Epithelial TIM-3-Expressing Mast Cells are Associated with Increased Severity of Chronic Rhinosinusitis with Nasal polyposis, Aspirin Exacerbated Respiratory Disease, and Asthma

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Objective
Determine correlation between TIM-3+ mast cells within nasal polyps and clinical severity of chronic rhinosinusitis with nasal polyposis (CRSwNP) with concomitant aspirin-exacerbated respiratory disease (AERD) and asthma.

Background
Mast cells and their activation in CRSwNP is an area that remains poorly understood. It has been reported that mast cells constitutively express cell surface T cell/transmembrane immunoglobulin and mucin domain protein 3 (TIM-3)3. It has been suggested that manipulation of TIM-3 activity on mast cells could be a promising target for the development of novel therapeutic modalities for chronic inflammatory diseases2.

Methodology
- Nasal polyp tissue (n=24) obtained at a tertiary care hospital (2015-2016) was enzymatically digested3
- Viable TIM-3+ mast cells identified using flow cytometry markers, while disease severity was assessed using clinical severity scales

Flow Cytometry Markers
- CD45 (hematopoietic cells)
- Live/dead (viable cells)
- c-kit
- FcεRI
- TIM-3

Clinical Severity Scales
- 22-item Sino-Nasal Outcome Test (SNOT-22)
- Lund Mackay staging system
- Lund Kennedy score
- Hematologic counts (eosinophil, basophil)

Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled patients with CRSwNP, n (%)</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>F</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Sinus</td>
<td></td>
</tr>
<tr>
<td>Ethmoid</td>
<td>13 (61.9)</td>
</tr>
<tr>
<td>Maxillary</td>
<td>8 (38.1)</td>
</tr>
<tr>
<td>Concomitant asthma</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Concomitant AERD</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Concomitant allergic rhinitis</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>OCS treatment (384mg/d)</td>
<td>18 (75)</td>
</tr>
</tbody>
</table>

Results

In CRSwNP patients with concomitant AERD and asthma:
- %TIM-3+ mast cells in the nasal polyp epithelial layer positively correlated with worsening endoscopic appearance post-operatively (r=0.949, p=0.014, n=5)
- Higher %TIM-3+ mast cells in the stromal layer of nasal polyps correlated with a greater change between pre- and post-operative endoscopic severity scores (r=−0.894, p=0.041, n=5)

Discussion
Viable mast cells present in nasal polyps with increased TIM-3 expression in the epithelial layer may play a role in perpetuating the inflammatory response after surgical intervention in CRSwNP patients.

Limitations of this pilot study include a small sample size and lack of comparison to healthy sinus control tissue.

Future Direction
Areas for future study include the effects of topical and/or inhaled corticosteroid treatment and environmental factors on the mast cell milieu.

Resources