EPOS2020 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

• Total CRS	20,000,000
• Total CRSsNP	16,000,000
• Total CRSwNP	4,000,000

• AERD	400,000
• AFS	500,000
• Cystic Fibrosis	30,000
• Autoimmune (GPA, EGPA)	10,000
• Kartagener's syndrome	7000

Age: CRS Phenotypes

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

CRS phenotypes

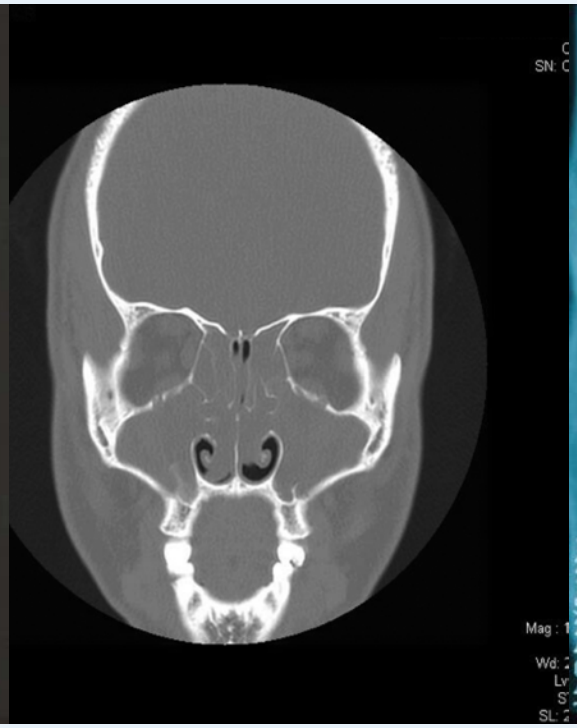
- Not usually very helpful in terms of patient counseling
- Not very helpful in terms of guiding treatment
- **Research into causes of CRS for 20+yrs to make treatment more precise**

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

Environment

- Fungal hypothesis
- Superantigen hypothesis
- Biofilm hypothesis
- Microbiome hypothesis
- Allergy

Host

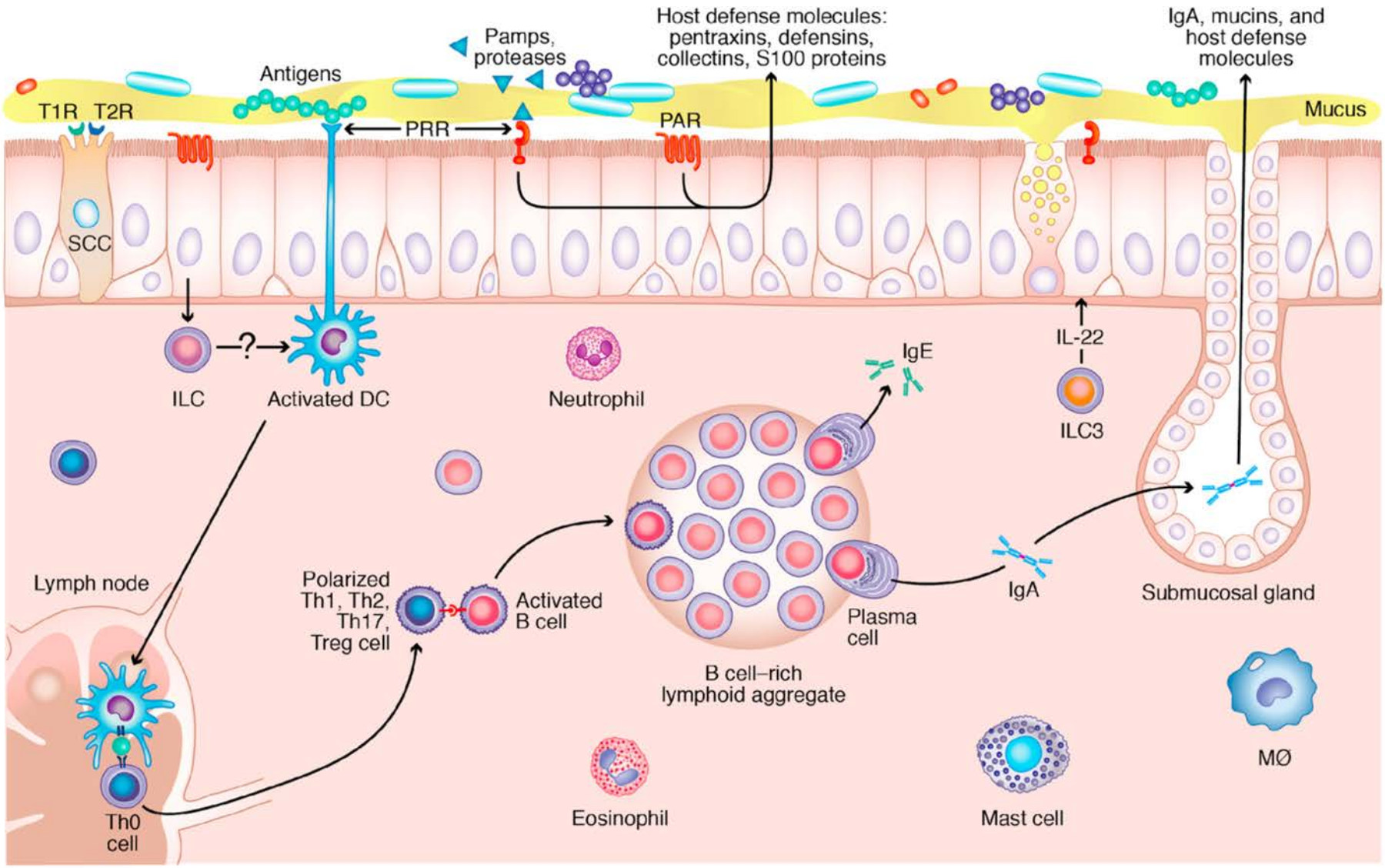
- Eicosanoid hypothesis
- **Immune barrier hypothesis**

- EPOS 2012
- Lam et al., 2015

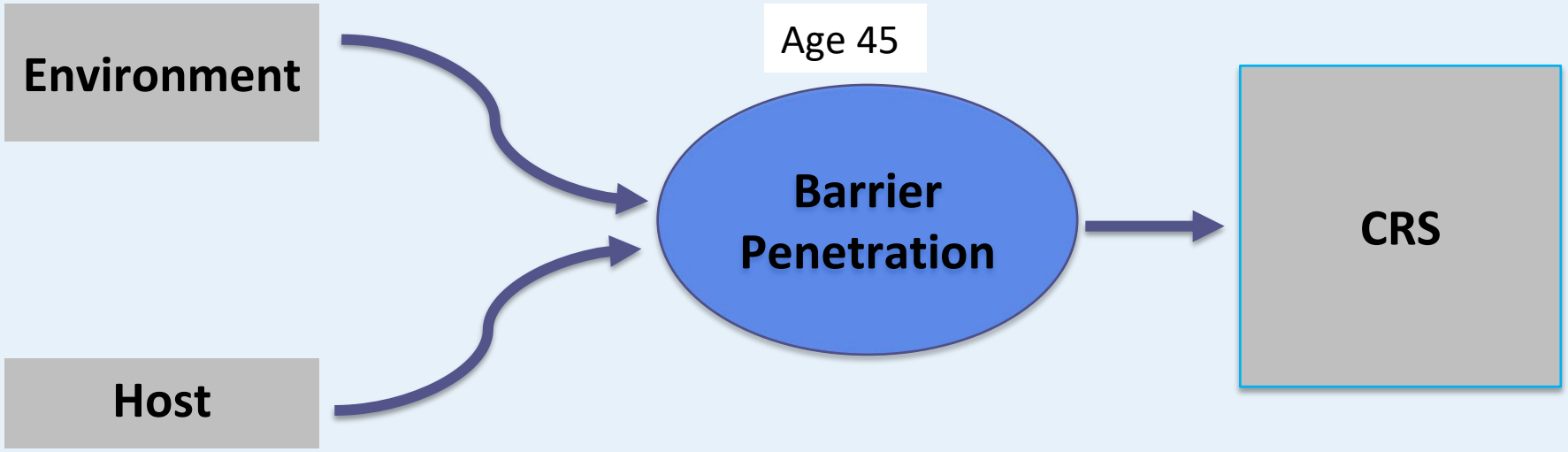
Nasal and Sinus Mucosa

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

Overview

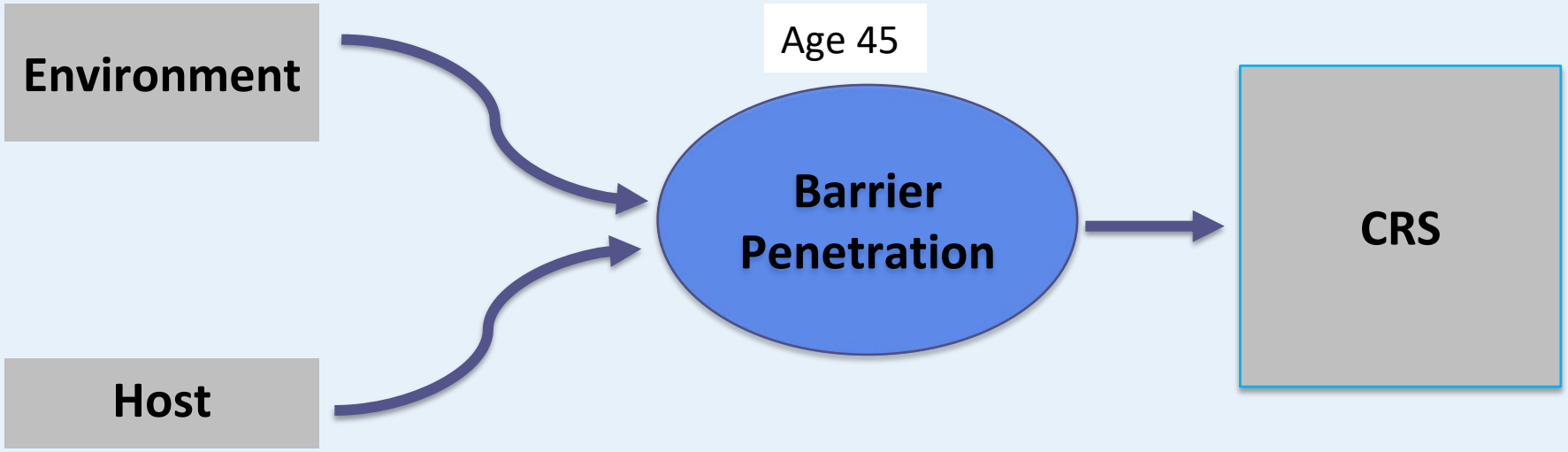

Host defense molecules:
pentraxins, defensins,
collectins, S100 proteins
IgA, mucins, and
host defense
molecules
Pamps,
proteases
Antigens
T1R T2R
PRR
PAR
Mucus
SCC
ILC
?
Activated DC
Neutrophil
IgE
IL-22
ILC3
Lymph node
Polarized
Th1, Th2,
Th17,
Treg cell
Activated
B cell
B cell–rich
lymphoid aggregate
Plasma
cell
IgA
Submucosal gland
Th0
cell
Eosinophil
Mast cell
MØ

CRS Etiology and Pathogenesis



- Host and Environment interact for 40+ years and then barrier is penetrated resulting in CRS
- With self perpetuating inflammation

CRS Etiology and Pathogenesis



- Typically, adult onset disorder
- Early 40's CRSsNP; Late 40's CRSwNP

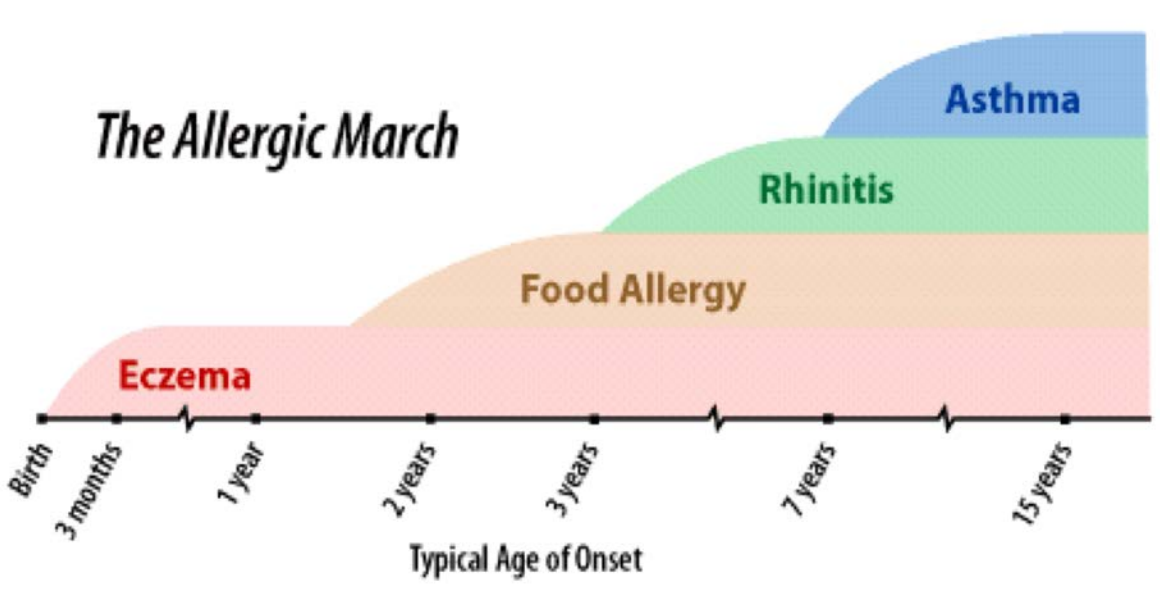
Nasal and Sinus Mucosa

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

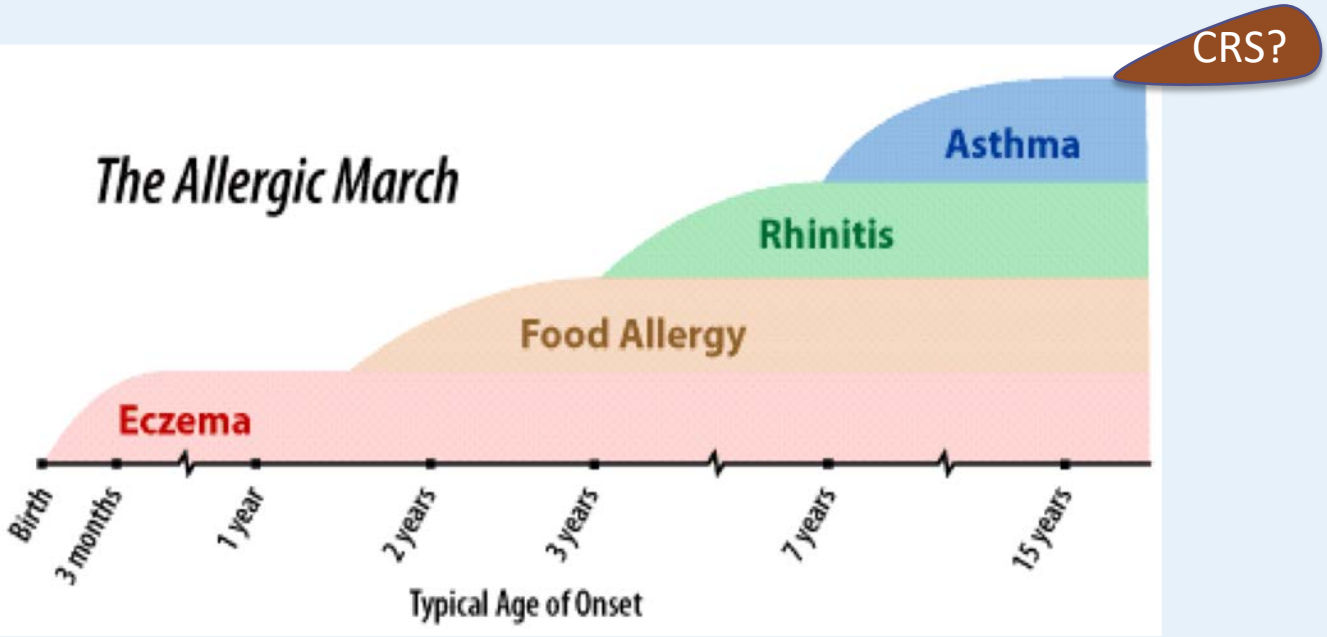
- Early life exposure protective; Hygiene Hypothesis
  - Strachan, *BJM*, 1989
- Gut/airway axis
  - Von Mutius, *JACI* 2016
  - Lynch and Boushey, *Curr Opin Allergy Clin Immunol*., 2016

- **SCFA,** other compounds-protective!

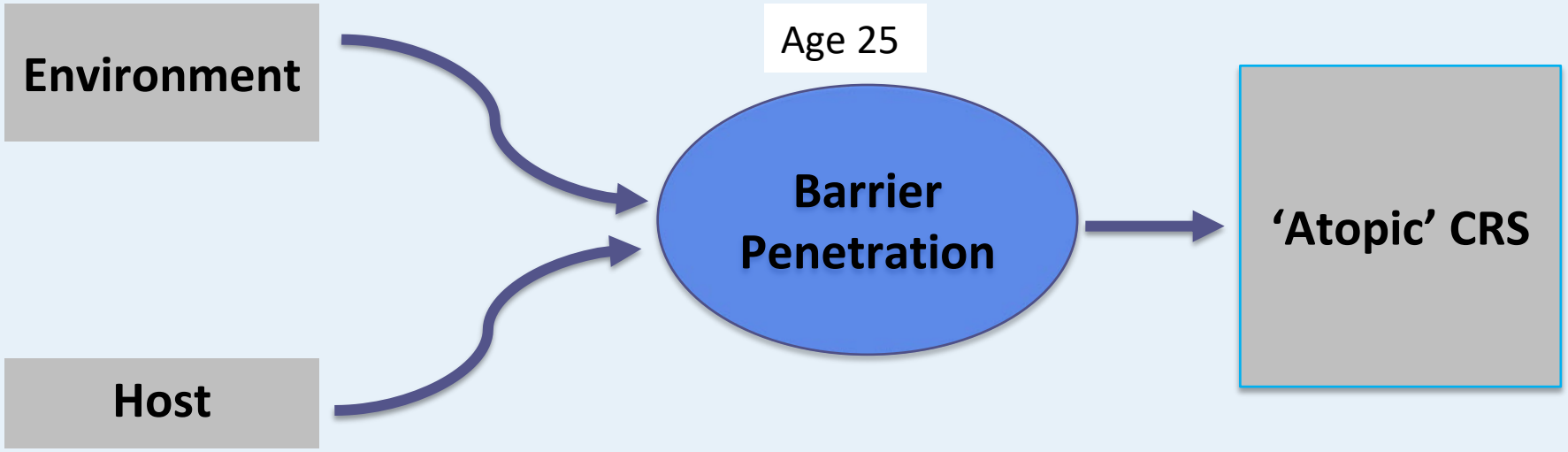
Atopic March



Early onset Atopic CRS?

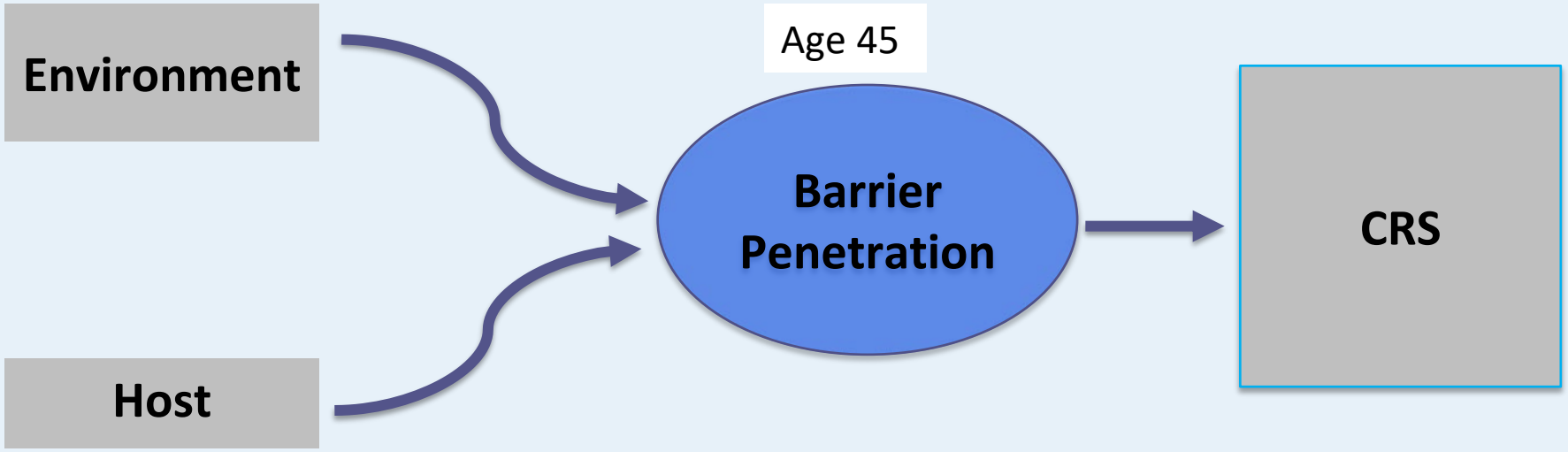


Early Onset CRS Phenotype?



- Milder, atopic, progression of childhood disease
- CRSsNP typically
- Mild asthma or childhood asthma

CRS Etiology and Pathogenesis



- 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

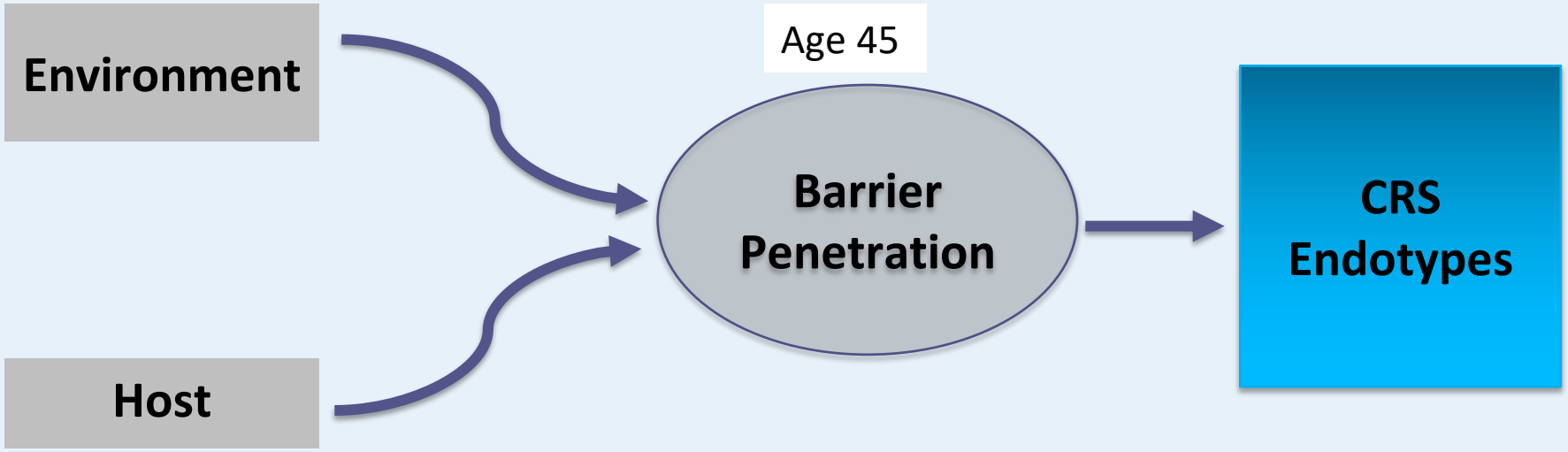
Host vs. Environment in CRS

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

Can we know in an individual patient?

Would it matter?

CRS Etiology and Pathogenesis



- Etiologic factors vary so…..the inflammation not the same in all CRS patients: **ENDOTYPES-mechanistic pathways, types/patterns**

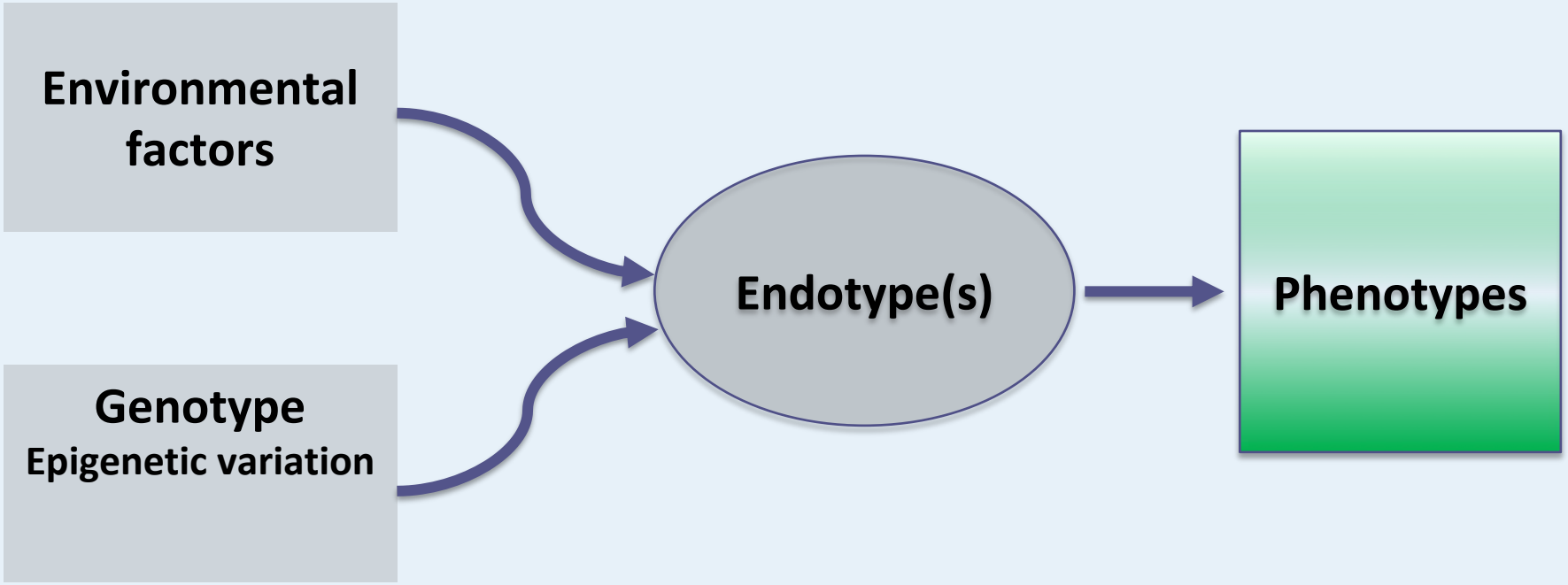
Personalized Medicine

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

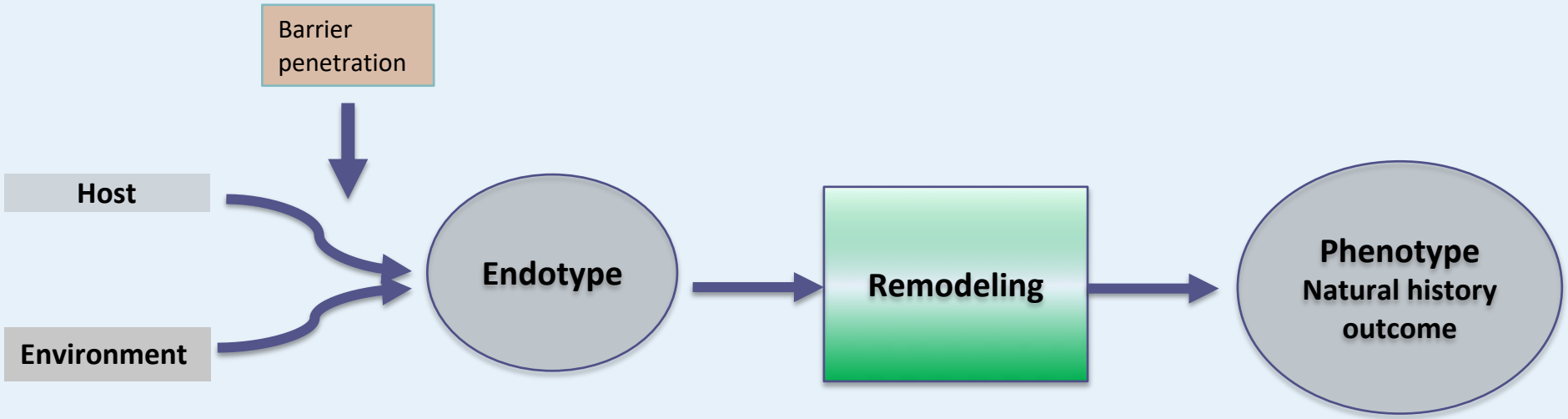
Chronic Rhinosinusitis

- **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

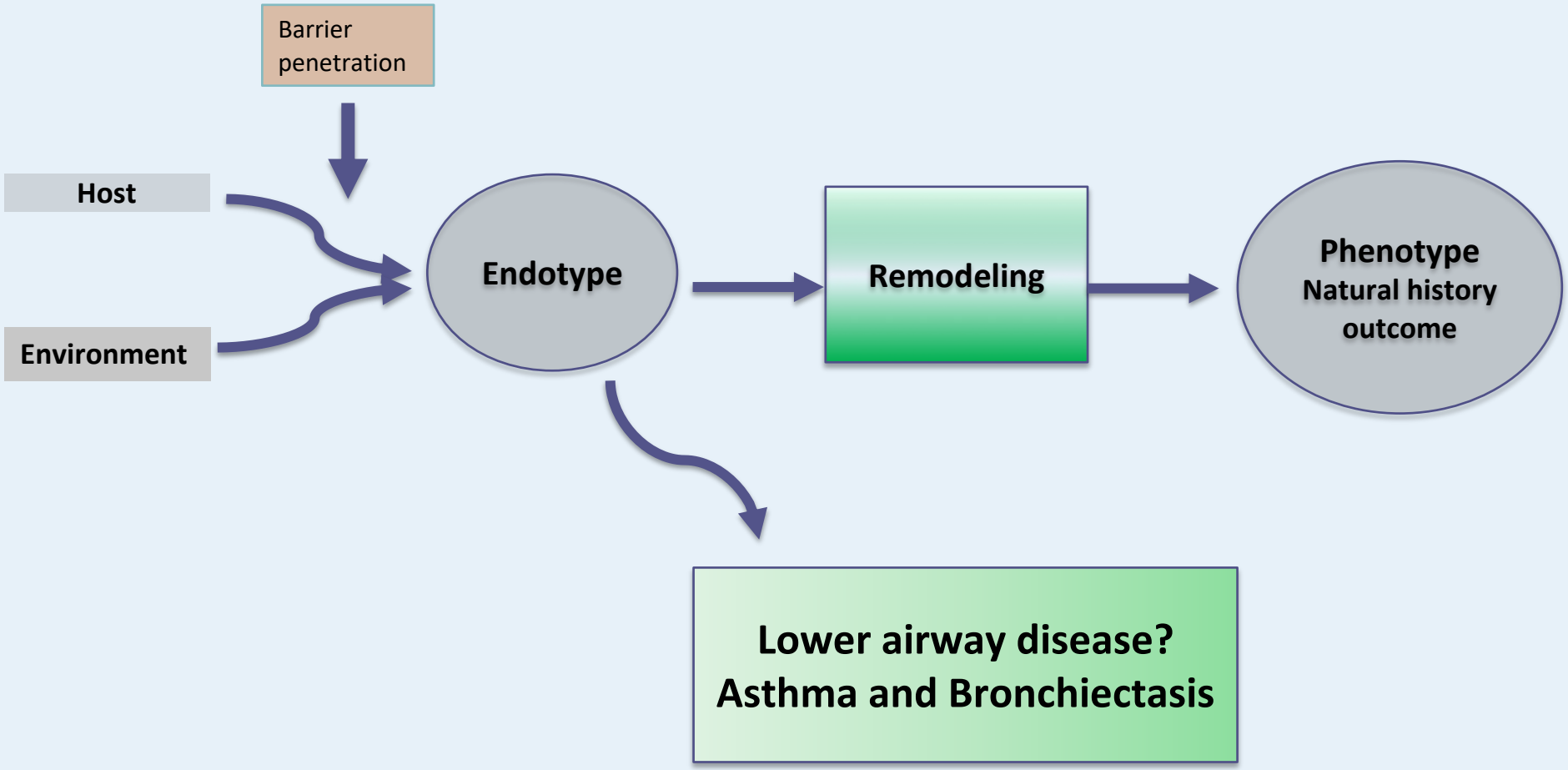
Etiology and Pathogenesis of CRS



Etiology and Pathogenesis of CRS



Etiology and Pathogenesis of CRS



Endotypes of CRS

- **Endotypes**: mechanistic pathway
- ***What are the endotypes of CRS?***
- ***How can they help guide treatment?***

Cluster	N	N/total	MPO (ng/mL)	IL-8 (pg/mL)	IL-6 (pg/mL)	IL-1b (pg/mL)	Albumin (mg/dL)	IL-5 (pg/mL)	IL-5 (ratio pos.)	ECP (µg/L)	IgE (kU/L)	SE-IgE (kUA/L)	SE-IgE (ratio pos.)	TGF-b1 (pg/mL)	IL-17 (pg/mL)	IL-17 (ratio pos.)	TNF-a (pg/mL)	TNF-a (ratio pos.)	IL-22 (pg/mL)	IFN-g (pg/mL)	IFN-g (ratio pos.)	prop. CRSwNP	prop. asthma	prop. allergy
1	27	16%	973	956	30	24	65	1	0%	407	20	1.29	7%	17853	0.1	0%	0.8	0%	307	43	0%	11%	15%	42%
2	17	10%	1299	442	5	14	54	1	0%	284	13	1.01	0%	13676	0.1	0%	5.4	100%	463*	48	12%	0%	7%	63%
3	16	9%	2714	2908	91	69	70	2	0%	498	28	1.18	6%	17111	0.1	13%	1.2	19%	311	213	100%	13%	14%	50%
4	15	9%	4582	6614	191	230	77	0	0%	601	16	1.01	0%	10598	36.9	100%	10.3	80%	493*	57	27%	47%	20%	40%
5	27	16%	1997	1964	79	21	104	109	100%	4333	122	1.01	0%	16055	0.1	4%	0.8	0%	335	43	0%	59%	27%	50%
6	11	6%	2096	2956	204	55	82	100	100%	7631	170	1.70	18%	21428	0.1	0%	1.1	9%	303	325	100%	64%	36%	45%
7	28	16%	2355	1711	108	29	112	151	100%	3690	148	1.06	4%	17489	0.1	0%	8.2	100%	457*	55	14%	64%	37%	37%
8	14	8%	4621	4777	487	114	168	406	100%	5588	154	1.01	0%	6790	10.7	100%	17.0	100%	349*	58	29%	93%	38%	23%
9	11	6%	3464	4916	184	52	167	483	100%	5626	1038	6.33	100%	13131	2.0	73%	18.5	100%	633	57	18%	91%	64%	82%
10	7	4%	4827	4806	637	59	133	257	100%	14143	988	5.69	100%	12380	0.1	0%	1.4	14%	237	43	0%	100%	71%	57%

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

Journal of Allergy and Clinical Immunology 2016 137, 1449-1456.e4DOI: (10.1016/j.jaci.2015.12.1324)
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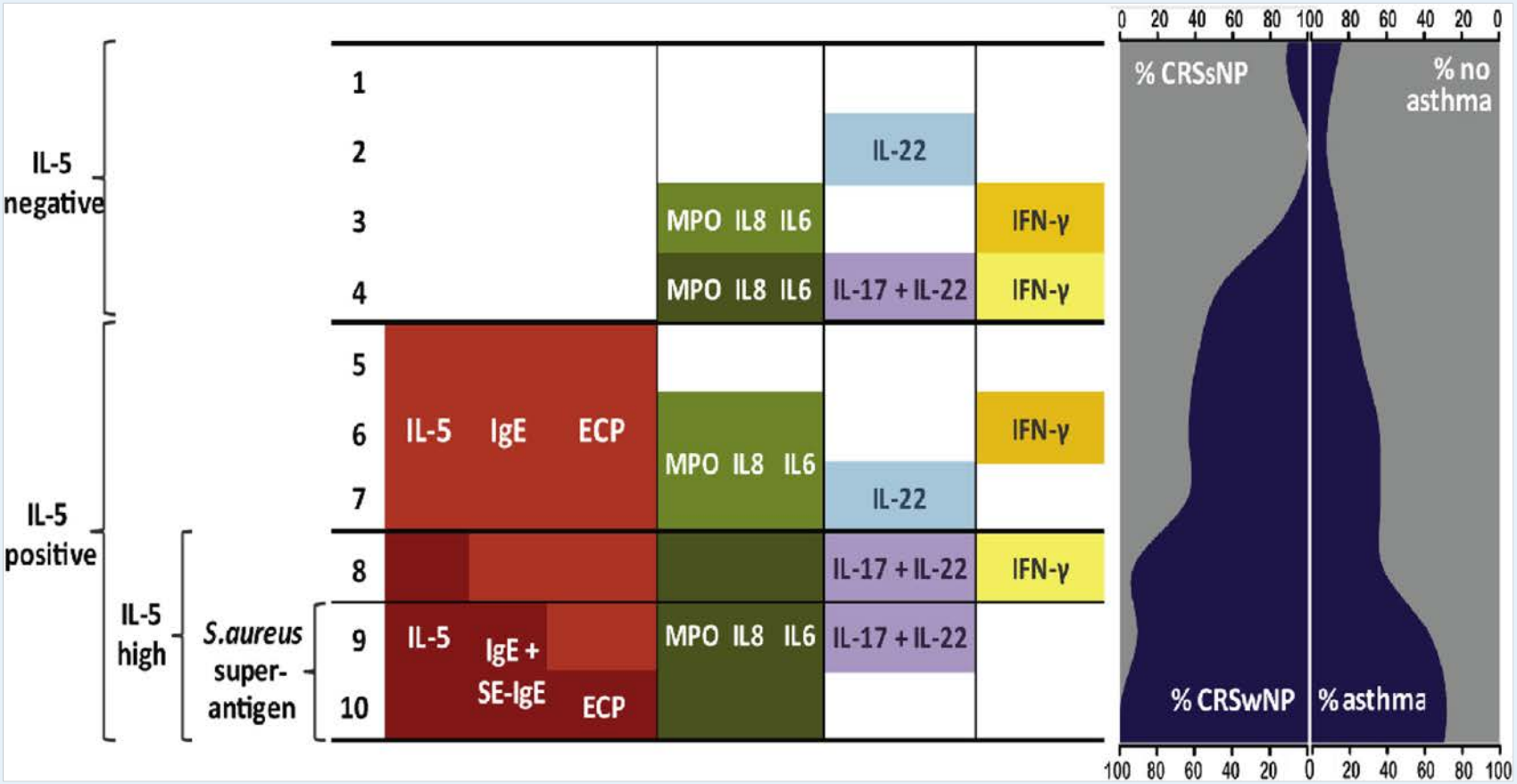
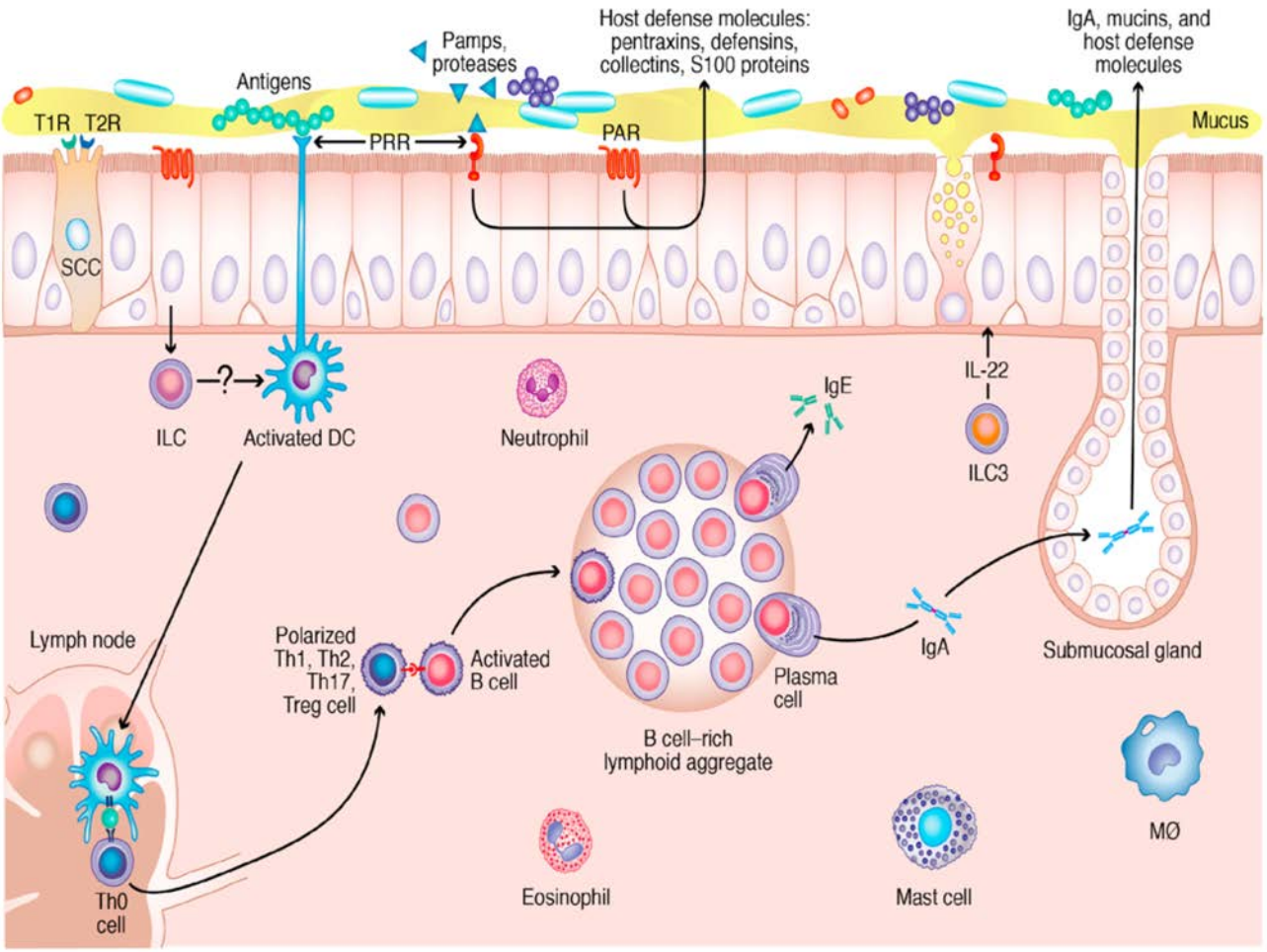
Endotyping CRS



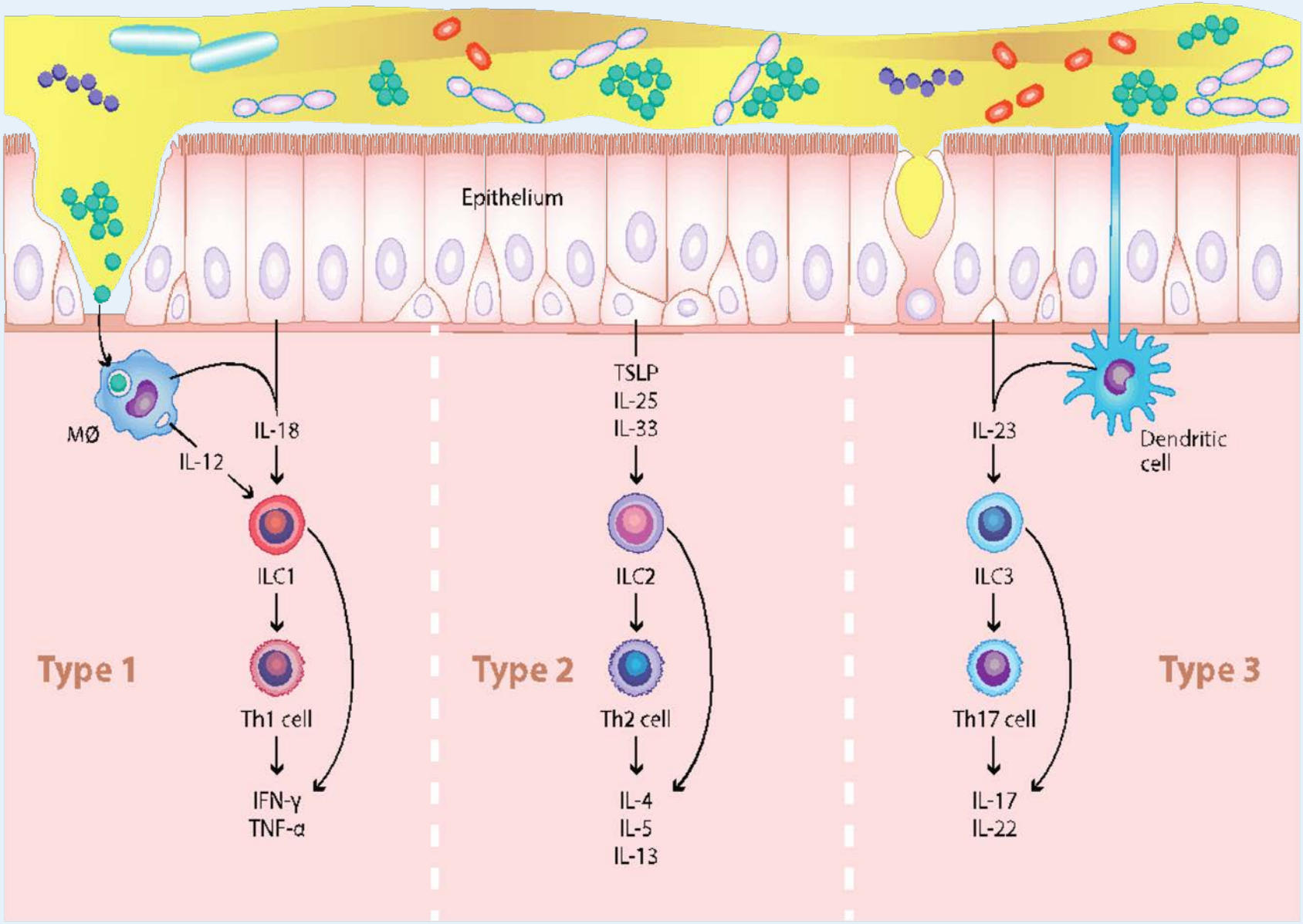
Tomassen et al., 2016

Sinonasal Immunity

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** → Type 1 inflammation; Th1

  Viruses, Intracellular organisms

- **ILC2** → Type 2 inflammation; Th2

  Parasites, **REPAIR**

- **ILC3** →Type 3 inflammation; Th17

  Extracellular organisms

Mucosal Immunity

- **ILC1** → Cytotoxic T cells, NK cells and neutrophils
- **ILC2** → Eosinophils, mast cells, B cells and neutrophils
- **ILC3** → Neutrophils

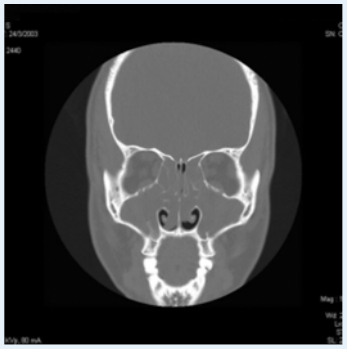
CRS Endotypes

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

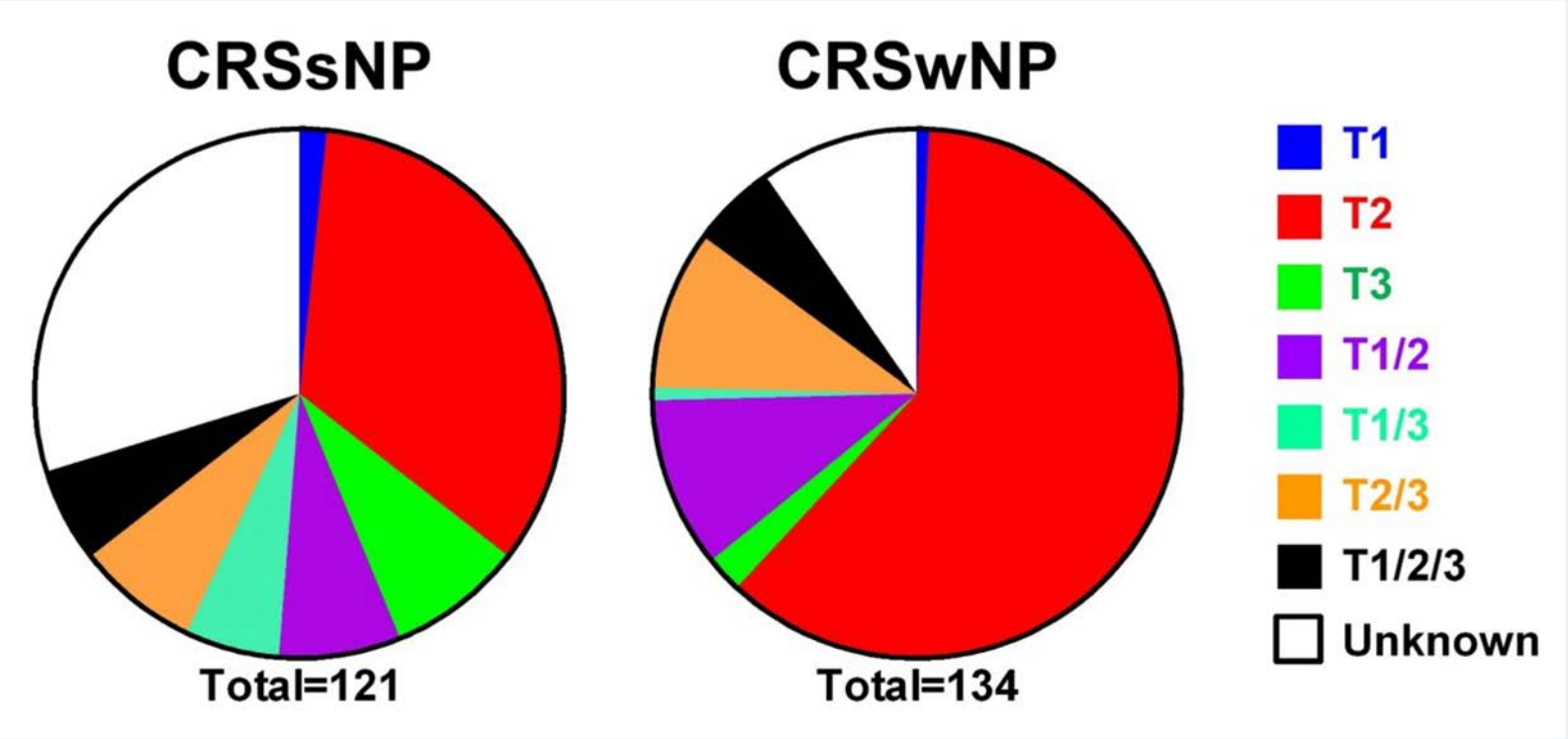
- *So we can determine tissue patterns based on markers of Type 1, 2 and 3 inflammation in the tissue*

CRS Endotype Patterns

- **T1**
- **T2**
- **T3**
- **T1,2**
- **T1,3**
- **T2,3**
- **T1,2 and 3**
- **Non typeable**



Inflammatory endotypes in CRS



T1sNP: total 21%

T2sNP: total 55%

T3sNP: total 27%

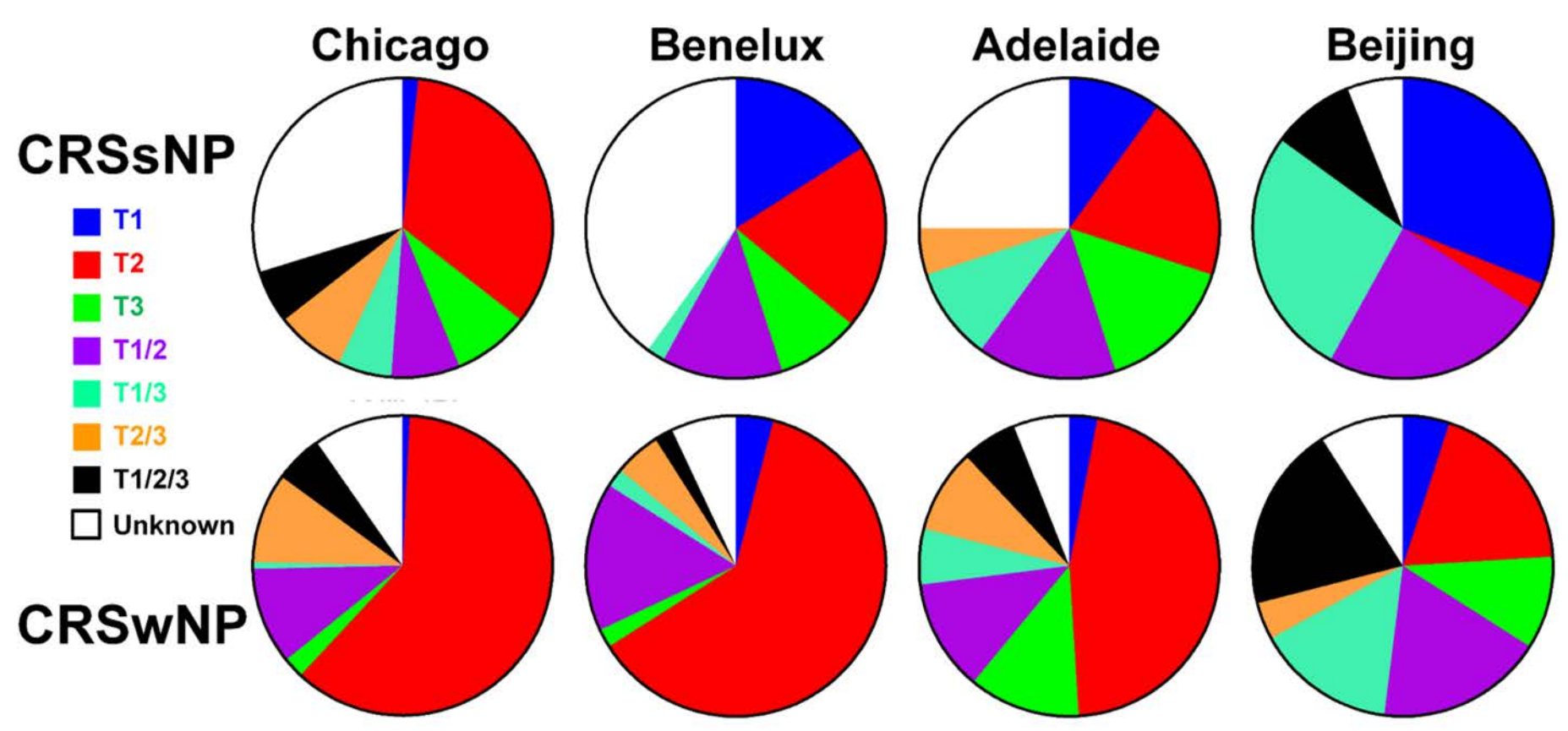
T1wNP: total 17%

T2wNP: total 87%

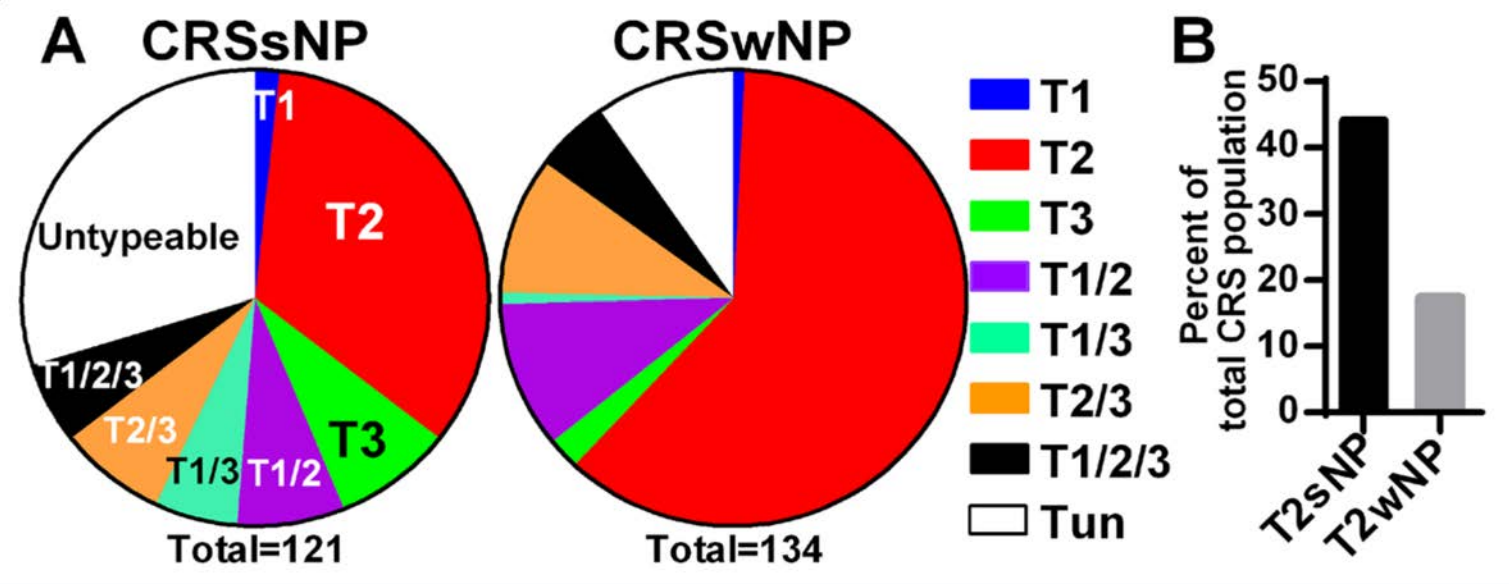
T3wNP: total 18%

Kato A et al., unpublished. 2018 (updated)

Similar inflammatory patterns in CRS are reported in Europe



Kato A et al., unpublished. 2018 (updated)
Wang X and Bachert C al., *J Allergy Clin Immunol.* 2016



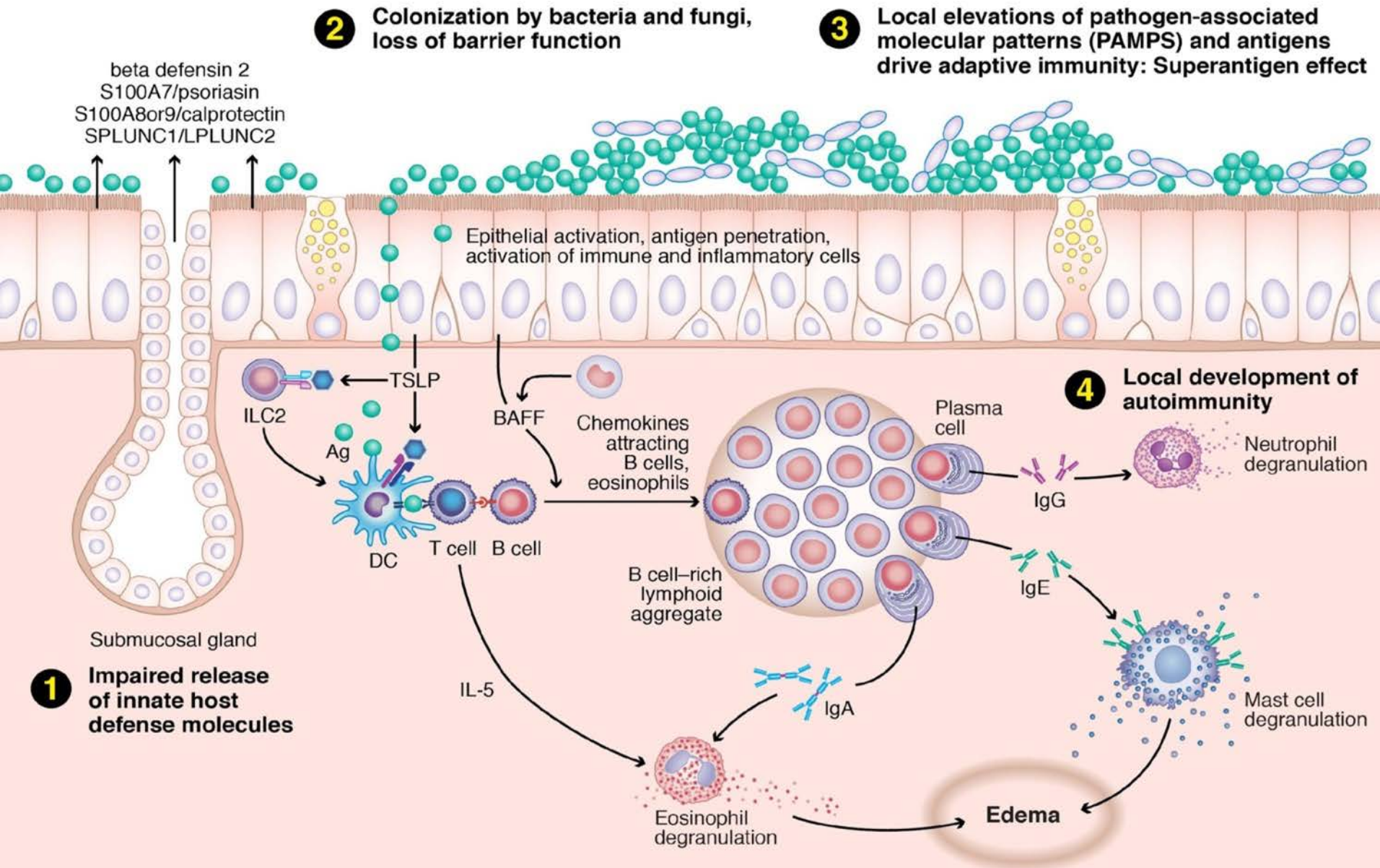
60+% of CRS in Chicago is T2

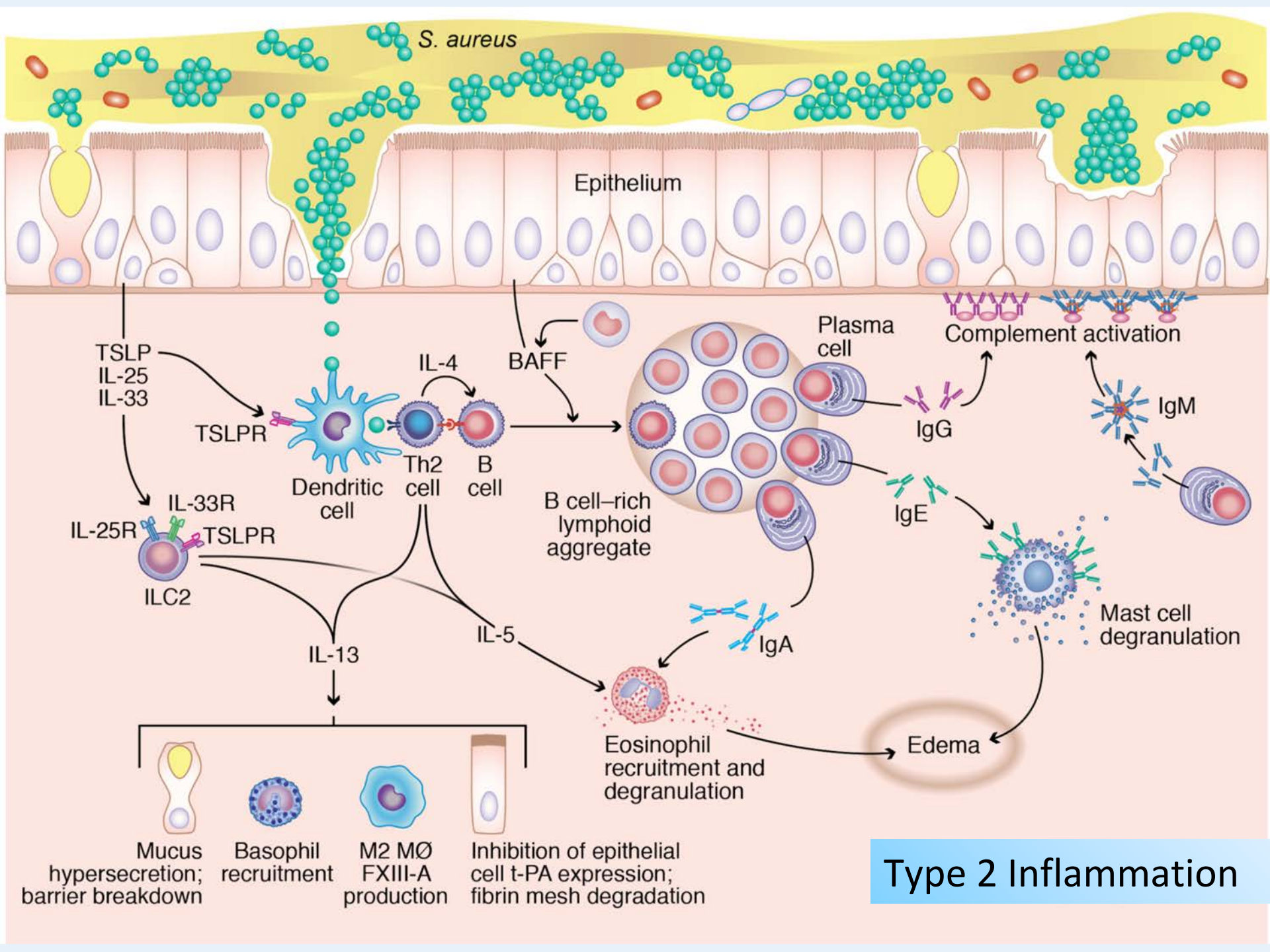
Type 2 Inflammation

- Associated with treatment failure
- Asthma
- Eosinophilia

- **Higher rate of polyp formation**

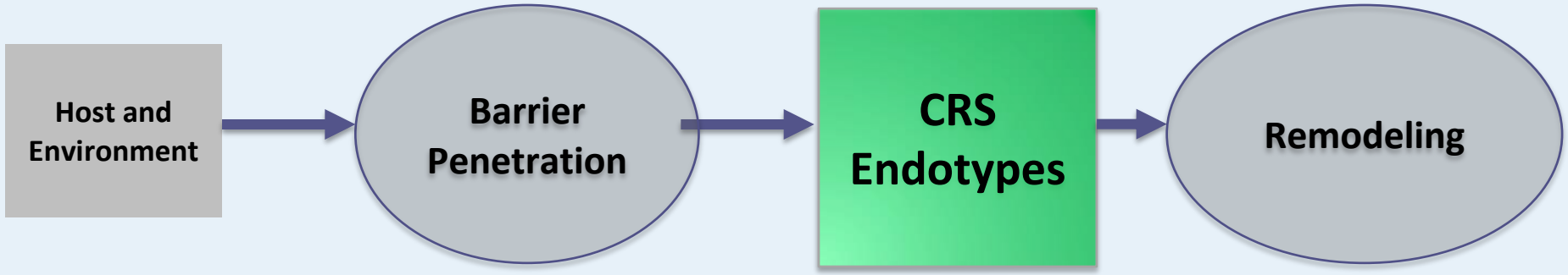
TYPE 2 Inflammation





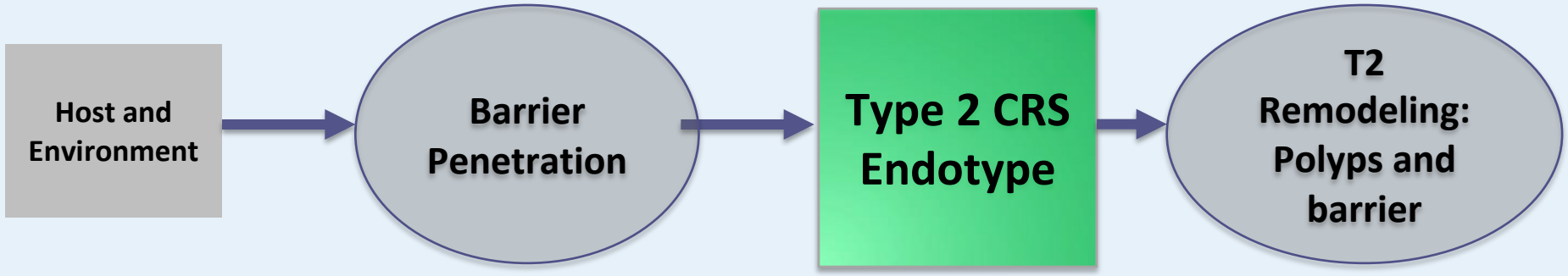
Type 2 Inflammation

Endotype Drives Remodeling



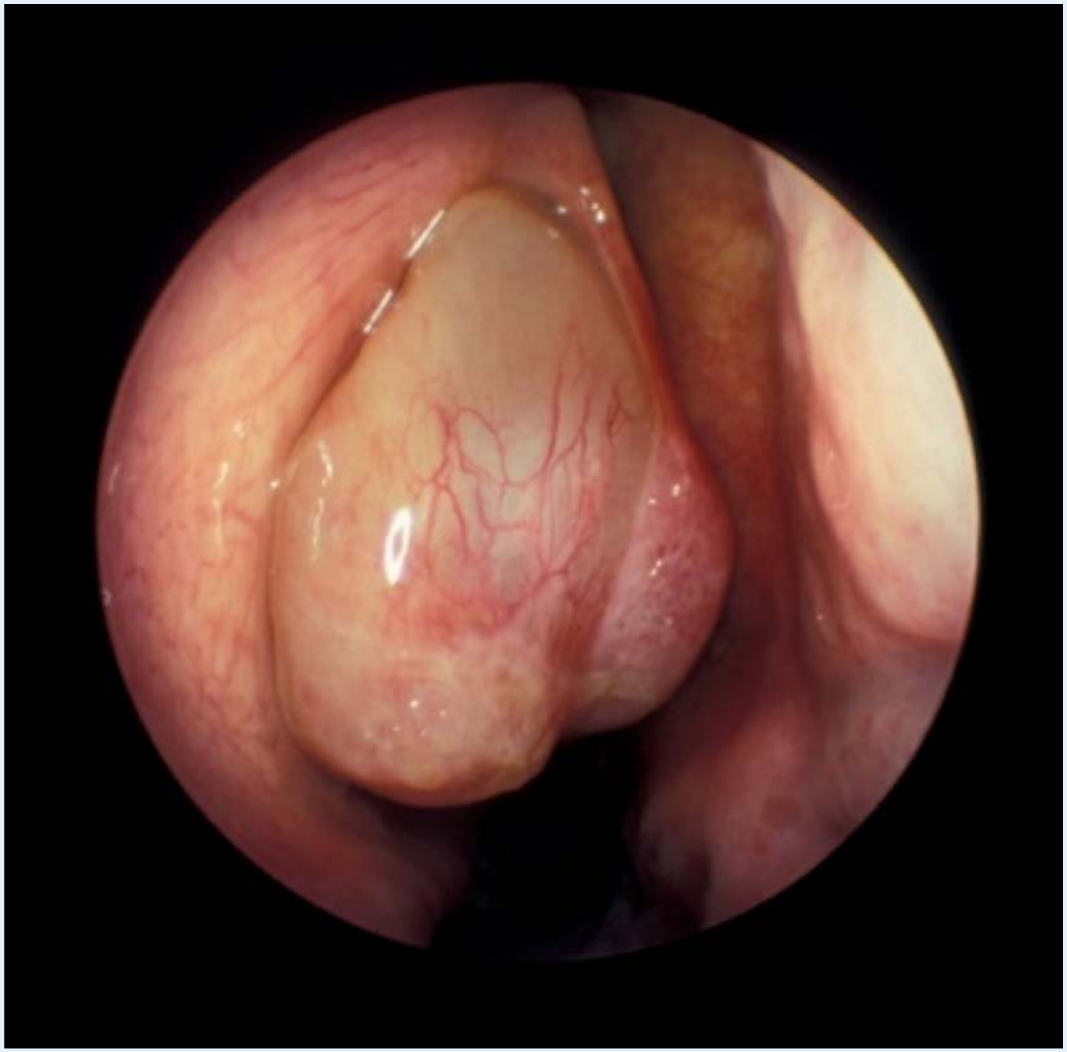
- *Remodeling includes polyp formation, barrier changes, fibrosis, glandular hypertrophy*

Type 2 CRS



- *<u>Polyps</u> and <u>barrier damage</u> are remodeling changes secondary to the Type 2 inflammation*

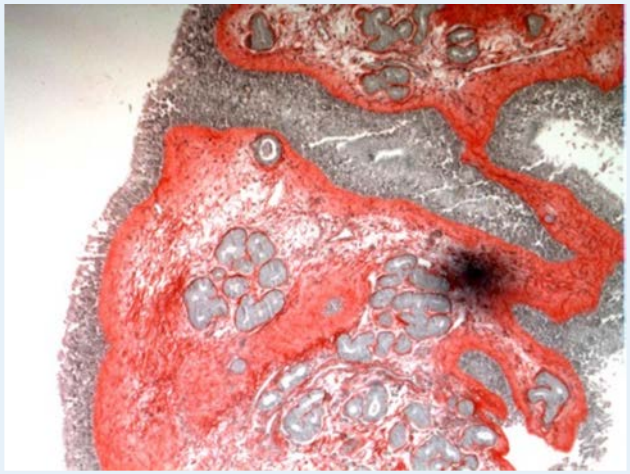
Nasal Polyp



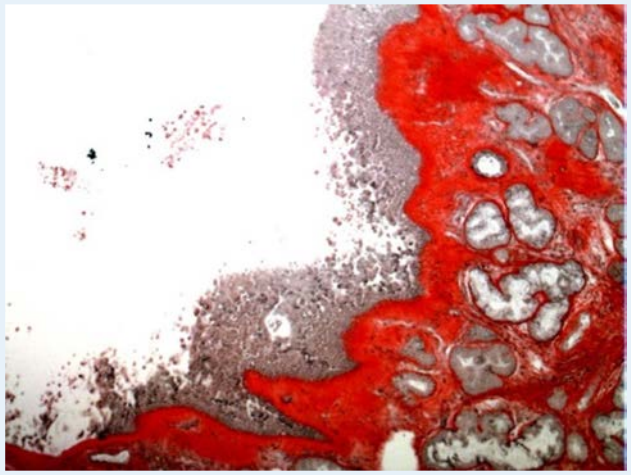
What are Polyps?

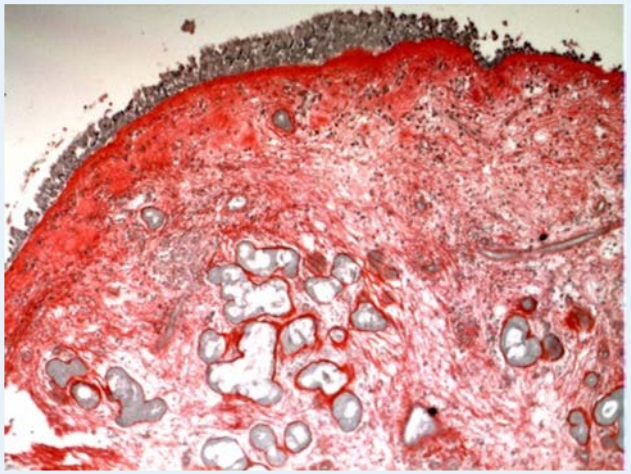
Picrosirius Red

Control UT

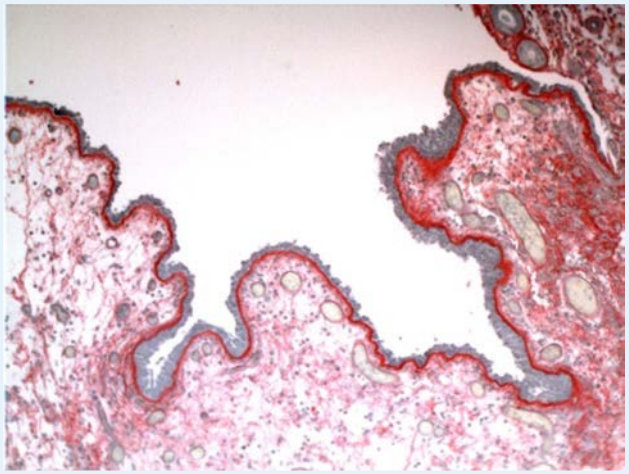


CRSsNP UT





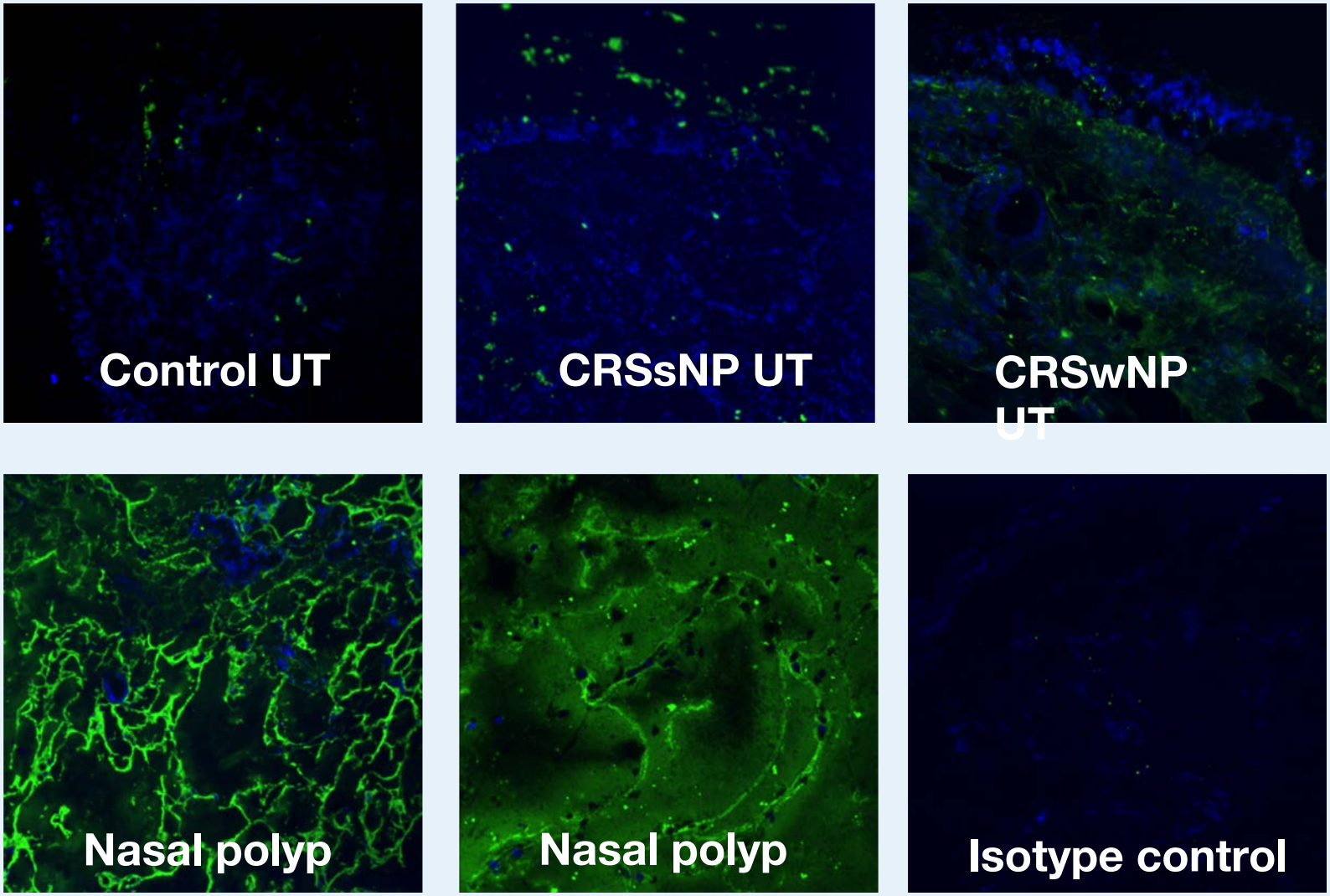
CRSwNP UT



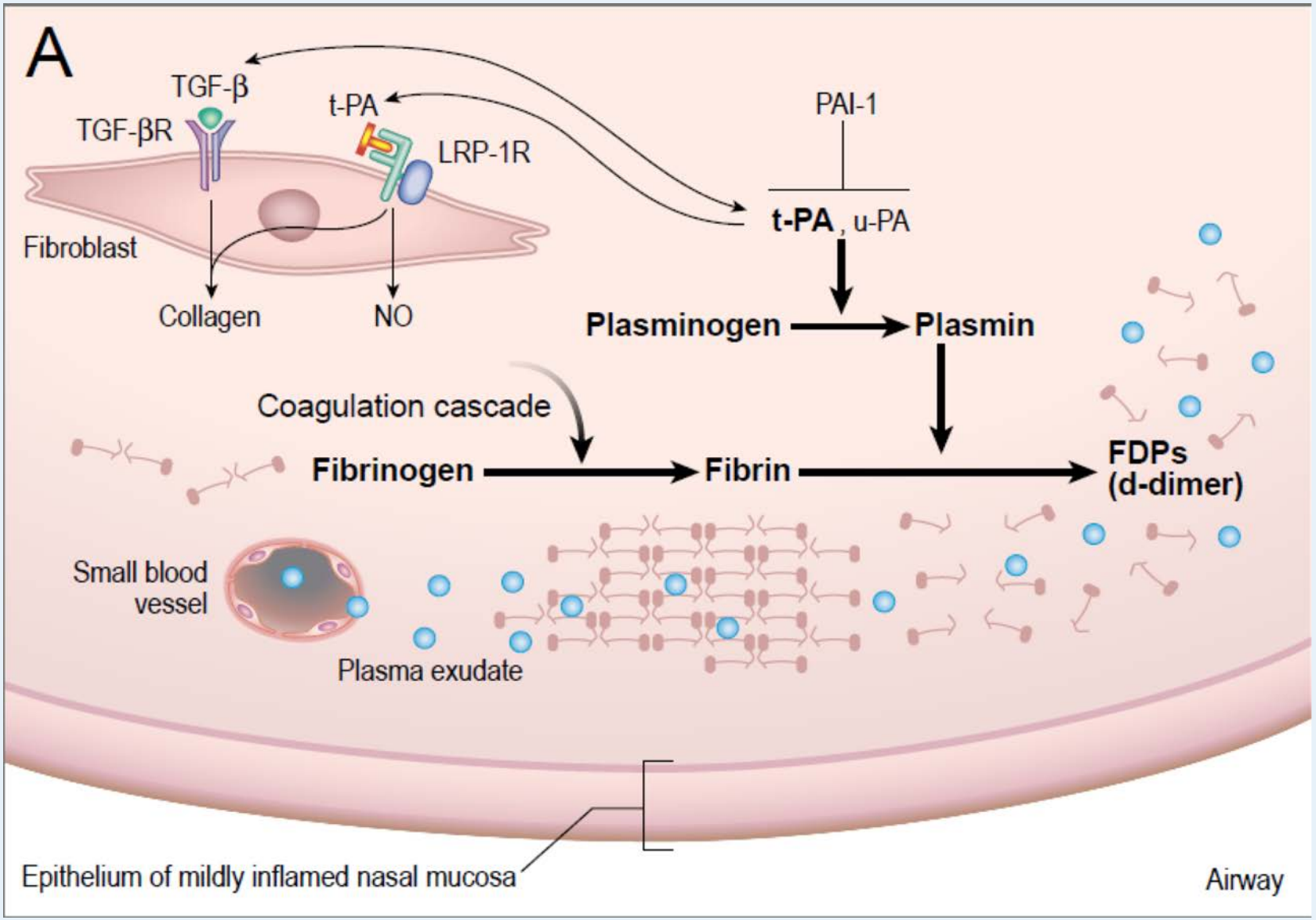
Nasal polyp

Takabayashi et al., Am. J. Resp. Crit. Care Med., 187:49, 2013

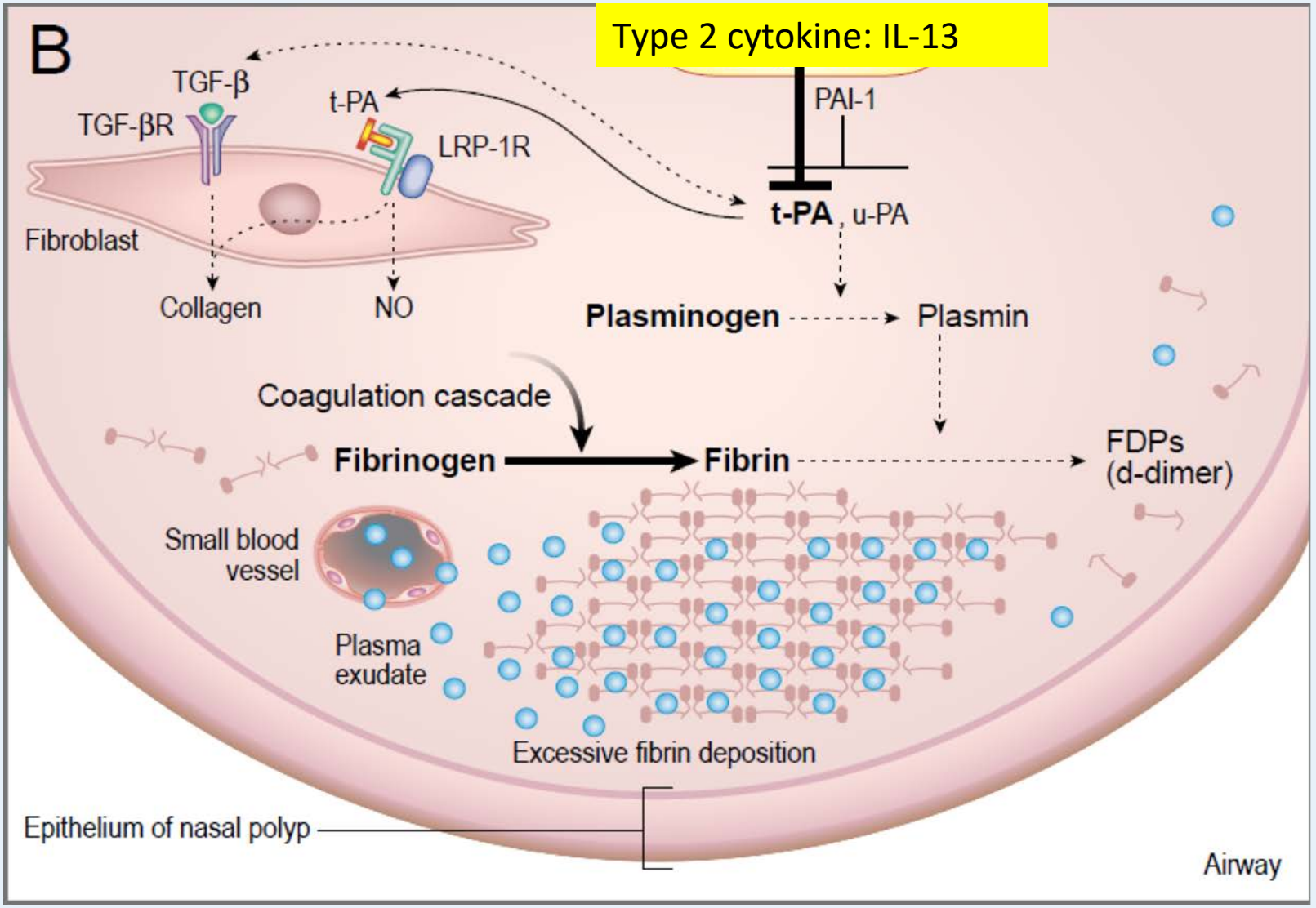
Fibrin deposition in nasal polyps in CRS



Takabayashi et al., Am. J. Resp. Crit. Care Med., 187:49, 2013

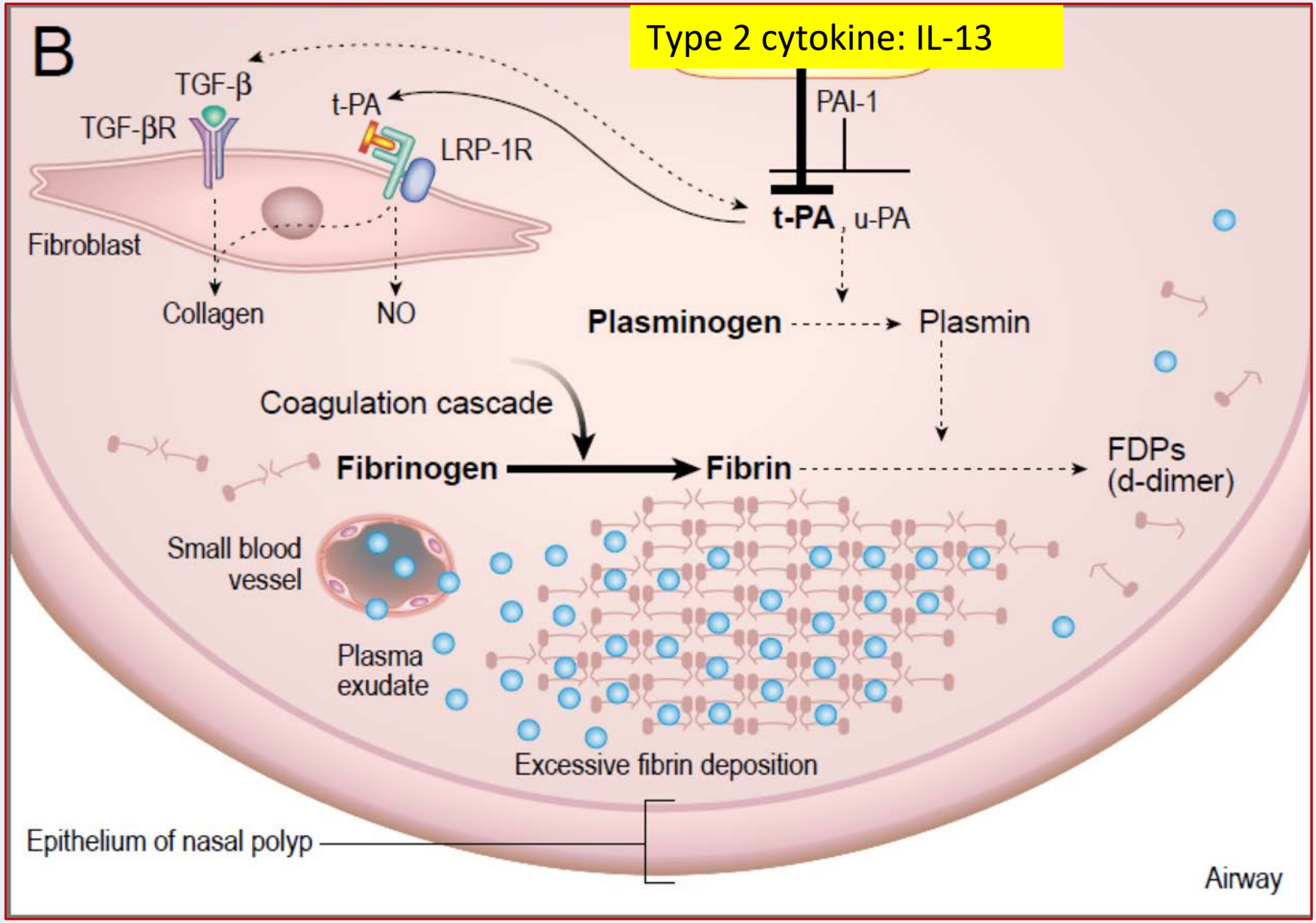


Professor Shimizu from Shiga University first suggested importance of coagulation cascade and polyps

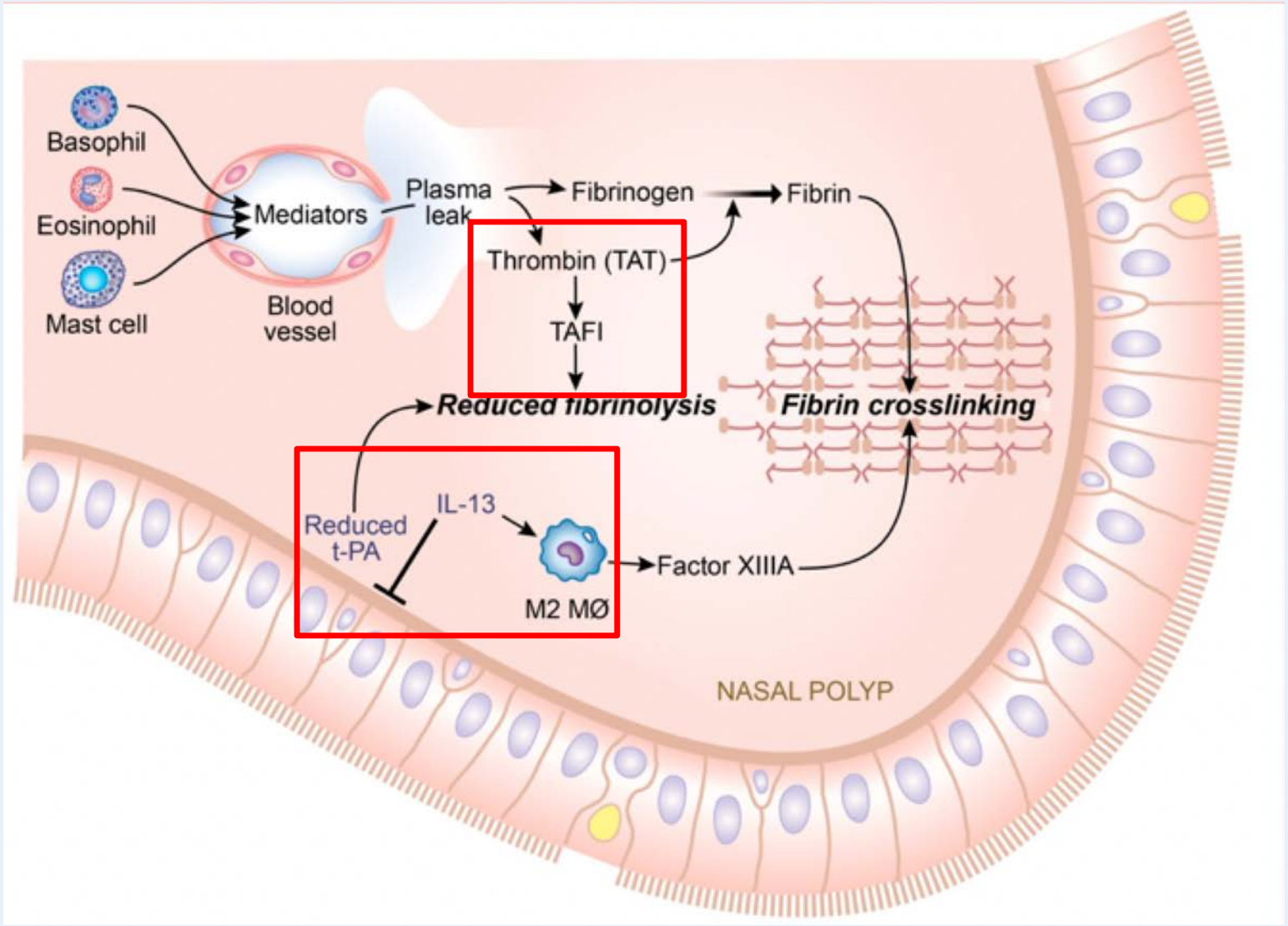


Takabayashi et. al., Am J RCCM, 2013

Tissue TPA levels vary!

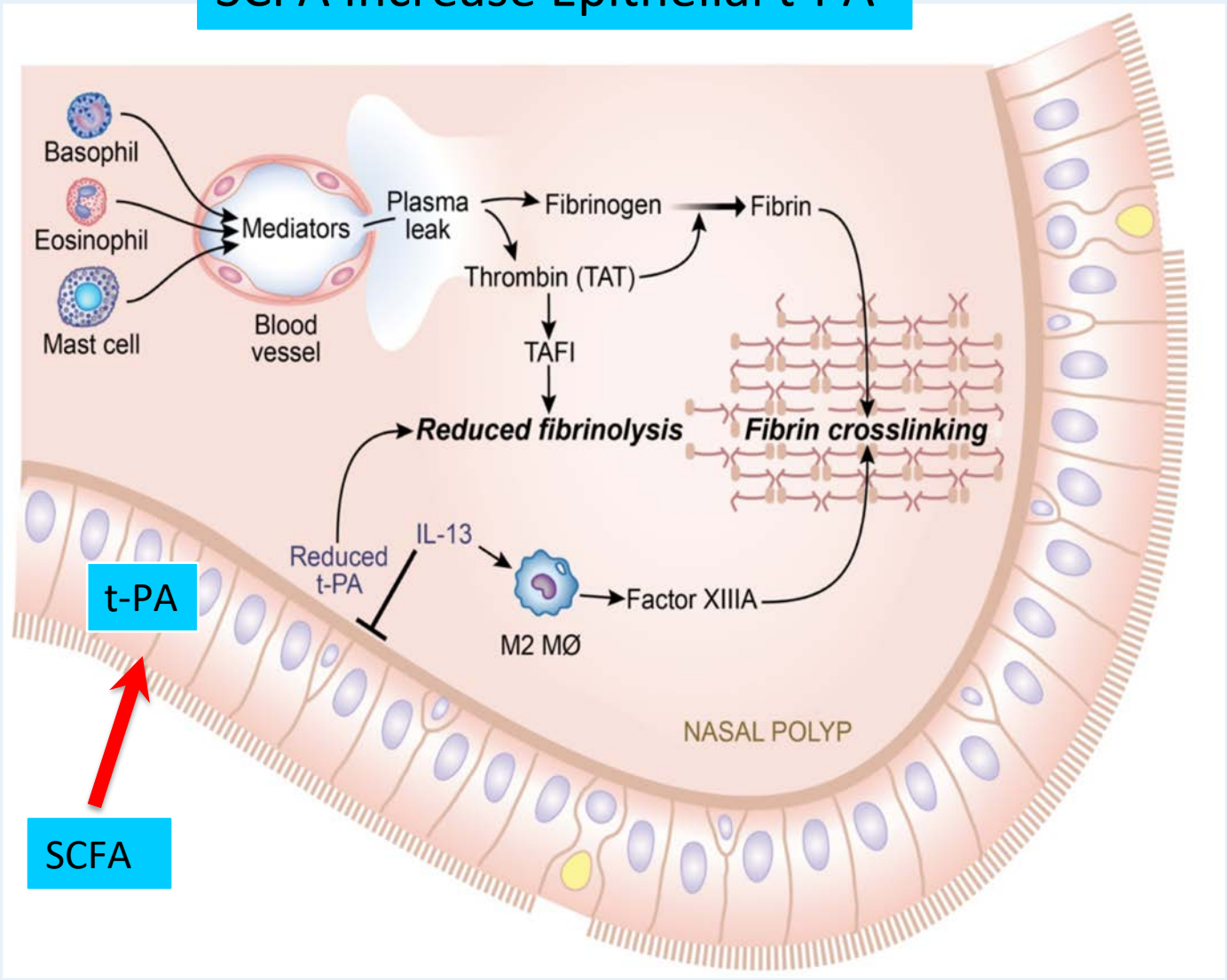


Regulation of pathways of fibrin deposition by IL-13



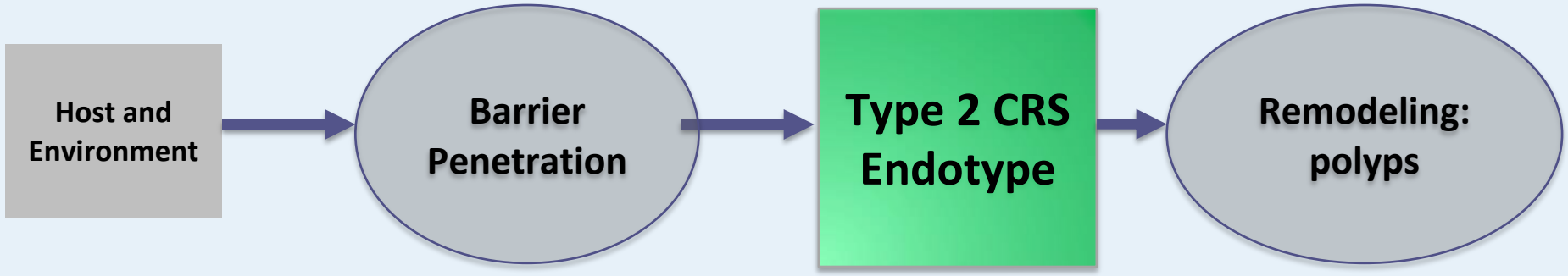
Imoto et al., JACI, in press 2019

SCFA Increase Epithelial t-PA



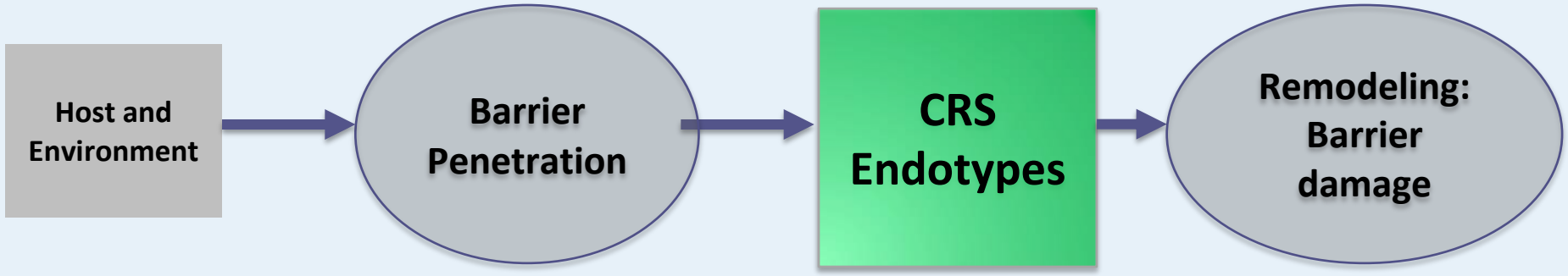
Imoto, Kato, Takabayashi, Sakashita et al., Clin Exp Allergy, 2018

Type 2 Remodeling: Polyps



- *Type 2 Polyp formation is the results of fibrin crosslinking when t-PA is suppressed by sufficient IL-13*

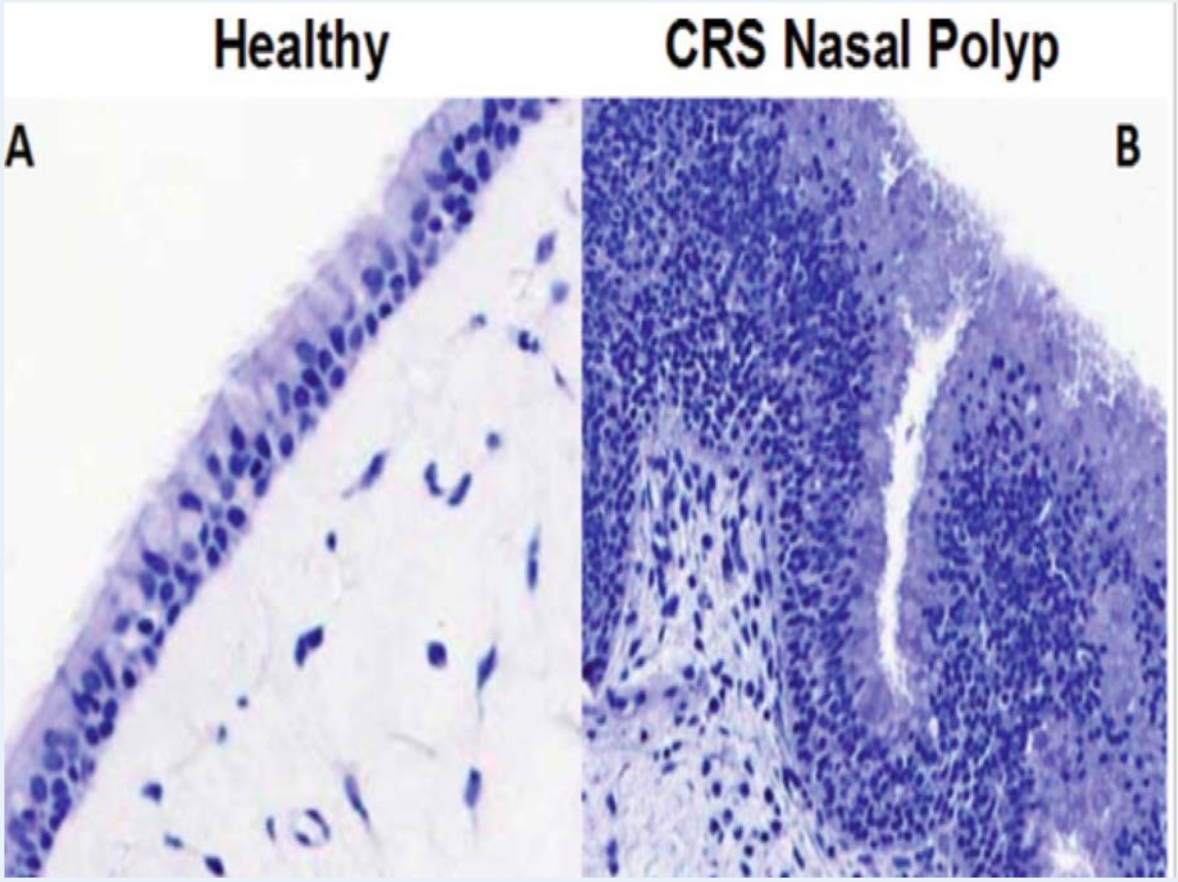
Type 2 Remodeling: Barrier Damage



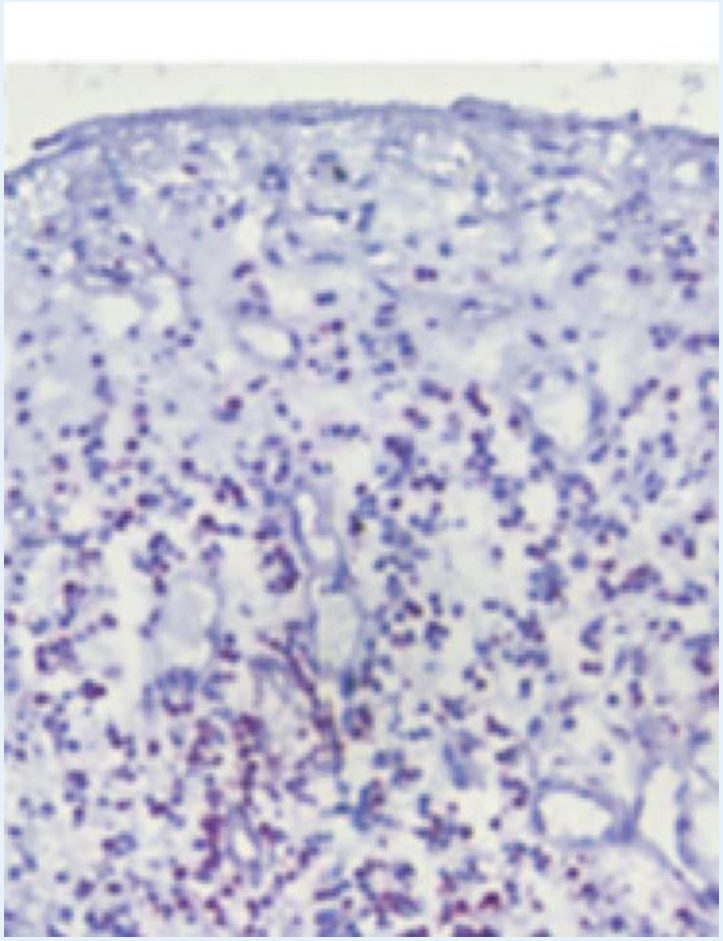
- *Barrier damage is also a type of remodeling seen with Type 2 inflammation*

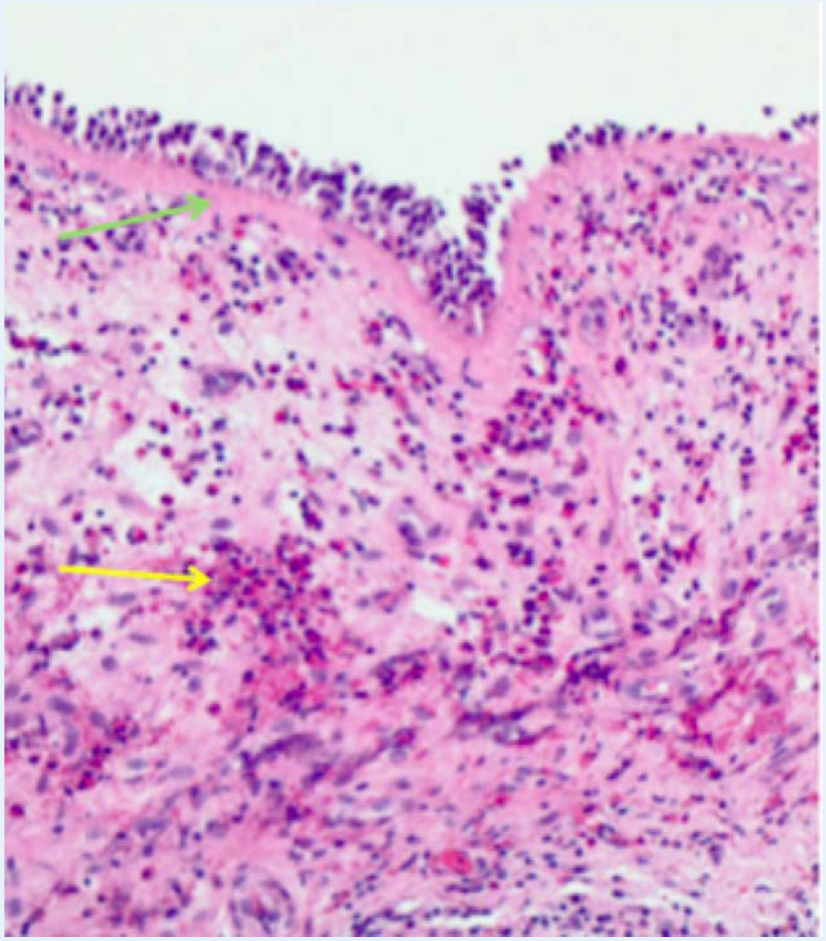
Type 2 Inflammation and Barrier

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


Healthy
CRS Nasal Polyp
A
B

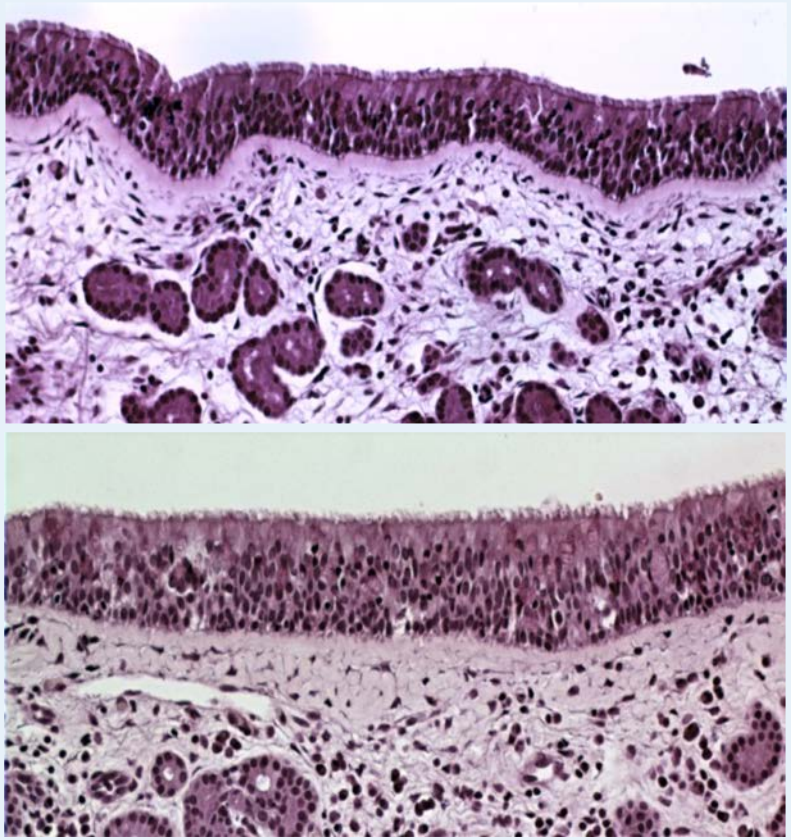
CRSwNP



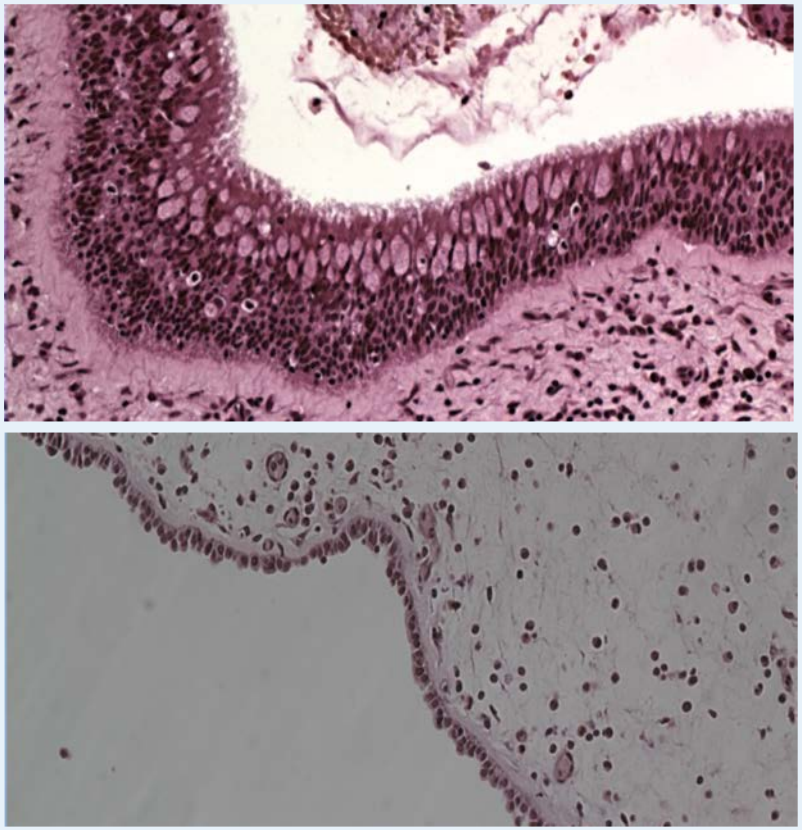


Kuhar et al. IFAR 2017

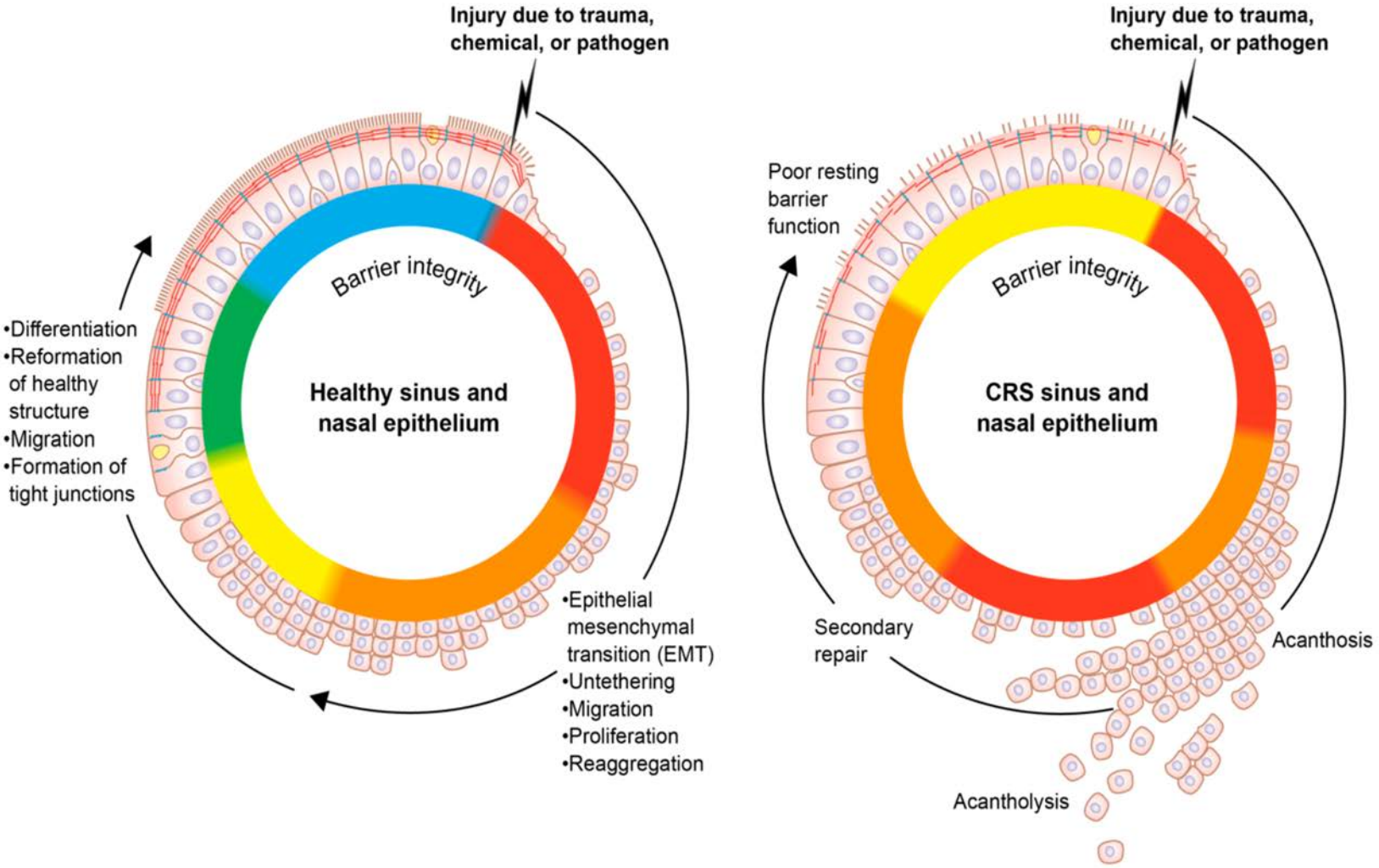
Control
Uncinate



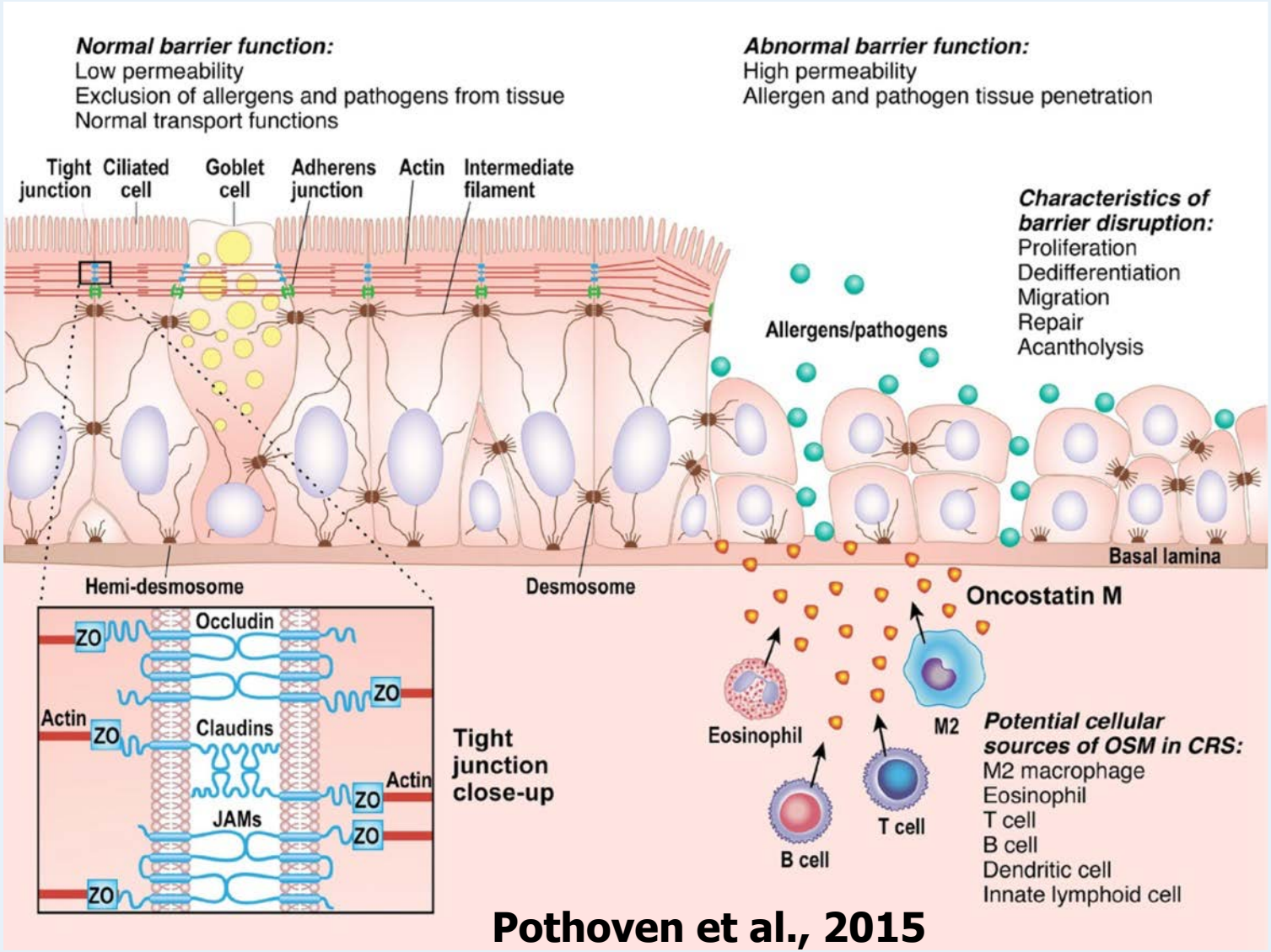
Nasal Polyp



Abnormal Repair in Type 2 CRS

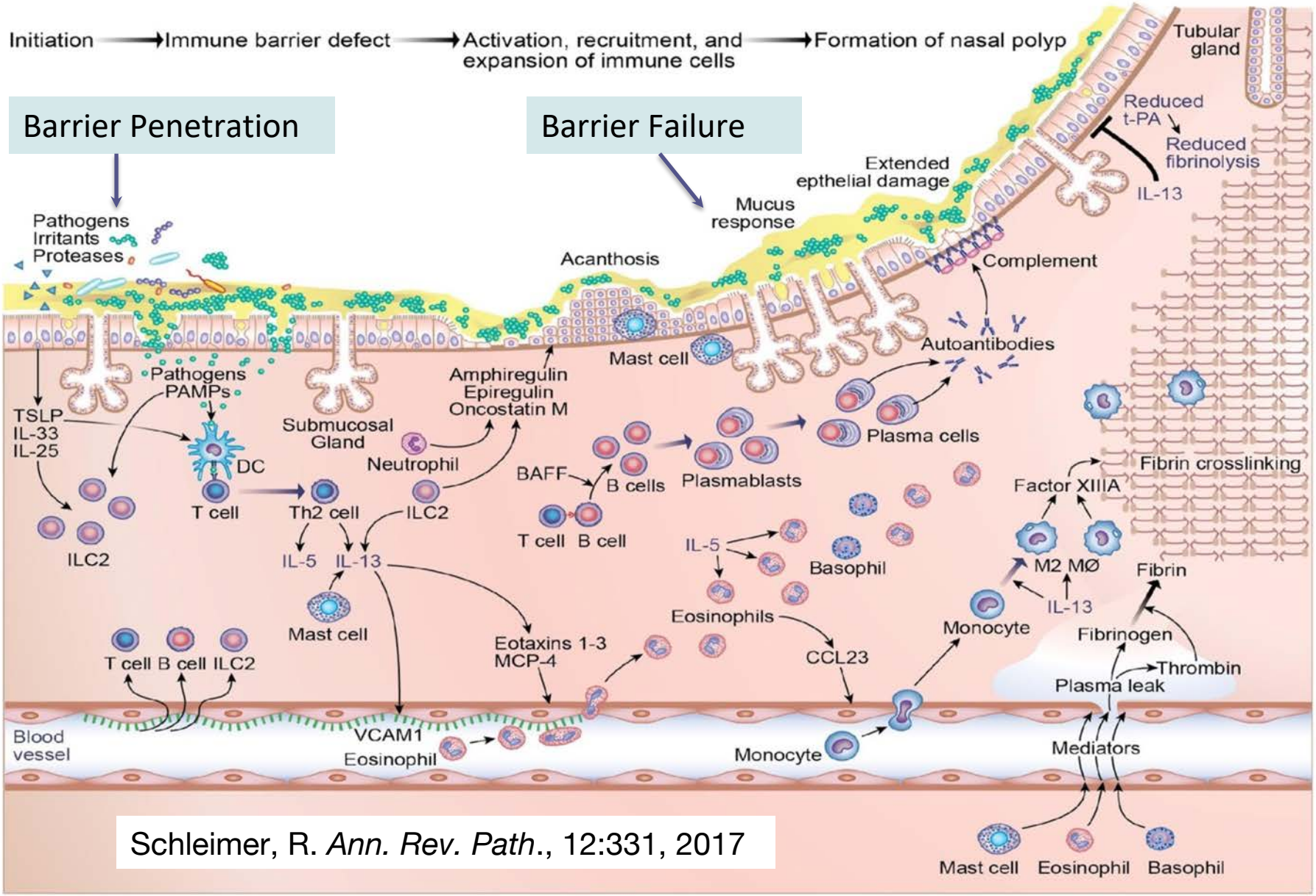


Barrier Failure and Type 2 CRS



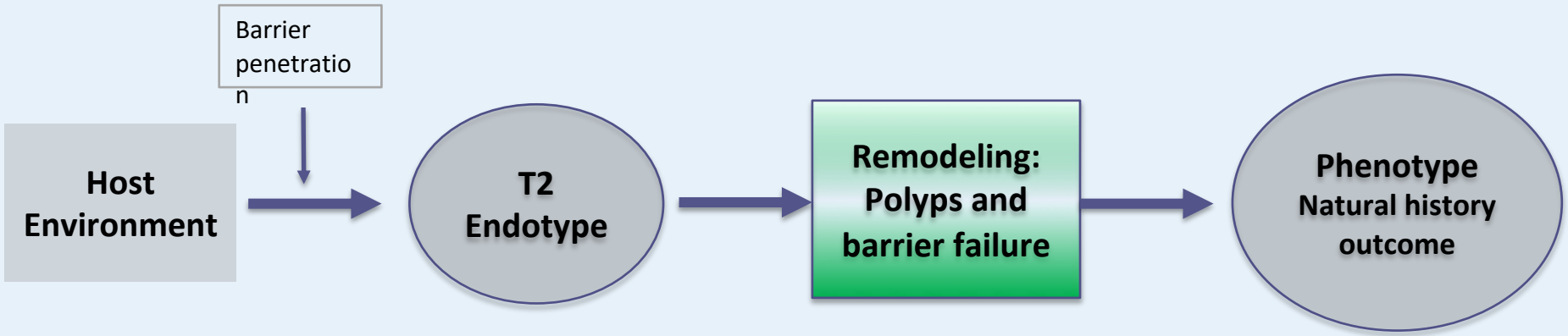
Pothoven et al., 2015

Hypothetical progression in Type 2 CRS



Schleimer, R. *Ann. Rev. Path.*, 12:331, 2017

Type 2 CRS



Barrier Failure is probably distinct from barrier penetration

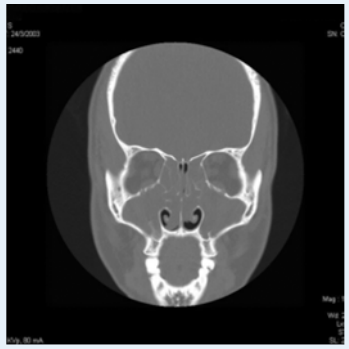
Type 2 Inflammation and Recurrence

- Chronically weak barrier
- Predisposes to recurrence

- Need steroid maintenance
- Severe cases need a biologic

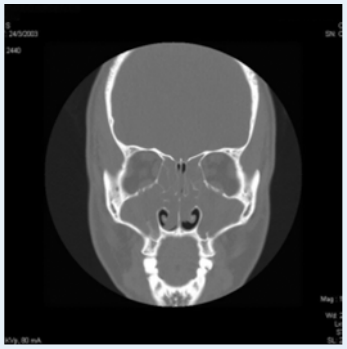
Not all CRS is Type 2!

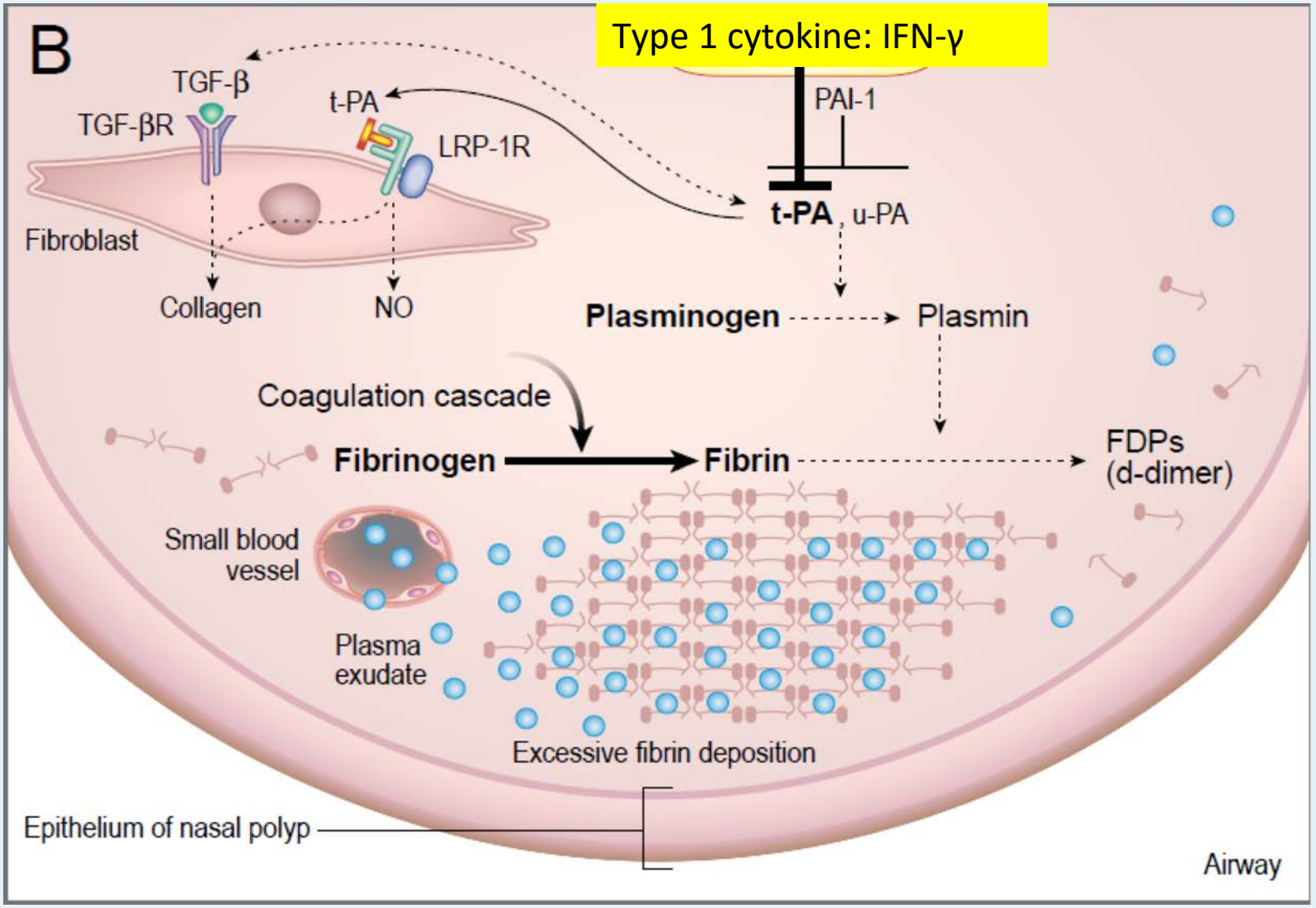
- T1
- T2
- T3
- T1,2
- T1,3
- T2,3
- T1,2 and 3
- Non typeable



What about Non-Type 2 Remodeling?

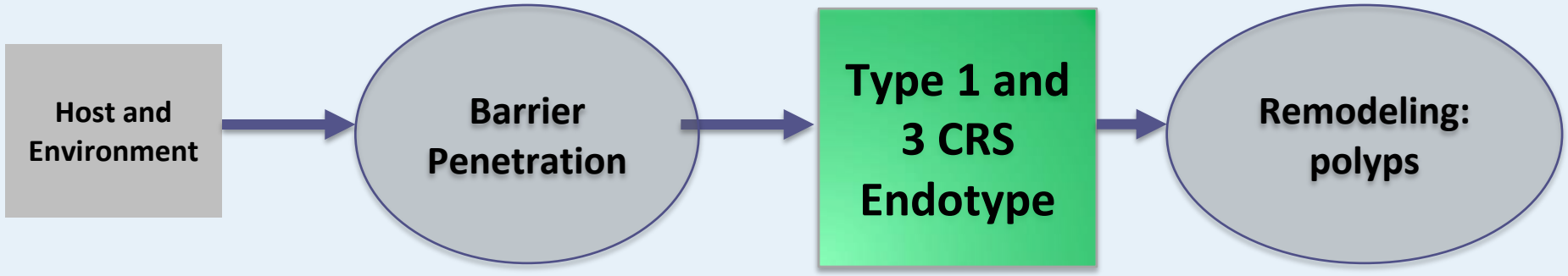
- T1
- T2
- T3
- T1,2
- T1,3
- T2,3
- T1,2 and 3
- Non typeable



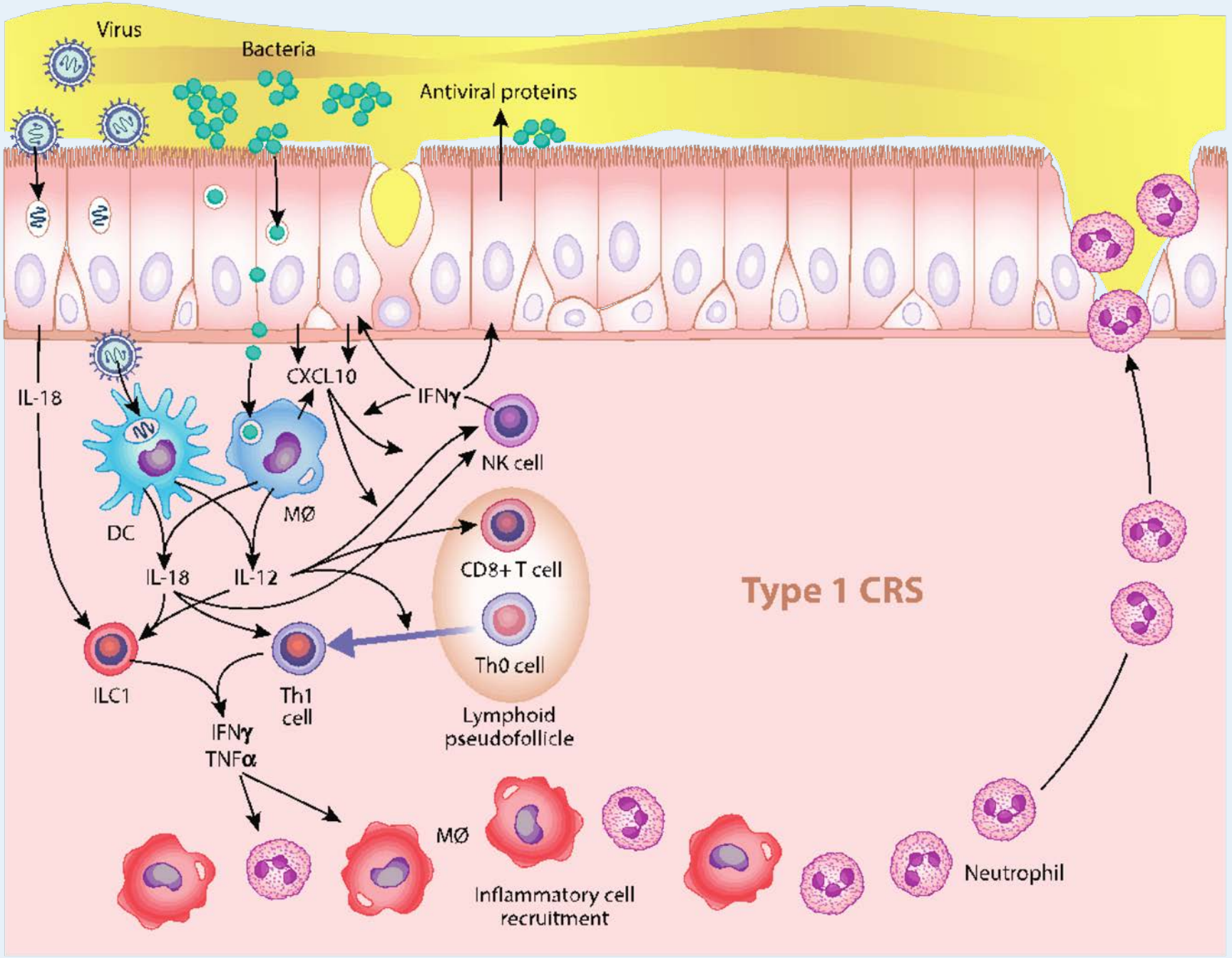


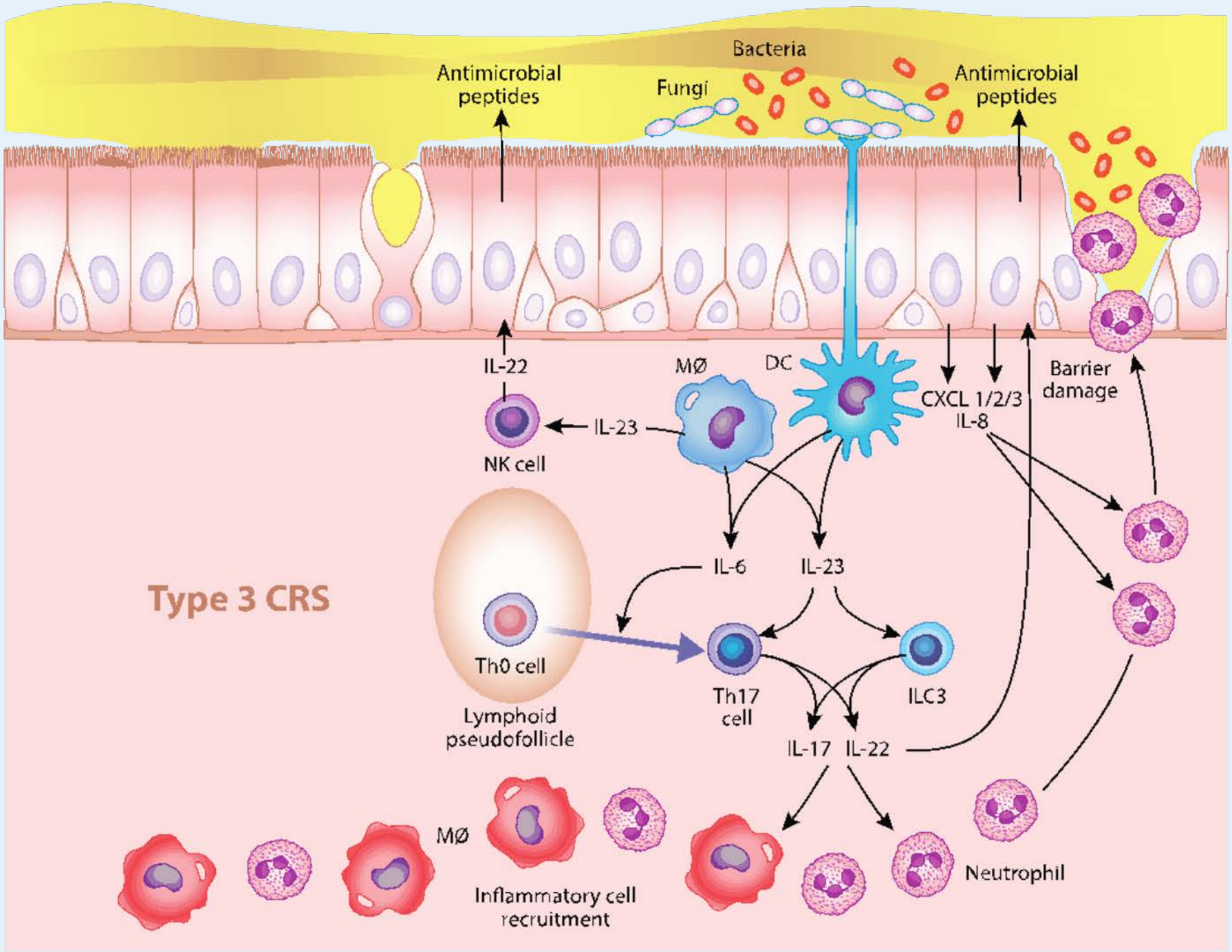
Takabayashi et. al., Am J RCCM, 2013

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*


Virus
Bacteria
Antiviral proteins
IL-18
CXCL10
IFNγ
NK cell
DC
MØ
IL-18
IL-12
CD8+ T cell
Th0 cell
Lymphoid pseudofollicle
ILC1
Th1 cell
IFNγ
TNFα
Type 1 CRS
MØ
Inflammatory cell recruitment
Neutrophil

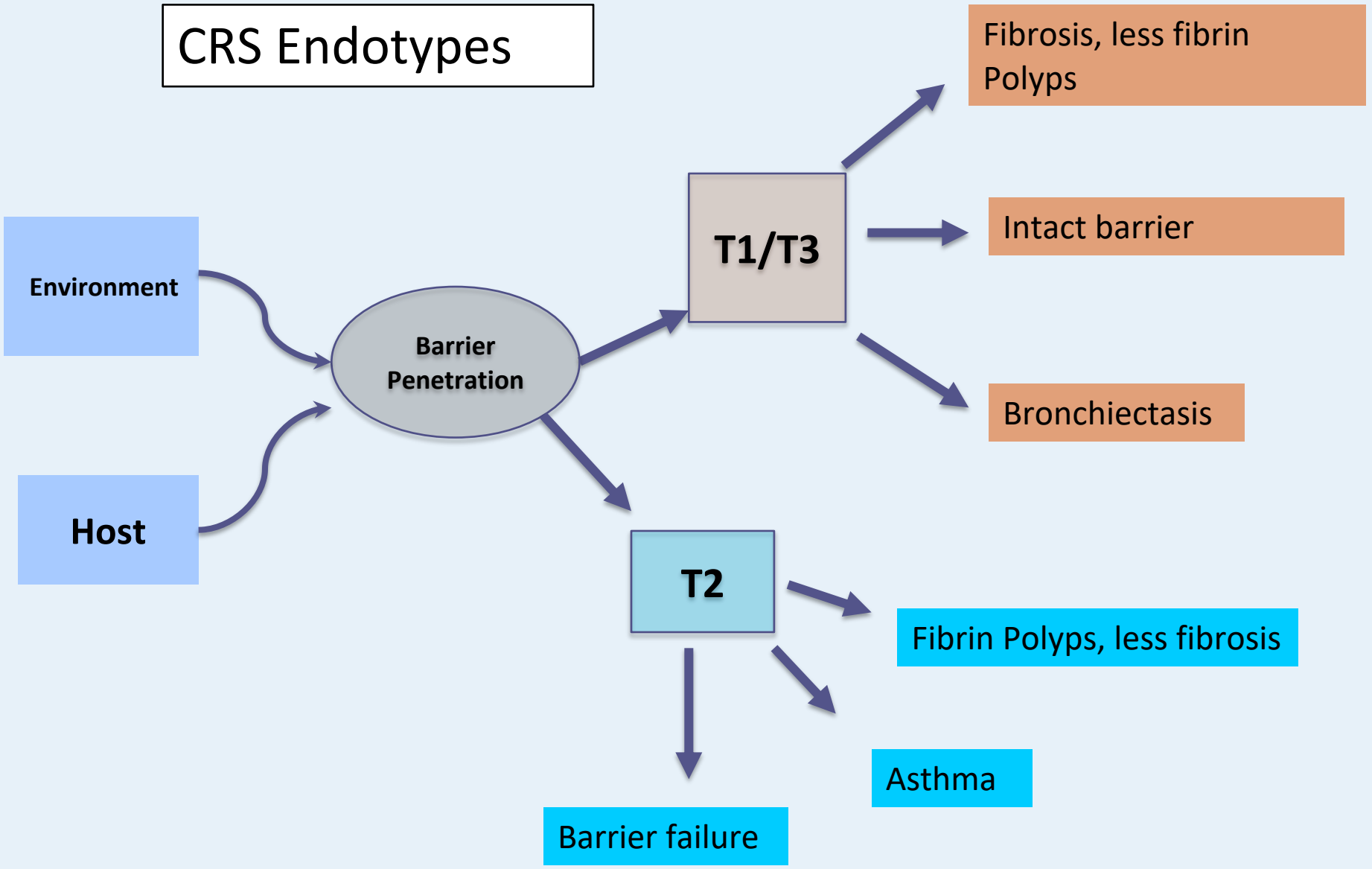

Bacteria
Fungi
Antimicrobial peptides
Antimicrobial peptides
IL-22
MØ
DC
CXCL 1/2/3
IL-8
Barrier damage
IL-23
NK cell
IL-6
IL-23
Type 3 CRS
Th0 cell
Lymphoid pseudofollicle
Th17 cell
ILC3
IL-17
IL-22
MØ
Inflammatory cell recruitment
Neutrophil

Non-Type 2 Inflammation

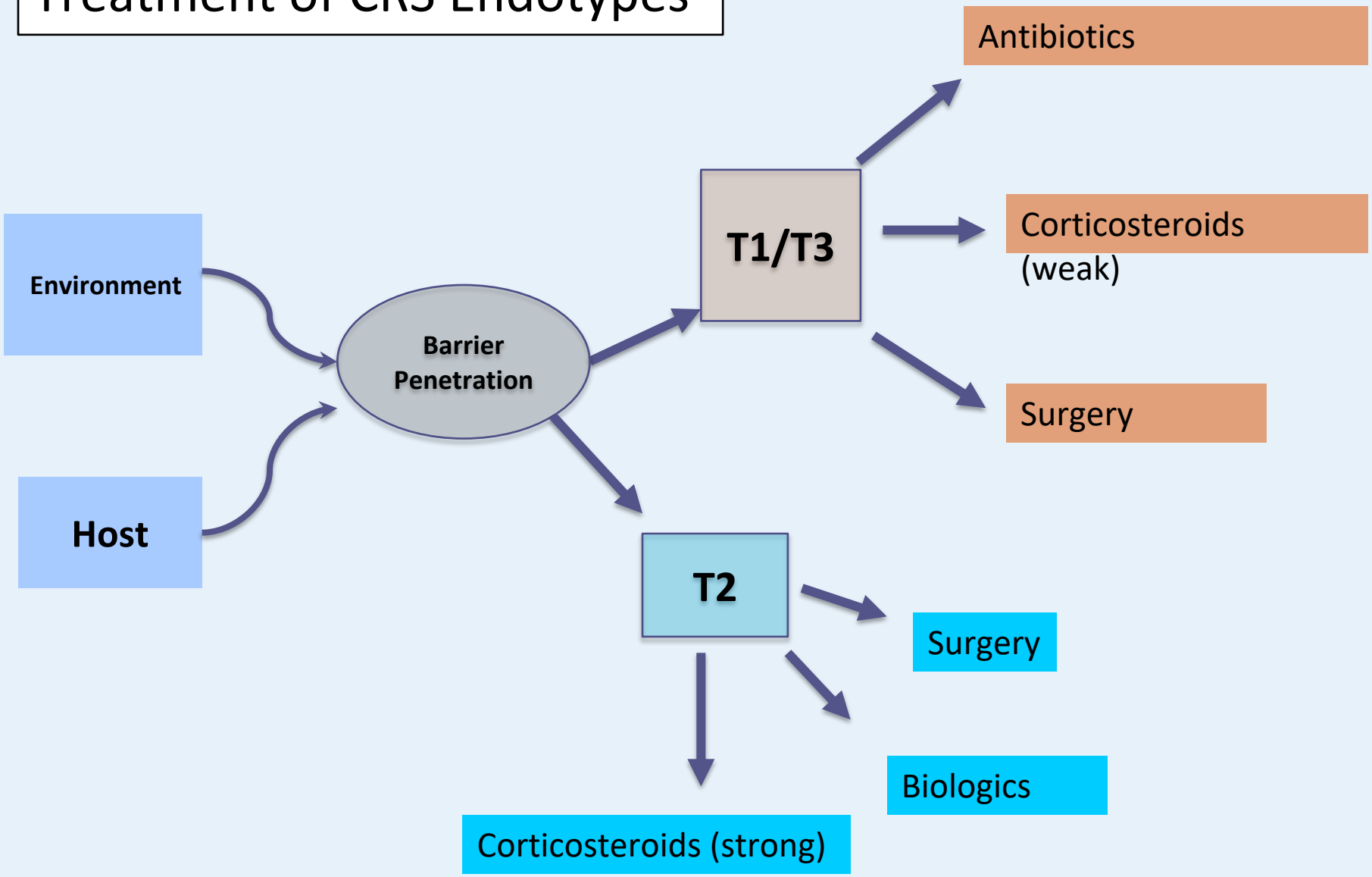
- Barrier more intact so recurrence less
- Polyps still fibrin
- Polyps less common because t-PA suppression weaker with T1/3 cytokines and no feed-forward mechanism because barrier more intact

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
Host
Barrier Penetration
T1/T3
T2
Fibrosis, less fibrin Polyps
Intact barrier
Bronchiectasis
Fibrin Polyps, less fibrosis
Asthma
Barrier failure

Treatment of CRS Endotypes



Thank you