The relationship between allergic rhinitis and viral infections

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Purpose of review
Viral airway inflammation is one of the most common respiratory conditions. The clinical symptoms of viral rhinitis, especially watery rhinorrhea and nasal congestion, may be similar to the symptoms of allergic rhinitis. Both conditions affect considerable numbers of patients and can lead to many upper airway consequences, especially secondary bacterial infection. Viral infection can also lead to lower respiratory traction conditions such as bronchitis, bronchiolitis, pneumonia and, especially, asthma. This article will review the existing scientific literature examining the linkage and relationship between viral infection and allergic airway disease.

Recent findings
The relationship between viral and allergic airway inflammation can be discussed in terms of the influence of pathogenesis from one condition to the other. Recently, many studies show how early infection can decrease the chance of allergic development. However, there is some evidence demonstrating that viral infection can deteriorate the clinical symptoms of airway allergy.

Summary
Viral infection can affect the immune system and allergy as both 'enhancing effect' and 'protective effect'. The influential factors depend on the virulence of the viral strain, the innate immune system and the environmental conditions.

Keywords
allergic rhinitis, relationship, viral infection

INTRODUCTION

Viral infections are one of the most common causes of infections in the respiratory tract. More specifically, viral rhinitis or common cold may present with the symptoms of runny nose, nasal blockage, sore throat, cough, etc.

Another common upper respiratory tract condition is allergic rhinitis, which affects 20–40% of the general population worldwide. Allergic rhinitis is the immunoglobulin (Ig)E–mediated inflammation of the nasal mucosa. The allergic inflammatory process releases many cytokines and other proinflammatory proteins.

Both allergic rhinitis and common cold are global health problems, which affect social life, daily activities and contribute to the economic burden on society because of indirect loss of productivity. A recent large survey of 4000 individuals in Sweden reveals indirect cost of 2.7 billion euros per year in terms of lost productivity because of respiratory conditions [1].

There are many publications reviewing the relationship between allergy and viral infection [2]. Most of them extensively review the linkage between viral infection and lower respiratory tract conditions. The first part of this article will review the role of viral infection to the immune system. The second part will explain how airway epithelium reacts to the viral infection. The third part of this article will focus on the upper respiratory viral infection and its relation to allergic rhinitis.

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IMMUNE SYSTEM AND VIRAL INFECTION

When a virus enters the airway, the body has two components of immune defense, which are innate and adaptive immunity. Innate immunity of the airway consists of three subcomponents, which are mucociliary, intercellular junctional complex and antimicrobial peptides [3]. If any subcomponent of innate immunity is impaired, viral organisms or allergens can enter through epithelium and the adaptive immune system will then be activated rapidly. Usually, both defensive systems are able to eradicate the virus. If the virus overcomes the immune system, it can increase intracellular enzyme and nitric oxide production, inhibit protein synthesis and increase epithelial permeability. This results in more contact between the virus, immune cells and neuronal elements.

Airway epithelial cells also serve as the host cells for viral replication and act to initiate more innate immune response. Epithelial cells recognize a virus by using a pattern recognition receptor (PRR) on their surface, which can bind a pathogen-associated molecular pattern (PAMs) on the viral surface [4∎]. Toll-like receptor (TLR) is a PRR family that expresses on most epithelial cells. The innate immune system reacts to the viral infection by secreting various cytokines, chemokines and mediators, such as interleukin (IL)-6, IL-8, granulocyte macrophage colony-stimulating factor (GM-CSF), eotaxin, interferon (IFN) α/β and chemokine motif ligand-5 (CCL-5), from the various immune cells [neutrophil, eosinophils, macrophage, natural killer (NK) cell and T lymphocyte].

The effect of viral infection on the immune system and allergy has been proposed as having both potential 'enhancing effects' and 'protective effects' [5]. The protective effect of viral infection is explained by the hygiene hypothesis [6]. The hygiene hypothesis states that repeated exposure to viral infections during early childhood may reduce the risk of allergen sensitization. Viral infection modulates the development of allergy by skewing the immune system away from the Th2-type response [6].

However, for someone who already has passed the stage of immune development, viral infection has an enhancing effect on allergic inflammation. Repeated severe lower respiratory tract infection in the first 2 years of life leads to increased function of concurrent aeroallergen-specific serum IgE titers. Rhinoviral infection, respiratory syncytial viral infection and paramyxoviral infection lead to more tissue inflammation, especially lower airway allergy [7∎,8,9∎,10–12].

REACTION OF AIRWAY EPITHELIUM TO VIRUS

Initial trigger of the inflammatory reactions is caused by an interaction between epithelium and virus. Virus infects the epithelial cells and causes impairment of T-helper cells (Th), leading to epithelial secretion of bradykinin and increased symptoms of common cold [13]. On the other hand, the stronger Th1 response during common cold also releases IFN-γ, resulting in alleviation of cold symptoms and more rapid clearance of the virus.

Both respiratory syncytial virus and rhinovirus lead to increased level of IL-15 [14,15]. IL-15 acts as linkage between innate and adaptive immunological response to viral infection via promotion of NK cell and CD8 T-memory cell response.

Mucosal barrier hypothesis

Airway epithelium not only acts as an epithelial barrier, but also contributes to the immune response by the production of cytokines and chemokines [16]. Transient breakdown in the epithelial barrier function (after viral infection) may open a window for transmucosal incursion by bacteria, leading to exacerbation of local inflammation [17]. Bacteria with superantigen character (such as *Staphylococcus aureus*) lead to increased local allergic inflammation; however, bacteria with nonsuperantigen character (such as *Haemophilus influenza* and *Streptococcus pneumonia*) may increase IL-4 and IL-13, which have anti-inflammatory properties.

ALLERGIC RHINITIS AND VIRAL COMMON COLD

Viral infection and allergic inflammation have synergistic effects. Virus can affect allergy by producing more allergic inflammation. According to the 'hygiene hypothesis', early viral infection during the early age, however, may reduce the chance of allergy.

The paradoxical theories are respiratory tract infection increases the likelihood of airway hyper-responsiveness (especially asthma) and protective effect by the early viral infection could prevent the development of allergy. Most of the data come from the study of the relationship between asthma and virus [8,9■,10–13]. The complex interaction between viral response and asthma are exacerbation or protective effect on asthma development. The study by Marsland et al. [18] in 2004 showed that the early phase of viral infection could increase asthma exacerbation and in the later time (14–100 days), the viral infection could suppress bronchial hyperresponsiveness (BHR) through the process of cytotoxic T cells.

The aggravation and exacerbation of airway status after viral infection may be caused directly by the harmful effects of the virus and indirectly by the immunopathologic process of the host immune response. Virus increases airway damage and the sensitivity of allergic airway triggers, such as allergens. During viral infection in peak allergen exposure, there was an increased basal level of intracellular adhesion molecule (ICAM)-1 in the nasal epithelium and nasal polyp [19]. The mechanism involved is the activation of transcription nuclear factor. Virus enhances histamine response and increases the epithelial permeability to tachykinin, nitric oxide and neuronal control. It also causes epithelial edema or shedding and increased mucus production.

Sensitization by aeroallergen during the first year of life predisposes children to viral wheezing. The hypothesis for virus-induced asthmatic exacerbation is as follows: epithelial disruption, mediator production, induction of inflammation, IgE dysregulation, airway remodeling and alteration of neural response. Allergic airway inflammation impairs both the epithelial barrier and its antiviral response. In allergic children, there is increased surface expression of FcεRIα on plasmacytoid dendritic cells and myeloid dendritic cells. The expression of FcεRIα is also inversely correlated with IFN-α and IFN-λ [11].

There are very few studies about the relationship between virus and allergic rhinitis. During allergic inflammation, there is upregulation of the expression of ICAM-1, which is the principal receptor for rhinovirus [20]. This phenomenon increases tissue susceptibility to rhinovirus infection. IL-13 is also released during allergic airway inflammation. IL-13 affects the ciliary beat frequency, thereby promoting viral invasion of nasal mucosa [19].

The common pathophysiologic findings during viral rhinitis in allergic and nonallergic rhinitis were the increased number of mucosal lymphocytes and mast cells, and increased vascular density. However, allergic patients had elevated eosinophils and T cells in the acute phase compared with nonallergic patients [21].

Viral rhinitis can cause ostiomeatal complex obstruction and impairment of ciliary clearance, which leads to sinusitis [21,22]. Allergic rhinitis has the additional effect to the impairment function of paranasal sinuses. The study by Alho et al. [23] in 2003 showed that individuals with allergic rhinitis had significantly higher computerized tomography (CT) scores compared with nonallergic individuals during common cold (median scores 16 vs. 6; $P = 0.04$). The high CT score is associated with both serum IgE levels and nasal subepithelial eosinophil counts.

Viral infection may contribute to the initiation and aggravation of allergic rhinitis. During common cold, there is accumulation of mast cells that lead to aggravation of a concomitant allergic condition [19]. The study by Marsland et al. [18] reports that influenza infection enhances the allergic response. The key factors to determine the direction of allergic response to viral infection are the stage of viral infection itself, the genetic background, sex and age.

Allergic inflammation may have protective effect against viral rhinitis as well [19]. IFN-γ (which is produced by Th cells after allergen encounter) has antiviral activity. Mediators from activated eosinophils [such as eosinophilic cationic protein (ECP)] also have antiviral properties. The influenced factors as to whether viral interaction will be protective or exacerbate the symptoms depend on the virulence of the viral strain, the innate immune system and the environmental conditions.

THERAPEUTIC OPTION FOR VIRAL INFECTION ON ALLERGIC RHINITIS

There is no vaccine for rhinovirus and respiratory syncytial virus. Live probiotics reduce the intensity and duration of inflammatory symptoms associated with respiratory infections.

However, in laboratory research, pretreatment by steroid can 'inhibit' rhinovirus-16-induced inflammation, increase in ICAM-1 surface expression, mRNA and promoter activation, without the alteration of viral infectivity or replication [24]. The clinical application of steroids may decrease the symptoms of an asthmatic attack when exposed to rhinovirus.

CONCLUSION

The effects of viral infection on immunologic outcome depend not only on the type of virus,

but also on the physiologic condition of the host. Maturation of T-cell response from a predominantly type II response (atopic predisposition) at birth to a predominantly type I ('optimal' viral immunity) response is affected and influenced by two main factors: genetic factors and the 'number' of infections. The protective role of viral infection is an inverse relationship between the evidence of respiratory infections and, later, the development of atopy.

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Conflicts of interest

There are no conflicts of interest.

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