

Understanding the immunopathology of chronic rhinosinusitis and treatment implications

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Disclosures

Consultant

- Arrinex
- Aerin Medical
- Intersect ENT
- Lyra Therapeutics
- ENTvantage
- Sanofi/Regeneron

Speaker's Bureau

- Intersect ENT

Department Research Support

- Novartis

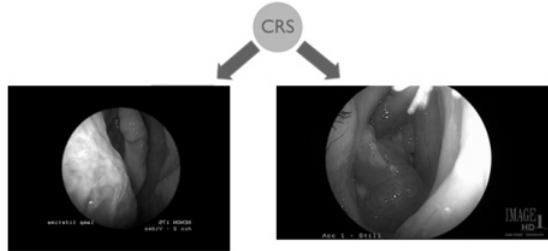
Objectives

- 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

Classic Clinical Classification of Chronic Rhinosinusitis



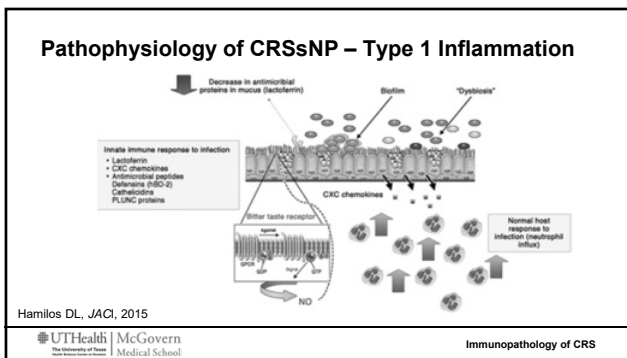
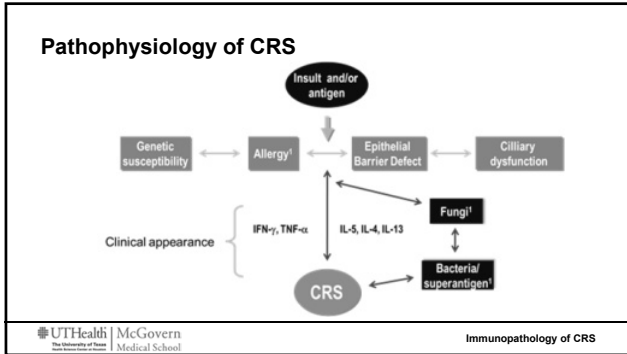
Chronic Rhinosinusitis (CRS)

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



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 CRSsNP patients were found to be tasters

Phenylthiocarbamide (PTC) tasting linked to polymorphisms in T2R38

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

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Therapeutic Implications for CRSsNP

Quinine

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

Workman AD, Cohen NA et al, Front Immunol, 2018

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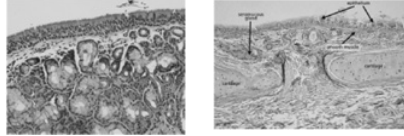
Pathophysiology of CRSwNP – Type 2 Inflammation

- Cells
 - Eosinophils
 - basophils
 - mast cells
 - T helper 2 cells
- Cytokines
 - IL-4: IgG switching
 - IL-13: goblet cell hyperplasia -> mucus production
 - IL-5: eosinophil stabilization
- Epithelial cell derived cytokines
 - IL-33
 - IL-25
 - TSLP

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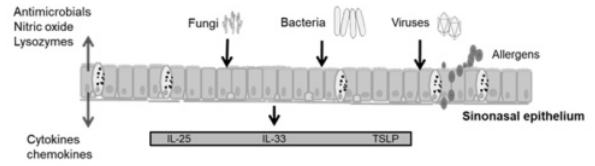
Unified Airway – CRS link to Asthma

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

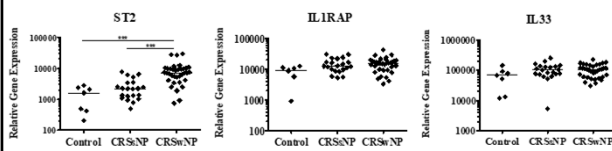


Nasal mucosa Lung respiratory mucosa

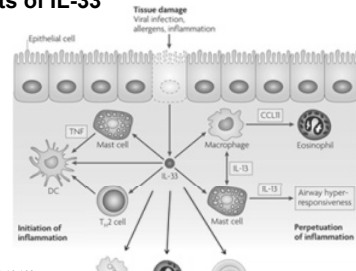
Epithelial cells play active immunologic role



Elevated Expression of ST2 in Inflamed Sinonasal Mucosa from CRSwNP Patients



Cellular Targets of IL-33

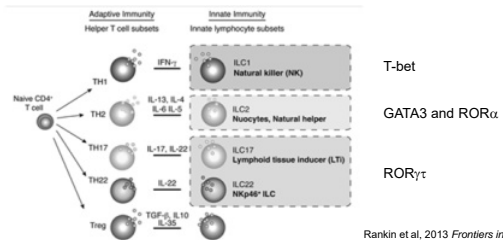


Adapted from Nat Rev Immunol (2010) 10:103

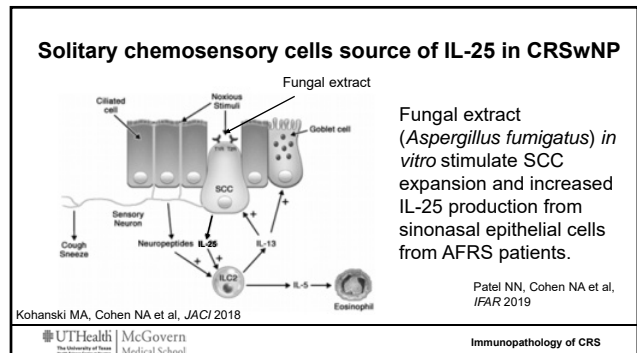
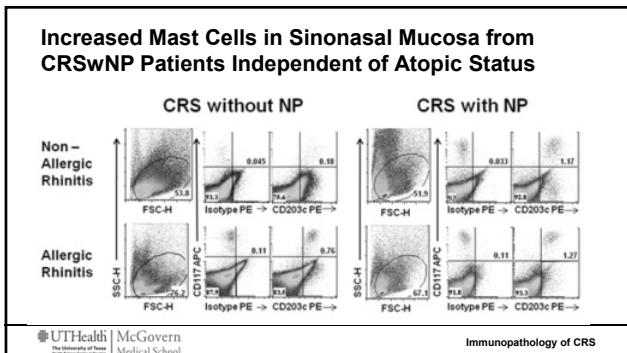
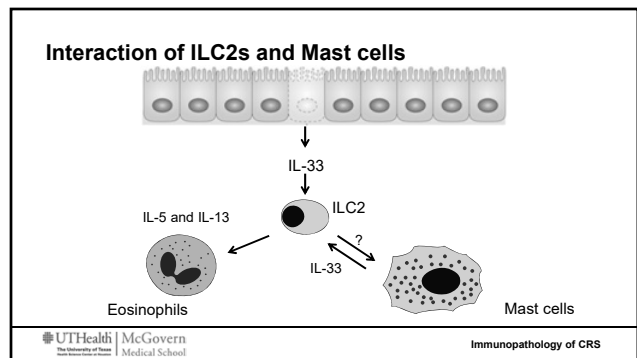
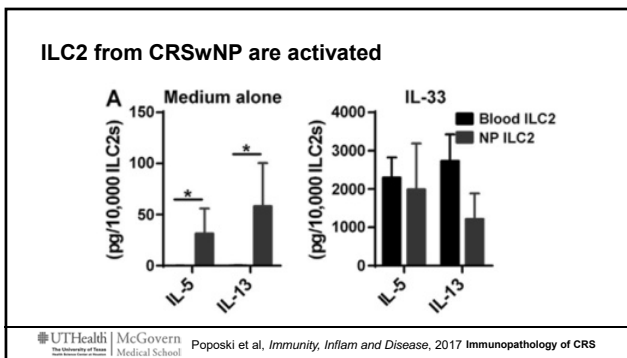
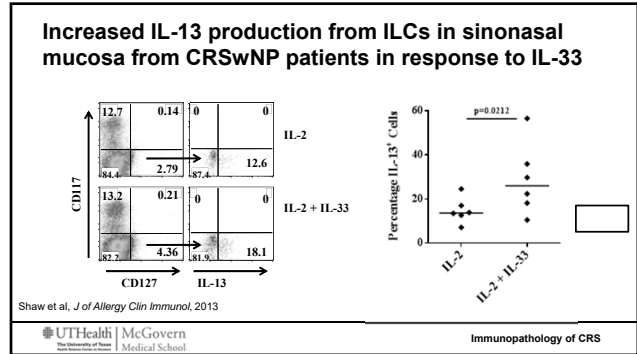
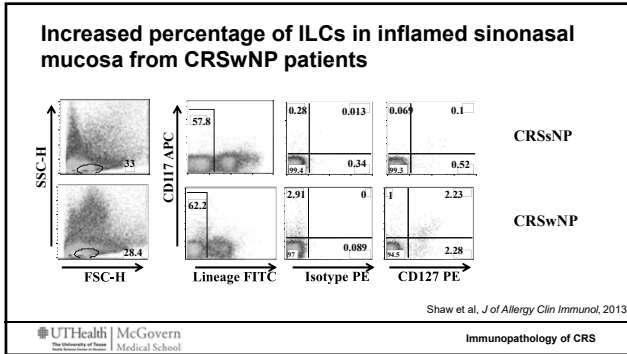
Innate lymphoid cells

- 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

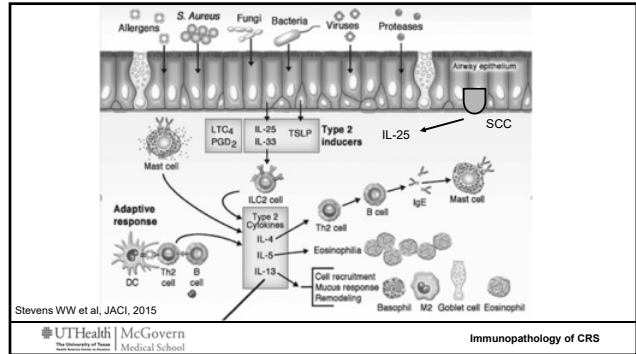
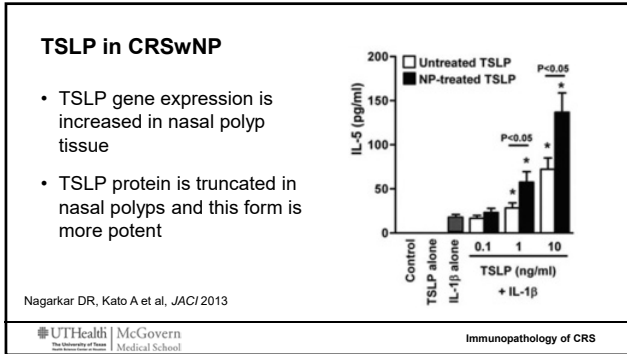


Rankin et al, 2013 *Frontiers in Immunology*



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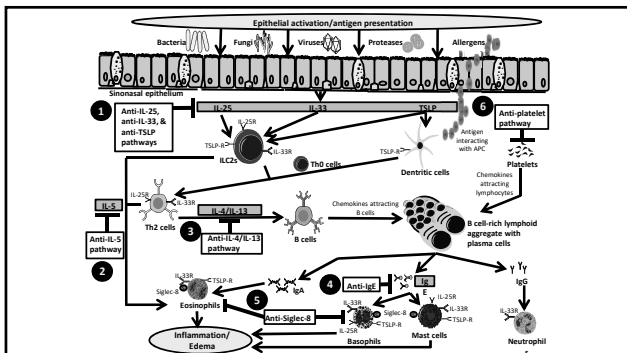
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Biologics for CRS

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.

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Anti-IgE (Omalizumab)

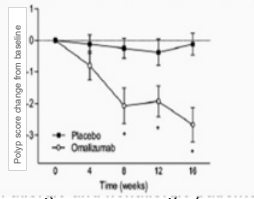
- Blocks crosslinking of IgE to FcεR1 by binding free IgE
- Brand: Xolair
- FDA approval
 - Moderate to severe allergic asthma ≥ 6 yrs
 - Chronic idiopathic urticarial ≥ 12 yrs
 - Prevention of severe food allergies
- Administration: SC injection
- Cost: \$10K - \$16,000/year
- 2 studies published on efficacy of omalizumab in pilot study with CRS

The infant's airway is more sensitive to allergens, mucus, and other irritants.

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Ameliorating “local allergy” in nasal polyps

- RDBPCT of comorbid asthma with NP and allergic rhinitis (n = 8) for 16 weeks
- Allergic and rhinitis
- Subjects recruited
- Results
 - Omalizumab nasal end compared
 - Benefits in



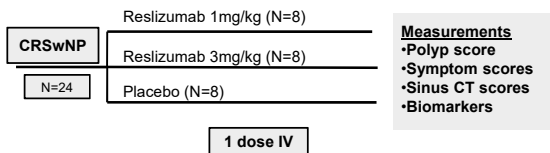
Anti-IL-5

- 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

Anti IL-5 therapy

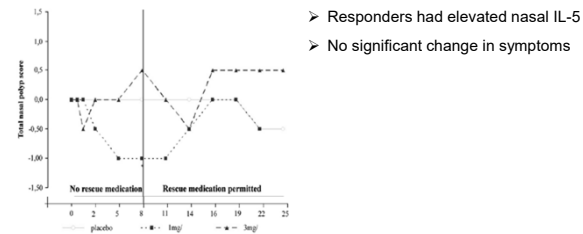
- FDA approval
 - Mepolizumab**
 - Severe eosinophilic asthma ≥12 yrs
 - Eosinophilic granulomatosis with polyangiitis
 - Reslizumab**
 - Severe eosinophilic asthma ≥18 yrs
 - Benralizumab**
 - Severe eosinophilic asthma ≥12 yr
- Two proof of concept study in CRS with nasal polyps – mepolizumab and reslizumab

Reslizumab in CRSwNP

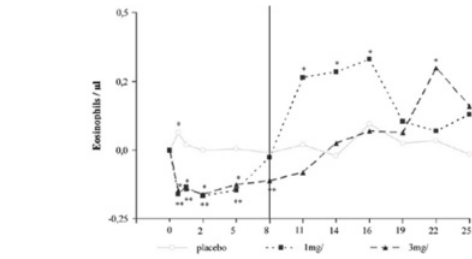


Gevaert et al. JACI 2006;118:1133

Total Polyp Score



Decrease in Blood Eosinophils

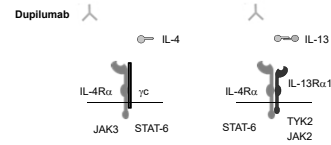


Dexrampipexole depletes blood and tissue eosinophils without decrease in polyps

- 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)

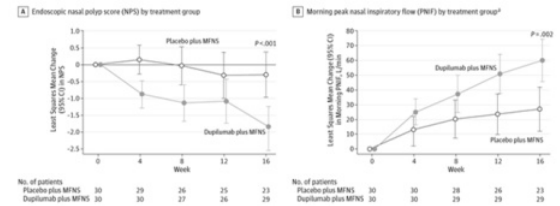
- Fully-human monoclonal antibody directed against IL-4R α subunit which inhibits signaling of both IL-4 and IL-13



Anti-IL-4R (Dupilumab)

- 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

Anti-IL-4R (Dupilumab) in CRSwNP



Bachert et al. JAMA 2016;315:469

Phase 3 Trial in Severe CRSwNP – TPS ≥ 5

- Placebo
- Dupilumab 300 mg Q2 wks
- Dupilumab 300 mg Q2 wks | Dupilumab 300 mg Q4 wks
- Dupilumab 300 mg Q2 wks

Primary endpoints
 Total polyp score change at 24 weeks
 Nasal congestion change at 24 weeks

Nasal polyp score scale



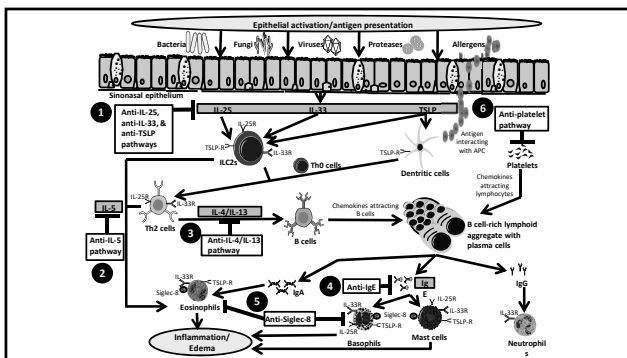
Polyp score	Polyp Size
0	No polyps
1	Polyps within the middle meatus
2	Polyps reaching below the lower border of middle turbinate
3	Polyps reaching lower border of inferior turbinate
4	Polyps touching nasal floor

Summary of Effect on Total Polyp Score

Methylprednisolone 3 week taper	Omalizumab 16 weeks	Mepolizumab 8 weeks (2 doses)	Dupilumab 24 weeks
-2.3	-2.3	-1.2	-2.3

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