Viral Infections, Allergy and Asthma, the Snot Thickens

Efren Rael1*, Arram Noshirvan2 and Andrew J. Long3
1Division of Pulmonary, Allergy and Critical Care Medicine, Stanford University School of Medicine, USA
2Sean N. Parker Center for Allergy and Asthma Research, Stanford University School of Medicine, USA
3California Pacific Medical Center/Stanford Lucille Packard Children’s Hospital Allergy and Asthma Clinic, Stanford University School of Medicine, USA

Received Date: February 21, 2016. Accepted Date: March 08, 2016, Published Date: March 20, 2016.
*Corresponding author: Efren Rael, Division of Pulmonary, Allergy and Critical Care Medicine, Stanford University School of Medicine, USA, E-mail: efenrael@gmail.com

Allergic Associations With Viral Infections

Asthma exacerbations account for more than 1.5 million emergency room visits per year, more than half a million hospitalizations, and thousands of deaths annually in the United States [1]. Viral infections in conjunction with allergy, increase asthma risk and are thought to account for an estimated 90% of pediatric, 75% of adult, acute clinical asthma events [1,2].

Rhinovirus (RV) is thought to account for 50-70% of virus associated asthma exacerbations [3,4]. Greater than 100 rhinovirus strains exist. Variable global infection rates and viral strains may account for population susceptibility differences. In a Brazilian cohort, rhinovirus was associated with 18.7% of pathogens identified in nasopharyngeal aspirates, implicating Rhinovirus-A vs RV cohort, rhinovirus was associated with 18.7% of pathogens identified in nasopharyngeal aspirates, implicating Rhinovirus-A vs Rhinovirus-C viral subtype in 23% vs. 5% respectively, p = 0.04, of asthma flares [5]. In a Mexican cohort, Rhinovirus-C was associated with asthma, but not Rhinovirus-A or B serotypes [6].

Virus associated hospitalization rates, in children under five years, are similar for Human metapneumovirus (HMPV), influenza virus, the combination of parainfluenza virus types 1-3 at 1:1000 children and highest for RSV at 3:1000 children [7].

A clearer understanding of immune pathways responsible for synergistic viral and allergic responses might provide novel opportunities at interventions aimed at improving patient outcomes. Below, are recent papers that highlight cytokine networks bridging allergies, infections, and asthma.

Interleukin 25 (IL-25)

IL-25, along with other IL-17 family members, binds a heterodimeric receptor composed of IL-17RA and IL-17RB. In contrast to other IL-17 family members, IL-25 receptor activation uniquely induces allergic Th2 cytokine expression. Specifically, IL-25 promotes innate lymphoid type 2 (ILC2) cell stimulation and differentiation, and promotes production of allergy associated Th2 cytokines IL-5 and IL-13. In addition to ILC2 cells, IL-25 is also produced by eosinophils, mast cells, epithelial cells, and polarized Th2 cells, all allergy associated cells.

Comparing asthmatics non-asthmatic respiratory epithelium, asthmatics produce higher IL-25 levels in RV infection, leading to eosinophil and neutrophil recruitment and the association with more severe asthma [8]. Blockade of IL-25 signaling via IL-17RB neutralization, abrogates RV associated asthma symptoms in mice [8].

Interleukin 33 (IL-33)

IL-33, primarily expressed in the epithelial cell nucleus and a member of the IL-1 family, is released from damaged cells and activates Th2 cells including mast cells, eosinophils, basophils and polarized Th2 cells via the IL-33 receptor, a heterodimer of ST2 and IL-33, primarily expressed in the epithelial cell nucleus and a member of the IL-1 family, is released from damaged cells and activates Th2 cells including mast cells, eosinophils, basophils and polarized Th2 cells via the IL-33 receptor, a heterodimer of ST2 and IL-1 receptor-like 1 (IL-1RAcP) [9]. Multiple viruses associated with respiratory disease, activate IL-33, including RV, RSV, influenza, and parainfluenza [10-12].

RSV infection promotes IL-33 expression resulting in lung ILC2

<table>
<thead>
<tr>
<th>Virus Name</th>
<th>Family</th>
<th>Variability</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>Picornaviridae</td>
<td>HRV-A 76 serotypes; HRV-B 25 serotypes; HRV-C</td>
<td>Accounts for 50-70% of virus associated exacerbations [3,4]</td>
</tr>
<tr>
<td>Influenzae</td>
<td>Orthomyxoviridae</td>
<td>Influenza A changes by antigenic shift and drift; Influenza B changes by antigenic drift</td>
<td></td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td>Paramyxoviridae</td>
<td>1 Serotype, A&amp;B antigenic subgroups with 4 genetic lineages [19]</td>
<td></td>
</tr>
<tr>
<td>Respiratory Syncitial Virus</td>
<td>Paramyxoviridae</td>
<td>2 antigenic subgroups A&amp;B</td>
<td></td>
</tr>
<tr>
<td>Parainfluenza Virus</td>
<td>Paramyxoviridae</td>
<td>4 Serotypes</td>
<td>PIV3 implicated with asthma [17]</td>
</tr>
</tbody>
</table>

Table 1: Known Infectious agents associated with asthma flares.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Product Description</th>
<th>Development Phase</th>
<th>Developing Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANB020</td>
<td>Anti-Interleukin 33 Monoclonal Antibody</td>
<td>Phase I planned for Q1-Q2 2016 in healthy volunteers followed by trials in adults with severe asthma and severe peanut allergy</td>
<td>AnaptysBio, Inc., San Diego, CA</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>Human Anti-Interleukin 17RA Monoclonal Antibody</td>
<td>Published Phase III trials demonstrating efficacy in moderate to severe plaque psoriasis</td>
<td>Valeant Pharmaceuticals International Inc Bridgewater, NJ</td>
</tr>
</tbody>
</table>

Table 2: Monoclonal antibodies under clinical trial evaluation.
and TH2 cell induction [10]. However, compared to adults, the increase in IL-33 is much greater in neonates when the infection is severe [10]. Influenza H3N1 induces expression of lung IL-33 by alveolar macrophages, independent of TH2 cell, NKT cell and adaptive immune mechanisms [11]. Interestingly, H3N1 does not affect IL-33 expression from airway epithelial cells [11].

RV infection increases IL-25 and IL-33 expression and can induce ILC2s and TH2 cells [13]. IL-25 induction occurs in neonates when infections are severe [14]. Patients who experience severe RSV or RV infections as an infant have a greater chance to develop asthma later in life [10,14].

**Thymic Stromal Lymphopoietin (TSLP)**

TSLP is expressed in skin, gut and lung epithelial cells and is responsible for TH2 promotion [15]. Human airway epithelial cell infection with RSV or RV leads to increased expression of TSLP through activation of nuclear factor kappa B [15]. TSLP is increased in infected epithelial cells from asthmatic children vs. non-asthmatic children in RV and in RSV infection [15]. Human metapneumovirus also induces TSLP expression in human airway epithelial cells [16]. Parainfluenza virus infection is not known to be associated with TSLP induction [17].

**Cytokine Networks**

Variation in viral responses has yet to be elucidated. It is unclear if there are different cytokine networks activated in response to different viruses and within serotypes of viruses. Pathway activation appears to be age determinant. Moreover, infection can alter induction of tolerance to allergens.

RV respiratory epithelium infection can block allergen tolerance via induction of IL-33, TSLP and OX40 ligand as well as predispose to asthma inflammation [18].

**Drug Discovery**

Anti-IL33, anti-TSLP and anti-17RA (IL-25 shared receptor) monoclonal antibodies are in, or are being evaluated for clinical trial.

**References**


