Understanding the immunopathology of chronic rhinosinusitis and treatment implications

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Objectives
• Describe the role of bitter taste receptors in chronic rhinosinusitis
• Discuss the immunologic role that respiratory epithelial cells play in the pathology of chronic rhinosinusitis
• Describe innate lymphoid cells and their interaction with immune effector cells
• Explain how targeted therapy can be effective in CRS management

Chronic rhinosinusitis
➢ Over 15.5% of all Americans suffer from chronic rhinosinusitis
   Along with asthma, 2nd most prevalent chronic disease
➢ Inflammation affecting nasal and paranasal sinus mucosa for over 3 months
➢ CRS describes a heterogeneous syndrome rather than a specific disease
➢ Certain CRS subtypes associated with asthma and atopy

Chronic Rhinosinusitis (CRS)

Chronic Rhinosinusitis without Polyps (CRSsNP)
• Type 1 inflammatory response
• Infiltration of neutrophils

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
• Type 2 inflammatory response
• Infiltration of eosinophils
Immunopathology of CRS

Pathophysiology of CRS

- Genetic susceptibility
- Allergy
- Extrinsic stimuli
- Ciliary dysfunction
- Bacterial superantigen

Clinical appearance

Immunopathology of CRS

Current medical treatment options for CRS

- Antimicrobial therapy
- Steroids
- Nasal saline washes
- Immune modulators

Immunopathology of CRS

Pathophysiology of CRSsNP – Type 1 Inflammation

- Pharyngitis
- Hypersensitivity
- T2R38 genetic variabilities

Phenylthiocarbamide (PTC) testing linked to polymorphisms in T2R38

- Supertasters – functional
- Tasters
- Non-tasters - nonfunctional

Immunopathology of CRS

Nonfunctional T2R38 Bitter Taste Receptor - CRSsNP

- Genetic variabilities of T2R38 linked to surgical improvement in SNOT-22 score at 6 months (Adappa et al, IFAR, 2015)

- PTC nontaster in non-Hispanic Caucasian CRS patients is linked to CRSsNP (Rowan NR et al, IFAR, 2018)

- Most CRSwNP patients were found to be tasters

Immunopathology of CRS

Pathophysiology of CRSwNP – Type 2 Inflammation

- Cells
  - Eosinophils
  - Mast cells
  - Basophils
  - T helper 2 cells

- Cytokines
  - IL-4: IgG switching
  - IL-5: eosinophil stabilization
  - IL-13: goblet cell hyperplasia -> mucus production

- Epithelial cell derived cytokines
  - IL-33
  - IL-25
  - TSLP

Immunopathology of CRS

Therapeutic Implications for CRSsNP

- Quinine
  - Bitter compound that activates several bitter taste receptors, but not T2R38

- Workman AD, Cohen MA et al, Front Immunol, 2018
Unified Airway – CRS link to Asthma

- Shared epidemiology: 60-80% CRSwNP patients have concurrent asthma and 80% of asthmatics have upper airway chronic inflammation
- Shared histology

Nasal mucosa

Lung respiratory mucosa

Epithelial cells play active immunologic role

Elevated Expression of ST2 in Inflamed Sinonasal Mucosa from CRSwNP Patients

Cellular Targets of IL-33

Innate lymphoid cells

- Existence first proposed when mice lacking conventional B and T cells could still be induced by IL-25 to make IL-5 and IL-13 (Hurst et al 2002; Fort et al 2001)
- In 2010, population of type 2 cytokine-producing lineage negative cells were characterized in mice which ultimately became known as Type 2 ILCs or ILC2s (Moro et al; Neill et al; Price et al)
- In humans, nasal polyps from CRS patients and lungs were one of the first sites where ILC2s were found (Mjosberg et al, 2011)

ILCs share analogous functions with T cells
**Increased percentage of ILCs in inflamed sinonasal mucosa from CRSwNP patients**

Shaw et al., *J of Allergy Clin Immunol*, 2013

**Increased IL-13 production from ILCs in sinonasal mucosa from CRSwNP patients in response to IL-33**

Shaw et al., *J of Allergy Clin Immunol*, 2013

**ILC2 from CRSwNP are activated**

Poposki et al., *Immunity, Inflammation, and Disease*, 2017

**Interaction of ILC2s and Mast cells**

**Increased Mast Cells in Sinonasal Mucosa from CRSwNP Patients Independent of Atopic Status**

**Solitary chemosensory cells source of IL-25 in CRSwNP**

Kohanski MA, Cohen NA et al., *JACI*, 2018

Patel NA, Cohen NA et al., *IFAR*, 2019
TSLP in CRSwNP

- TSLP gene expression is increased in nasal polyp tissue
- TSLP protein is truncated in nasal polyps and this form is more potent

Nagarkar DR, Kato A et al, JACI 2013

Current medical treatment options for CRS

Biologics for CRS

A preparation, such as a drug, a vaccine, or an antitoxin, that is synthesized from living organisms or their products and used as a diagnostic, preventive, or therapeutic agent.

Anti-IgE (Omalizumab)

- Blocks crosslinking of IgE to FcεRI by binding free IgE
- Brand: Xolair
- FDA approval
  - Moderate to severe allergic asthma ≥ 6 yrs
  - Chronic idiopathic urticarial ≥12 yrs
- Prevention of severe food allergies
- Administration: SC injection
- Cost: $10K - $16,000/year
- 2 studies published on efficacy of omalizumab in pilot study with CRS
Ameliorating “local allergy” in nasal polyps

- RDBPCT of omalizumab as a treatment for patients with NP and comorbid asthma.
- Allergic and nonallergic patients were included.
- Subjects received omalizumab (n = 16) or placebo (n = 8) for 16 weeks.

Results

- Omalizumab treatment was associated with a decrease in total nasal endoscopic NP and sinus CT scores after 16 weeks compared to placebo.
- Benefits in both allergic and nonallergic patients.


- Polyp score change from baseline

Anti-IL-5

- Three anti-IL5 drugs:
  - Mepolizumab (Nucala) - SC injection monthly
  - Reslizumab (Cinqair) - IV monthly
  - Benralizumab (Fasenra) - SC injection monthly then every 8 weeks
- Targeted against IL-5 receptor
- Expected effect to decrease eosinophil levels and activity locally and systemically.
- Cost about $32,500-$38,000/year

- Cost about $32,500-$38,000/year

Anti IL-5 therapy

- FDA approval
  - Mepolizumab
    - Severe eosinophilic asthma ≥12 yrs
    - Eosinophilic granulomatosis with polyangiitis
  - Reslizumab
    - Severe eosinophilic asthma ≥18 yrs
  - Benralizumab
    - Severe eosinophilic asthma ≥12 yr

- Two proof of concept study in CRS with nasal polyps – mepolizumab and reslizumab

Reslizumab in CRSwNP

- N=24
  - Placebo (N=8)
  - Reslizumab 1mg/kg (N=8)
  - Reslizumab 3mg/kg (N=8)

Gevaert et al. JACI 2006;118:1133

Measurements

- Polyp score
- Symptom scores
- Sinus CT scores
- Biomarkers

Total Polyp Score

- Responders had elevated nasal IL-5
- No significant change in symptoms

Decrease in Blood Eosinophils

- Decrease in blood eosinophils
Dexpramipexole depletes blood and tissue eosinophils without decrease in polyps

- Drug to treat ALS and found to serendipitously to deplete eosinophils
- Small trial in 16 CRSwNP treated for 6 months with 150 mg BID
  - No significant change in polyps
  - No significant change in other clinical endpoints

**Anti-IL-4R (Dupilumab)**

- Fully-human monoclonal antibody directed against IL-4Rx subunit which inhibits signaling of both IL-4 and IL-13

**Anti-IL-4R (Dupilumab) in CRSwNP**

- Brand: Dupixent
- FDA approval
  - Moderate-to-severe atopic dermatitis ≥18 yrs old
  - Moderate-to-severe asthma ≥ 12 yrs old
- Administration: SC injections Q2 weeks
- Cost: $37,000/year

**Phase 3 Trial in Severe CRSwNP – TPS ≥5**

<table>
<thead>
<tr>
<th>Group</th>
<th>Nasal polyp score scale</th>
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<tbody>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Dupilumab 300 mg Q2 wks</td>
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<tr>
<td>Dupilumab 300 mg Q2 wks</td>
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<tr>
<td>Dupilumab 300 mg Q4 wks</td>
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**Primary endpoints**
- Total polyp score change at 24 weeks
- Nasal congestion change at 24 weeks

**Nasal polyp score scale**

<table>
<thead>
<tr>
<th>Polyp score</th>
<th>Polyp Size</th>
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<tbody>
<tr>
<td>0</td>
<td>No polyps</td>
</tr>
<tr>
<td>1</td>
<td>Polyps within the middle meatus</td>
</tr>
<tr>
<td>2</td>
<td>Polyps reaching below the lower border of middle turbinate</td>
</tr>
<tr>
<td>3</td>
<td>Polyps reaching lower border of inferior turbinate</td>
</tr>
<tr>
<td>4</td>
<td>Polyps touching nasal floor</td>
</tr>
</tbody>
</table>
Summary of Effect on Total Polyp Score

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effect</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Methylprednisolone 3 week taper</td>
<td>-2.3</td>
<td></td>
</tr>
<tr>
<td>Omalizumab 16 weeks</td>
<td>-2.3</td>
<td></td>
</tr>
<tr>
<td>Mepolizumab 8 weeks (2 doses)</td>
<td>-1.2</td>
<td></td>
</tr>
<tr>
<td>Dupilumab 24 weeks</td>
<td>-2.3</td>
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Limitations

- Cost
- Not curative
- Unknown long-term side effects of manipulating immune response
- Lack of biomarkers
- Some require IV infusion

Conclusion

- The molecular understanding of the pathophysiology of CRSwNP is expanding with introduction of potential therapeutic targets.
- Biologics may be justified in severe CRSwNP with concurrent asthma.