Targeting epithelial initiation of rhinovirus induced asthma exacerbations: development of a potent, neutralizing antibody to IL-25

Jason Girkin1, Thomas Vincent2, Crystal Jackson2, Yonghua Luo2, N. Kirby Alton2, Richard Shimkets2 and Nathan Bartlett1
1University of Newcastle, NSW Australia, 2Abeome Corporation, Athens, GA USA
poster link: www.abeomecorp.com/category/news

Background

Viral respiratory infections are the most important trigger for acute asthma flares, with asthma susceptible to more serious effects from viruses that would usually only cause the symptoms of the common cold – most prominently rhinovirus (RV). Viral replication in airway epithelium leads to production of inflammatory mediators that can trigger the immune cascade that underpins an asthma exacerbation. The airway epithelium is the site of RV infection and is the focus of research seeking to develop new treatments to suppress infection and associated triggering of inflammatory responses that drive asthma exacerbations. Several studies have reported that asthmatic airway epithelium responds abnormally to infection. In this context, we and others have provided key evidence showing that asthmatic epithelium can exhibit abnormal immune responses to RV infection including deficient anti-viral immunity and exaggerated production of mediators such as IL-25. We have reported that uninfilitrated asthmatic bronchial epithelial cells (BECs) exhibit up-regulated expression of the type I inflammatory cytokine IL-25 during rhinovirus (RV) infection identifying this molecule as a target for mAb-based therapy for asthma exacerbations.

Air liquid interface culture of asthmatic bronchial epithelial cells

To investigate if the IL-25 phenotype was present in fully differentiated asthmatic primary bronchial epithelial cells (ABECs), we recruited mild, moderate and severe eosinophilic asthma (>3% sputum eosinophils). BECs were obtained by bronchoscopy and cultured on transwell inserts at the air-liquid interface for 28 days before use (0.1 MOI infection with minor group FV1B or major group FV43).

Clinical and immunological characteristics of asthmatic ABEC donors

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Gender</th>
<th>FEV1 % predicted</th>
<th>RV1B</th>
<th>RV43</th>
<th>Mock</th>
<th>IL-33 mRNA</th>
<th>IL-8 mRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>72</td>
<td>Female</td>
<td>96</td>
<td>7.5</td>
<td>10</td>
<td>37</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Asthmatics</td>
<td>75</td>
<td>Female</td>
<td>85</td>
<td>8.0</td>
<td>50</td>
<td>8</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>RA-Asthmatics</td>
<td>70</td>
<td>Female</td>
<td>78</td>
<td>10</td>
<td>8</td>
<td>1</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>RA Controls</td>
<td>70</td>
<td>Female</td>
<td>90</td>
<td>10</td>
<td>2</td>
<td>1.5</td>
<td>1.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Type-2 inflammatory mediators associated with IL-25 treatment

Mouse model of RV-induced exacerbation of allergic airways disease with anti-IL-25 (ABM125) treatment.

ABM125 treatment suppresses eosinophilic airway inflammation

Summary

- **ALI**-differentiated asthmatic epithelium responds to RV infection with elevated IL-25, which was associated with more severe disease.
- **Epithelial IL-25** was also associated with increased levels of the related type-2 inflammatory mediators, CCL5 and CCL22.
- **Neutralizing IL-25 in vivo with mAB ABM125, suppressed airway eosinophil recruitment in a model of RV-induced exacerbation of allergic airways disease.**
- **Reduced eosinophilic inflammation was associated with a trend towards reduced IL-5 mRNA expression.**