [14] and a large amount of proinflammatory cytokines and chemokines. These include IL-6, IL-8, epithelial-derived neutrophil-activating peptide 78 (or CXCL5), C-C motif ligand 5, and IFN-γ-induced protein 10 kD (or CXCL10) [15-17].

IFNs are key drivers in the innate immune response of the airway epithelium to viral infection. They have antiviral properties through direct inhibition of viral replication in cells and stimulation of innate and adaptive immune responses [18,19]. Type I IFNs mediate their antiviral effects via a number of mechanisms, including blocking of viral entry into cells, control of viral transcription, cleavage of RNA, blocking of translation, and induction of apoptosis [18,19]. Supporting these protective effects are the induction of IFN-stimulated genes and the production of antiviral proteins. The indirect effect of IFNs is mediated through the induction of cytokines and chemokines, which induces recruitment of natural killer cells and CD4 and CD8 T cells, up-regulation of the expression of major histocompatibility complex class I on cells, and up-regulation of antigen-presenting cell costimulatory molecules [20]. Therefore, IFN response elicited by airway epithelium is central to effective antiviral responses and resolution of virus infection.

The novel mechanistic investigation conducted by Wark and colleagues demonstrated the impaired innate immune response to virus infection in the asthmatic epithelium. There was increased rhinovirus replication in asthmatics-derived primary human bronchial epithelial cells (HEBCs) to a greater extent than those from normal subjects [21]. This further elucidated resulted from the delayed or deficient induction of IFN-β in asthmatic patients [21]. The abnormal IFN response was restored by the administration of exogenous IFN-β, which resulted in induced apoptosis and reduced virus replication, thereby demonstrating a causal link between deficient IFN-β and increased virus replication [21]. The observation with regard to a restored antiviral response with administration of type I IFN was validated by a subsequent study [22]. In addition to impaired IFN-β response, deficient IFN-λ induction in HEBCs and alveolar macrophages from atopic asthmatics infected *ex vivo* with rhinovirus-16 was demonstrated and was associated with asthma exacerbation severity [14]. In clinical studies, there are the relationships between asthma severity and IFN response [23-26], and IFN delay/deficiency is detected more readily in more severe/less well-controlled disease. In addition, inhaled IFN-β effectively prevented virus-induced worsening of asthma symptoms [27].

The mechanisms underlying impaired induction of IFN in response to virus infection in those with asthma are not fully understood. Suppressor of cytokine signaling (SOCS)1 and SOCS3 are proteins acting on airway epithelium as negative regulators of cytokines [28-30]. Rhinovirus induced increased epithelial SOCS1 mRNA expression that was associated with impaired IFN induction and increased virus replication in HBECs from children with severe asthma [28], which is consistent with influenza A virus and respiratory syncytial virus (RSV) infection [31,32]. This makes antagonism of SOCS1 as an attractive therapeutic target. Transforming growth factor (TGF)-β is of interest because it mediates suppression of both IFN-λ and IFN-β in primary bronchial epithelial cells from healthy subjects following exposure to rhinovirus [33,34]. In addition, TGF)-β further enhanced IFN production in the cocultured system containing rhinovirus-infected BEAS-2B monolayers and eosinophils [35]. This means that rhinovirus infection simultaneously occurring in eosinophilic airway inflammation may contribute to an increase risk of asthma exacerbations. An alternative mechanism of IFN suppression is mediated through the enriched Th2 cytokine microenvironment. In this context, IL-13 involves the induction of the upregulation of IL-1 receptor–associated kinase M that promotes lung epithelial rhinovirus replication and autophagy [36] but crucially inhibits rhinovirus-induced IFN-β and IFN-λ1 expression [37]. The IFN-inhibitory effects of IL-13 tested in vitro using recombinant IL-13 confirmed IL-13-mediated IFN-λs suppression in airway epithelial cells [37], suggesting a link between the actions of Th2 cytokines and IFN expression [38]. Inhaled cortico-

steroid used as asthmatic treatment suppressed type I IFN induction and aggravated the severity of influenza A virus infection in a murine model, whereas adjuvant IFN treatment markedly reduced glucocorticosteroid-amplified infections in human airway cells [39,40].

Viral infection typically induces a type 1 immune response; however, there is clear evidence to indicate the ability of rhinovirus to induce a type 2 inflammatory pattern in asthma. The type 2 cytokines IL-4, IL-5, and IL-13 are all induced in vivo in those with asthma, but not in healthy control subjects, in a rhinovirus-induced exacerbation model. Higher levels of IL-5 and IL-13 during rhinovirus infection correlated significantly with asthma exacerbation severity, suggesting the functional importance of the induction of type 2 cytokines [41]. The mechanism of rhinovirus-induced type 2 immune response is mediated through epithelial-derived mediators, including thymic stromal lymphopoietin, IL-25, and IL-33 that promote type 2 immune response [42-46]. Experimental rhinovirus infection exacerbated IL-25 release from airway epithelial cells from asthmatics, which was consistent with the observations in mice that rhinovirus infection induced and enhanced allergen-induced IL-25. In contrast, IL-25 receptor blockade markedly inhibited rhinovirus-induced exacerbation of type 2 inflammatory response involving the recruitment of eosinophils, lymphocytes and neutrophils, IL-4+ basophils and Th2 cells, as well as innate lymphoid cells (ILC2s) [47]. This indicated that IL-25 is a key mediator of rhinovirus-induced exacerbations of pulmonary inflammation in asthma. Rhinovirus infection of human primary BECs *in vitro* strongly induced IL-33 expression and cocultures of human T cells and ILC2 with supernatants of rhinovirus-infected BECs containing virus-induced IL-33 released from BECs strongly induced type 2 cytokines (IL-4, IL-5, and IL-13 in T cells, and IL-5 and IL-13 in ILC2s). T cells and ILC2 in the culture system are IL-33-responsive because blocking the IL-33 receptor in these cocultures completely suppressed the inductions of type 2 cytokine expression in both cell types [41]. This suggested that epithelial-derived IL-33 is key cytokine driving mechanistic link between viral infection and exacerbation of asthma.

In conclusion, there is evidence that epithelial antiviral innate immune response is defective (delayed or deficient) in asthmatic patients and this defect is likely to be associated with increased disease severity following virus infection in asthma. Additional studies are required to determine whether these impairments are unique to a phenotype cluster or to more severe and less-controlled asthma. Epithelial cell-derived cytokines (IL-25 and IL-33) with their receptors underlying enhancement of viral infection may be interesting new molecular targets for development of novel therapies for asthma exacerbations.

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