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Inflammatory Mechanisms of Chronic Rhinosinusitis

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Definition of CRS

• 12 consecutive wks of subjective sinonasal symptoms

• 4 cardinal symptoms: blockage, drainage, smell loss, pressure or pain

• Objective confirmation of inflammation via endoscopy or CT
CRS Phenotypes

- Broad clinical syndrome
  - Symptom complex with objective confirmation
  - Historically, divided into CRS into 2 phenotypes: CRSwNP and CRSsNP
  - Simplistic, multiple clinical patterns exist
## Advanced CRS Phenotypes in USA

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Total CRS</td>
<td>20,000,000</td>
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<tr>
<td>Total CRSsNP</td>
<td>16,000,000</td>
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<tr>
<td>Total CRSwNP</td>
<td>4,000,000</td>
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<tr>
<td>AERD</td>
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<tr>
<td>AFS</td>
<td>500,000</td>
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<tr>
<td>Cystic Fibrosis</td>
<td>30,000</td>
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<tr>
<td>Autoimmune (GPA, EGPA)</td>
<td>10,000</td>
</tr>
<tr>
<td>Kartagener’s syndrome</td>
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Age: CRS Phenotypes

- Older onset CRS/asthmatics do poorly
- Early onset CRS patients do better
CRS phenotypes

• Not usually very helpful in terms of patient counseling

• Not very helpful in terms of guiding treatment

• Research into causes of CRS for 20+yrs to make treatment more precise
What is CRS?

- **Broad clinical syndrome** - not a disease

- 2 basic pathways to CRS:
  - OMC blockage
  - *Primary mucosal inflammation*
CRS Syndrome

OMC Inflammation  Primary Inflammation  Mixed
Primary Mucosal inflammation in CRS

Causes ????
Etiology and Pathogenesis of CRS

<table>
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<tr>
<th>Environment</th>
<th>Host</th>
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<tr>
<td>• Fungal hypothesis</td>
<td>• Eicosanoid hypothesis</td>
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<td>• Superantigen hypothesis</td>
<td>• <strong>Immune barrier</strong> hypothesis</td>
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<td>• Biofilm hypothesis</td>
<td>• EPOS 2012</td>
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<td>• Microbiome hypothesis</td>
<td>• Lam et al., 2015</td>
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<td>• Allergy</td>
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Nasal and Sinus Mucosa

- Site of Interface with the external environment
- In health, this occurs with minimal if any inflammation
- Mucosa serves as an “immune barrier”
CRS Etiology and Pathogenesis

- Host and Environment interact for 40+ years and then barrier is penetrated resulting in CRS
- With self perpetuating inflammation
Typically, adult onset disorder
Early 40’s CRSsNP; Late 40’s CRSwNP
Nasal and Sinus Mucosa

• Cross talk between host and environment
• Microbiome
• Defense vs. symbiosis
• Stochastic events such as viral infection at a young age

• Early life exposure protective; Hygiene Hypothesis
  • Strachan, *BJM*, 1989

• Gut/airway axis
  • Von Mutius, *JACI* 2016
  • Lynch and Boushey, *Curr Opin Allergy Clin Immunol.*, 2016

• **SCFA**, other compounds—protective!
Atopic March

The Allergic March

- Eczema
- Food Allergy
- Rhinitis
- Asthma

Typical Age of Onset

Birth, 3 months, 1 year, 2 years, 3 years, 7 years, 15 years
Early onset Atopic CRS?
Early Onset CRS Phenotype?

- Milder, atopic, progression of childhood disease
- CRSsNP typically
- Mild asthma or childhood asthma
Host and Environment interact for 40+ years and then barrier is penetrated resulting in CRS

• More severe, probably more likely to need surgery
• CRSsNP early 40’s; CRSwNP late 40’s
Host vs. Environment in CRS

Which are more important host factors or environmental factors in an individual patient?

Can we know in an individual patient?

Would it matter?
Etiologic factors vary so....the inflammation not the same in all CRS patients: ENDOTYPES-mechanistic pathways, types/patterns
Personalized Medicine

- **Genotype** - genetic makeup that underwrites a disease
- **Endotype** - subtype of a disease defined by a distinct pathophysiological mechanism
- **Phenotype** - observable clinical characteristics
Chronic Rhinosinusitis

- **Genotype** - complex, multiple genes, *ALOX 15, CFTR*; Environmental factors probably more important

- **Endotype** - new classification systems

- **Phenotype** - clinical groupings; basis of most treatment at present
Etiology and Pathogenesis of CRS

- Environmental factors
- Genotype
  - Epigenetic variation

Endotype(s) → Phenotypes
Etiology and Pathogenesis of CRS
Etiology and Pathogenesis of CRS

- Host
- Environment
- Barrier penetration
- Endotype
- Remodeling
- Phenotype
  - Natural history outcome
  - Lower airway disease?
    - Asthma and Bronchiectasis
Endotypes of CRS

- **Endotypes**: mechanistic pathway

- *What are the endotypes of CRS?*

- *How can they help guide treatment?*
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<th>IL-8 (pg/mL)</th>
<th>IL-6 (pg/mL)</th>
<th>IL-1β (pg/mL)</th>
<th>Albumin (mg/dL)</th>
<th>IL-5 (ratio pos.)</th>
<th>IL-5 (pg/mL)</th>
<th>ECP (μg/L)</th>
<th>SE-IgE (KU/L)</th>
<th>SE-IgE (ratio pos.)</th>
<th>TGF-β1 (pg/mL)</th>
<th>IL-17 (pg/mL)</th>
<th>IL-17 (ratio pos.)</th>
<th>TNF-α (pg/mL)</th>
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<th>IL-22 (pg/mL)</th>
<th>IFN-γ (pg/mL)</th>
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<td>237</td>
<td>43</td>
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<td>71%</td>
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</tbody>
</table>

**Legend:**
- Concentration significantly higher than controls and higher than 6 or more other clusters
- Concentration significantly higher than controls and higher than 3 or more other clusters
- Concentration significantly higher than controls and higher than 2 or more other clusters
- Concentration significantly higher than controls but not higher than other clusters

Tomassen et al., JACI 2016
Endotyping CRS

Tomassen et al., 2016
1. Mucus/Cilia
2. TJs
3. HDM and sIgA
4. ILC1, 2 and 3
5. Innate cells
6. T cells
7. B cells
Innate Lymphocytes Guide Immune Responses
Mucosal Immunity

- **ILC1** $\rightarrow$ Type 1 inflammation; Th1
  Viruses, Intracellular organisms

- **ILC2** $\rightarrow$ Type 2 inflammation; Th2
  Parasites, REPAIR

- **ILC3** $\rightarrow$ Type 3 inflammation; Th17
  Extracellular organisms
Mucosal Immunity

- **ILC1** $\rightarrow$ Cytotoxic T cells, NK cells and neutrophils
- **ILC2** $\rightarrow$ Eosinophils, mast cells, B cells and neutrophils
- **ILC3** $\rightarrow$ Neutrophils
CRS Endotypes

• Type 1 inflammation: IFN-γ
• Type 2 inflammation: IL-4, IL-5, IL-13
• Type 3 inflammation: IL-17

• So we can determine tissue patterns based on markers of Type 1, 2 and 3 inflammation in the tissue
CRS Endotype Patterns

- T1
- T2
- T3
- T1,2
- T1,3
- T2,3
- T1,2 and 3
- Non typeable
Inflammatory endotypes in CRS

**CRSsNP**
- T1sNP: total 21%
- T2sNP: total 55%
- T3sNP: total 27%

**CRSwNP**
- T1wNP: total 17%
- T2wNP: total 87%
- T3wNP: total 18%

Kato A et al., unpublished. 2018 (updated)
Similar inflammatory patterns in CRS are reported in Europe

Kato A et al., unpublished. 2018 (updated)
60+% of CRS in Chicago is T2
Type 2 Inflammation

• Associated with treatment failure
• Asthma
• Eosinophilia

• Higher rate of polyp formation
TYPE 2 Inflammation

1. Impaired release of innate host defense molecules

2. Colonization by bacteria and fungi, loss of barrier function

3. Local elevations of pathogen-associated molecular patterns (PAMPS) and antigens drive adaptive immunity: Superantigen effect

4. Local development of autoimmunity

- TSLP
- BAFF
- Chemokines attracting B cells, eosinophils
- Plasma cell
- Neutrophil degranulation
- Mast cell degranulation
- IgE
- IgG
- IgA
- Il-5
Type 2 Inflammation
Endotype Drives Remodeling

- Remodeling includes polyp formation, barrier changes, fibrosis, glandular hypertrophy
Type 2 CRS

- **Polyps** and **barrier damage** are remodeling changes secondary to the Type 2 inflammation.
Nasal Polyp
What are Polyps?

Control UT

CRSsNP UT

Picrosirius Red

CRSwNP UT

Nasal polyp

Fibrin deposition in nasal polyps in CRS

Professor Shimizu from Shiga University first suggested importance of coagulation cascade and polyps
Tissue TPA levels vary!

Type 2 cytokine: IL-13
Regulation of pathways of fibrin deposition by IL-13

Imoto et al., JACI, in press 2019
SCFA Increase Epithelial t-PA

Imoto, Kato, Takabayashi, Sakashita et al., Clin Exp Allergy, 2018
Type 2 Remodeling: Polyps

- Type 2 Polyp formation is the results of fibrin crosslinking when t-PA is suppressed by sufficient IL-13
Type 2 Remodeling: Barrier Damage

- **Barrier damage** is also a type of remodeling seen with **Type 2 inflammation**
Type 2 Inflammation and Barrier

- Weakened and Immature epithelial barrier
- Chronic immature EMT state
- *Barrier failure*
CRSwNP

Kuhar et al. IFAR 2017
Abnormal Repair in Type 2 CRS

Healthy sinus and nasal epithelium:
- Differentiation
- Reformation of healthy structure
- Migration
- Formation of tight junctions

CRS sinus and nasal epithelium:
- Epithelial mesenchymal transition (EMT)
- Untethering
- Migration
- Proliferation
- Reaggregation
- Secondary repair
- Acanthosis
- Acantholysis
Barrier Failure and Type 2 CRS

Pothoven et al., 2015
Hypothetical progression in Type 2 CRS

Type 2 CRS

Barrier Failure is probably distinct from barrier penetration
Type 2 Inflammation and Recurrence

- Chronically weak barrier
- Predisposes to recurrence
- Need steroid maintenance
- Severe cases need a biologic
Not all CRS is Type 2!

- T1
- T2
- T3
- T1,2
- T1,3
- T2,3
- T1,2 and 3
- Non typeable
What about Non-Type 2 Remodeling?

- T1
- T2
- T3
- T1,2
- T1,3
- T2,3
- T1,2 and 3
- Non typeable
Type 1 cytokine: IFN-γ
Type 1 and 3 Remodeling: Polyps

- Type 1 and 3 Polyp formation is also the result of fibrin crosslinking when t-PA is suppressed but less common in Western Societies.
Non-Type 2 Inflammation

• Barrier more intact so recurrence less

• Polyps still fibrin

• Polyps less common because t-PA suppression weaker with T1/3 cytokines and no feed-forward mechanism because barrier more intact
Nasal polyps

- Polyps are mostly a fibrin matrix in all CRS endotypes

- More common in T2 inflammation because IL-13 more effective at suppressing t-PA than Type 1 and 3 cytokines

- Also more common in T2 because Barrier Failure more likely to drive T2 cytokine levels
CRS Endotypes

Environment

Barrier Penetration

Host

T1/T3

Fibrosis, less fibrin Polyps

Intact barrier

Bronchiectasis

T2

Fibrin Polyps, less fibrosis

Asthma

Barrier failure
Treatment of CRS Endotypes

Environment

Host

Barrier Penetration

T1/T3

Corticosteroids (weak)

Surgery

Antibiotics

T2

Corticosteroids (strong)

Surgery

Biologics
Thank you