Airway allergy and viral infection

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Summary

There are complex interactions between airway allergy and viral infection. Available evidence suggests that viral respiratory infection can initiate, maintain and activate exacerbation of allergic conditions in respiratory tract. Innate and inflammatory responses to acute viral infection play important roles in its relationship to allergic reactions. On the other hand, biased immune responses toward Th2 caused by an allergic reaction may make the immune response ineffective in combating viral infection. It was previously shown that allergy can increase the expression level of rhinovirus receptors on mucosal epithelial cells. This suggests that airway allergy may increase the risk of rhinovirus infection. We have recently shown that allergy may also increase the expression level of influenza virus receptors. This suggests that airway allergy and viral infection may have a reciprocal interaction. The effect of allergy on the risk and outcome of viral infection needs to be further confirmed in clinical studies and its potential implication for clinical practice should be considered. *(Asian Pac J Allergy Immunol 2011;29:113-9)*

Key words: *airway, allergy, virus, influenza, inflammation, glucocorticoids, viral infection, viral receptor, asthma, Th2, airway epithelium*

Abbreviations

Th	=	T helper
APC	=	Antigen-presenting cell
IL	=	Interleukin
sIgE	=	Specific immunoglobulin E
T reg	=	Regulatory T cell
TGF-β	=	Transforming growth factor beta
iTreg	=	Inducible regulatory T cell
CD	=	Cluster of differentiation
FoxP3	=	Forkhead box P3
IDO	=	Indoleamine 2,3-deoxygenase
TLR	=	Toll-like receptor
TSLP	=	Thymic stromal lymphopoietin
DC-SIGN	=	Dendritic cell-specific inter-cellular adhesion molecule-3-grabbing non-integrin
ADAM33	=	A disintegrin and metallo-proteinase – 33
EGF	=	Epidermal growth factor
MMP	=	Matrix metalloproteinase
PAMP	=	Pathogen-associated molecular pattern
RIG1	=	Retinoid-inducible gene 1
MDA5	=	Melanoma differentiation-associated gene 5
ICAM	=	Intercellular adhesion molecule
GC	=	Glucocorticoids

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Allergic inflammation of the airway

Development of allergic inflammation

Allergic inflammation is caused by IgE-mediated allergy. It can be divided into two phases. The first phase is the sensitization phase. In this phase, an allergen absorbed through airway epithelium is taken up by antigen-presenting cells (APC) and after internal processing a portion of the antigen is presented to T cells. In individuals whose signals from APC cause differentiation of T-helper 2 cell (Th2), production of cytokines, especially interleukin (IL) 4 and IL13, will drive a B cell class-switch leading to the production of allergen-specific IgE (sIgE)[1]. The sIgE will bind to the surface of mast cells and becomes "sensitized". The particular person who has sensitized mast cell and usually has a hereditary background is an "atopic" person.

The second phase is called the re-exposure phase. In this phase, the sensitized mast cells encounter the same allergen which is specific to the IgE bound on their surfaces. The mast cells become activated and release several inflammatory mediators such as histamine and proteases. When allergic inflammation occurs, the clinical manifestation can be recognized as allergic rhinitis,

allergic asthma or dermatitis depending on the organ involved, which is called the "shock" organ.

In normal individuals, exposure to common and non-harmful antigens results in immune tolerance, which prevents unnecessary and detrimental immunological and inflammatory responses[2]. Tolerance is not merely a lack of immune response; on the contrary, it is a specific immunological response that is mediated by T cells. Regulatory T cells (Treg) expressing Foxp3 play a pivotal role in the induction of tolerance[3]. Induction of the Foxp3+ peripheral induced Treg (iTreg) requires TGF-β[4], which is produced by various cell types including Th3 CD4+ T cells. In the presence of TGF-β, antigen presenting cells, such as B cells and dendritic cells (DCs), can present antigens to naïve T cells and induce antigen-specific iTreg resulting in immune tolerance[5]. The CD4+CD25+FoxP3+ iTreg cells produce IL-10, which is an anti-inflammatory cytokine[6].

Allergic sensitization takes place by a failure in tolerance induction or maintenance resulting in the induction of a Th2 type response. The Th2-produced IL4 and IL13 are the most important cytokines for the pathogenesis of allergic asthma. IL4 is important for IgE production and eosinophilic inflammation, while IL13 is responsible for the changes in lung tissue, such as bronchial hyper-responsiveness, overproduction of mucus, thickening of smooth muscle and subepithelial fibrosis[7].

Other factors known to influence tolerance induction include the tryptophan-catabolizing enzyme indoleamine 2,3-deoxygenase (IDO). The observation that IDO and other enzymes that catabolize essential amino acids are upregulated under conditions stimulating tolerance suggests that local immune responses may be tightly controlled by the availability of specific essential amino acid[8].

It is not clear how allergens break tolerance. Specific properties of allergens may be involved in the sensitization. Many allergens such as the dust mite allergens Der p1and Der p3 contain protease activity and their allergenicity has been shown to require protease activity[9]. Protease activity may disrupt the tight junctions in airway epithelium, compromise its barrier function and allow access of allergens to the local immune system. The protease activity may also cleave certain cell surface molecules resulting in abnormal cellular signaling. It was shown that the Der p1 may also break tolerance by down-regulating IDO expression in a protease-dependent manner[10]. Some other non-protease properties of allergens that may be involved in allergic sensitization include the ability to bind to or induce signaling through innate receptors such as Toll-like receptor (TLR) and DC-SIGN and the enzymatic activity that causes oxidative stress, which can activate epithelial cells and DCs[9].

Airway epithelium and its interaction to various microbes

Airway epithelium was initially considered to function solely as a physical barrier to a wide variety of environmental stimuli , such as allergens, infection (particularly virus) , airborne pollutants and drug[11]. Recently more understanding of a balance between the functions of innate immune cells and the induction of adaptive immunity has been proposed[12, 13]. Airway epithelium can respond to various stimuli, such as allergens, infections (particularly viruses) and airborne pollutants. Respiratory epithelial cells play a crucial role in the initiation of innate immune responses by producing various cytokines. Epithelial-derived cytokines that have been implicated in initiating Th2 responses and allergic sensitization include TSLP, IL-33, and IL-25. TSLP is an epithelial cell-derived cytokine that can activate myeloid DC and the TSLP-activated DC promotes Th2 response. IL-33 is produced by epithelial cells, fibroblasts, and endothelial cells. It is released when the cells become necrotic and binds to ST2 (IL-1RL1), a receptor expressed on Th2 cells, to activate the Th2 response. IL-25 is produced by Th2 cells, mast cells, alveolar macrophages and epithelial cells with allergic reactions. It stimulates the production of Th2-type cytokines and can induce allergic inflammation. [14, 15]

More importantly, a new model for asthma pathogenesis has recently been proposed, in which epithelial and mesenchymal tissues play the dominant role instead of the immune cells[16]. In this model, an "epithelial mesenchymal trophic unit" is the starting point of allergic sensitization and immune cells play a passive role and become activated as the result of exposure to foreign antigens that gain access into the subepithelial tissues because of defects in epithelial integrity and function. This concept was proposed because of the finding that many genetic polymorphisms associated with asthma are in those genes expressed in epithelial or mesenchymal tissues, for example, ADAM33[17]. This is somewhat surprising since one would expect to see the association with only polymorphisms of genes expressed in the immune system. A logical explanation of this finding is that

the genetic polymorphisms alter gene expression and function in epithelial cells and subepithelial mesenchymal cells causing some functional defects. Since the main function of the epithelium is to provide a barrier between the external environment and body tissues, it is reasonable to hypothesize that epithelial defects may lead to over-exposure to foreign materials such as allergens. This over-exposure may lead to the breakdown and failure of the immune tolerance[16]. Tissue damage itself may also provide harmful signals through TLR and induce inflammation, which can promote immune activation and sensitization to allergens caught in the same local milieu. Further supporting evidence for the role of epithelial cells is the up-regulation of EGF receptor on asthmatic airway epithelium[18]. EGF is the major trophic factor involved in epithelial repair, and up-regulation of its receptor suggests a feedback response to epithelial damage. In this model, viral infection may contribute to the epithelial damage that leads to allergic sensitization.

Potential effects of viruses on allergy

Two different hypotheses have been proposed to explain the effect of viral infection on allergic sensitization: the hygiene hypothesis, which regards viral infection as an inhibitor of allergic sensitization, and the alternative view that some viral infections can enhance allergic sensitization.

The famous 'hygiene hypothesis' was based on the observation that children in large families who were exposed to more infections in early childhood were less likely to be allergic. It was hypothesized that infection especially by viruses may induce specific immune responses those are biased towards Th1. Because of this Th1 bias, allergic reactions requiring Th2 responses occur less effectively[19]. Alternatively, frequent exposure to bacterial components may facilitate the development of iTreg through the availability of IL-2 from effector T cells and the maturation of DCs, which are required for iTreg induction[20]. An under-developed iTreg compartment and the failure of tolerance may be therefore caused by lack of exposure to microbes.

On the other hand, epidemiological data from various studies showed an association between viral respiratory tract infection in early life and subsequent childhood asthma. Most studies focused on acute bronchiolitis in infants caused by respiratory syncytial virus (RSV) [21]. Although the link is supported by evidence, the reason for the association is unclear. It has been debated whether viral infection increases the risk of asthma by damaging the developing airway and immune system or merely unmasks the genetic predisposition to asthma, providing that there are common genetic predispositions to viral infection and asthma[21]. Viral infection can damage the developing airway and leads to airway remodeling which causes airway narrowing leading to airflow limitation and wheeze. Viral infection can cause an increase of DC numbers in the lung[22], which can increase the chance of allergen presentation by DCs and allergic sensitization. Enhanced allergic sensitization after viral infection has been also observed in mice. It was shown that IL-13-producing macrophages persisted in the lungs of mice after they had recovered from viral infection and enhanced allergic sensitization [23]. The other possibility to explain the link between viral infection in early life and asthma is that some genetic and epigenetic predisposition may make the immature immune system in infants ineffective in mounting a Th1 response to viral infection. This would increase the susceptibility to viral infection and facilitate spread to lower airway. The same genetic and epigenetic factors may also bias the immune system toward a Th2 response and hence increase the risk of allergic sensitization[24].

Viral infection, especially rhinovirus, can trigger exacerbation of asthma, probably by inducing inflammation in asthmatic persons who already have a sensitized airway.[25] It has been shown that the anti-viral immune response in asthmatic persons can lead to up-regulation of a high affinity IgE receptor, FcεR1, on circulating monocytes and DCs[25]. This would enhance allergen uptake and presentation to presensitized Th2 effector cells leading to acute exacerbations of asthma. In addition, viral infection may also directly affect airway remodeling. It was recently shown that rhinovirus infection could up-regulate the matrix metalloproteinase MMP-9 in airway epithelial cells[26] and induce extracellular matrix protein deposition on airway smooth muscle cells[27].

Potential effects of allergy on viral infection

Innate antiviral response

Innate antiviral mechanisms involving type I interferon play an important role in the outcomes of viral infection. The system employs several pathogen-associated molecular pattern (PAMP) receptors, such as Toll-like receptors, RIG-I, and MDA5 to detect infection through the presence of unique molecules produced by viruses, such as double-stranded RNA. Signaling induced by binding

of PAMP receptors to their specific ligands activates transcription of interferon genes. Binding of interferon to its receptor leads to an interferon-induced cellular anti-viral state. The interferon-induced anti-viral state inhibits viral infection through a number of cellular factors, such as protein kinase R and oligo-A-synthase, which are able to inhibit translation. It has been shown that peripheral blood leukocytes from atopic individuals and atopic asthmatic patients produce less interferon than those from non-allergic individuals after stimulation by virus, lipopolysaccharide, phytohemagglutinin or phorbol ester[28, 29]. In an allergic rat model sensitized to *Aspergillus fumigatus* extract, a delayed clearance of respiratory syncytial virus infection was found to be associated with reduced production of type II interferon (interferon γ)[30]. On the other hand, an allergic mouse model sensitized by cockroach allergen did not show an interferon defect in adenovirus infection and showed normal viral clearance[31]. Whether the difference between these two models was due to the use of different animals or to the different kind of viruses is not clear. It is quite possible that different viruses interact differently with the deranged innate defenses in allergic patients. Using primary human bronchial epithelial cells as a model, type I interferon (α, β) and type III interferon (λ) responses to rhinovirus infection were shown to be defective in cells from asthmatic persons. In accordance with the defective interferon response, bronchial epithelial cells from asthmatic persons were more effectively infected by rhinovirus.[32, 33] Interferon is a major defense against viruses and many viruses developed specific mechanism to inhibit interferon function in order to replicate effectively. Although it has not been shown in a clinical study, it is likely that the defective interferon function in allergic persons can have some effects on susceptibility to and the outcome of some viral infections.

Th1 and Th2 balance

T helper cells can be categorized, according to the pattern of their cytokine production and downstream effector functions, into two major subpopulations, Th1 and Th2. The Th1 response produces interferon and promotes cell-mediated immunity, whereas Th2 response produces interleukin, i.e. IL-4, -5, -6, -10 and -13 and promotes B cell proliferation, class switching and antibody production. Th1- and Th2-type cytokines promote T helper cell differentiation toward the same Th-type and suppress each other. This causes an immune response to polarize toward either Th1 or Th2, depending on the type of pathogen. The Th1 response is more effective in getting rid of intracellular pathogens, such as viruses, whereas Th2 response is designed to combat extracellular pathogens, i.e. parasites. The allergic immune response is biased toward Th2 polarity[34, 35]. Th2-type cytokines were shown to be higher in the sera of asthmatic patients and the levels of these cytokines correlated with the severity of asthma[34, 36]. Because effective control and elimination of viral infection usually requires a Th1 response, preexisting Th2 bias may interfere with the immune response to viral infection[37]. The impairment of interferon production and delayed viral clearance observed in animal models is likely to be the result of this bias in the T helper response[30]. (Figure 1)

Viral receptors

In some animal models, viral receptors to avian and human influenza A were abundantly present in the trachea, bronchus and bronchioles[38]. Human primary bronchial epithelial cells from allergic asthmatic patients were shown to support rhinovirus infection more efficiently than those from normal subjects. It was shown that ICAM-1, which is the receptor for rhinovirus, is up-regulated in respiratory epithelial cells in allergic patients[39]. The reasons for the higher susceptibility to virus infection of bronchial epithelial cells from asthmatic patients therefore included this up-regulation of the viral receptor and the impairment of type I interferon production.

We have recently described an up-regulation of both 2,3- and 2,6 linked sialic acid, which are the receptors for avian and human influenza viruses respectively, on the epithelial cells of nasal polyps. Tissue explants from nasal polyps were also more effective for replication of both avian and human influenza viruses than those from normal nasal mucosa[40]. Whether the up-regulation of sialic acid resulted from the chronic inflammatory process or was specific to the allergic reaction is being further studied.

Avian and human influenza viruses are different in their receptor preference, which is an important part of the avian-human inter-species barrier. Adaptation of receptor usage from avian to human type is associated with the emergence of pandemic influenza virus from avian origin. Although the H5N1 highly pathogenic avian influenza virus is able to infect humans, it retains the avian type

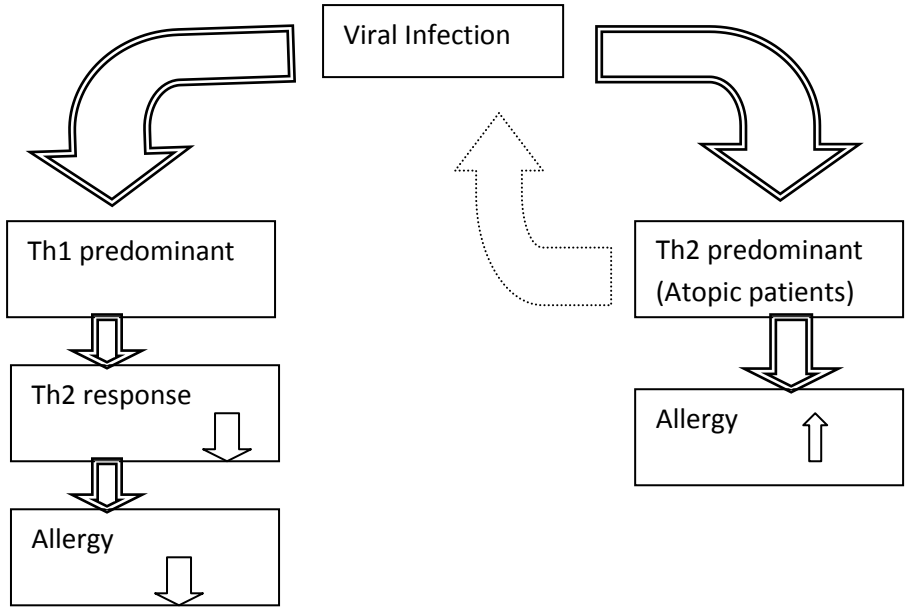

Figure 1. Possible relationship between viral infection and allergic status

receptor preference. Host factors are believed to play crucial roles in H5N1 infection in humans. Sialic acid levels in respiratory mucosa can be highly variable and may play an important role in the susceptibility to H5N1 infection.

The data from the experiments in vitro and in animals discussed above suggest an increased susceptibility to some respiratory viral infection occurs via two mechanisms: i) impaired innate and specific immune responses and ii) up-regulation of viral receptors on airway epithelium. Although it has not been shown in a clinical study, two possible outcomes are expected for viral infection in allergic patients: 1) increased incidence of acute respiratory viral infection and 2) increased severity or increased length of symptoms and viral shedding. It is clear that an increased incidence of acute respiratory infection would negatively affect the quality of life of asthmatic patients, since respiratory infection would in turn cause exacerbation of asthma. On the other hand, increased viral shedding may not have much effect on the quality of life of the patients, but would affect disease spread and the likelyhood of an outbreak. If increased viral shedding is confirmed in allergic individuals, this subpopulation may play an important role in maintaining and accelerating outbreaks. Although further clinical studies are required to confirm these hypotheses, it is prudent to provide the best protection for this group of patients by promoting hand hygiene practice, face-mask wearing, and influenza vaccination.

Clinical Implementation

Besides the vaccination, face-mask use and hand hygiene, airway inflammation should be treated and this can be achieved principally by glucocorticoids (GCs). The effect of GCs on the immune system depends on the dose, treatment duration and the type of infectious agent[41]. The increased level of GCs may cause a selective suppression of the Th1 production of IFN-γ, IL-12, TNF-α but up-regulate the production of IL-4, IL-10 and IL-13 by Th2[42]. For lower airway inflammation, eg viral-induced asthma, treatment with GCs inhalers can inhibit the viral-induced immune response[19].

Regarding upper airway inflammation, intranasal corticosteroids (INCSs) have been highly recommended for allergic rhinitis (AR) treatment. GCs are also used for treatment of laryngotracheobronchitis, but GCs have a limited effect on viral rhinitis or common cold. Gustafson et al[43] reported that oral prednisolone reduced kinin levels in experimental rhinovirus infections, but the reduction was not associated with a significant reduction in symptoms. Intranasal beclomethasone dipropionate (BDP) 400 µg/day did not significantly reduce common cold symptoms or shorten the recovery time of viral rhinitis, as compared with placebo. It was also noted that BDP-INCS did not prolong the recovery time so the authors suggested no need to discontinue INCS in the AR patient with superimposed viral rhinitis[41].

For the newer generation of INCSs, fluticasone propionate (FP) has been studied to determine its efficacy in the naturally occurring common cold[44]. The study was done in 199 young adults who randomly received FP versus placebo. FP showed significant reduction of nasal congestion on day 5,7,8 and cough on day 5 and 9, but did not influence the symptoms of rhinorrhea and throat soreness. The newest INCS, fluticasone furoate (FF), has been studied in various types of rhinitis. It showed good efficacy and safety in the treatment of seasonal and perennial allergic rhinitis including ocular symptom[45, 46]. But FF in regular dosage (110 µg/day) produced similar improvement to placebo in the treatment of irritant (non-allergic) rhinitis[47]. Until now, there is no study of FF and mometasone furoate (MF) in the treatment of viral rhinitis.

Conclusion

The airway epithelium is the major route for viral exposure. Viral infection has both positive and negative effects on the development of airway allergy. The epithelial cells are involved in an innate immunity and also influence the induction of adaptive immunity. Allergic patients may have more severe symptoms when exposed to some types of virus and the potential mechanism is the up-regulation of viral receptors on their respiratory epithelial cells. Inhaled GCs have established their efficacy in treating lower airway inflammation, caused by both viruses and allergy. However, they do not appear to be as effective in the treatment of viral rhinitis. More clinical trials are needed to elucidate the role of INCSs for treating viral rhinitis.

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