Pathogenesis of Severe asthma
- We've just started -

Department of Internal medicine
Chungnam National University Hospital
Sunyoung Yoon

CNU HOSPITAL | 충남대학교병원 CHUNGNAM NATIONAL UNIVERSITY HOSPITAL

Pathogenesis

- 그리스어: Pathos (질병) + Genesis (기원)
- 질병의 기원
- 치료방법 모색의 출발점

Contents

- Intro
- Airway remodeling
- Airway inflammation
- Steroid resistance

Definition_GINA 2018

- **Uncontrolled asthma**
  - Frequent symptoms and/or flare-ups (exacerbations)
  - Many of these patients may potentially have mild asthma, i.e. their asthma could be well-controlled with low dose ICS, if taken regularly

- **Difficult-to-treat asthma**
  - Not difficult patients!
  - Asthma uncontrolled despite prescribing high dose preventer treatment

  Contributory factors may include incorrect diagnosis, incorrect inhaler technique, poor adherence, comorbidities

- **Severe asthma**
  - Asthma that is uncontrolled despite maximal optimised therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased i.e. relatively refractory to corticosteroids (rarely completely refractory)

With the advent of biologic therapies, the word 'refractory' is no longer appropriate.

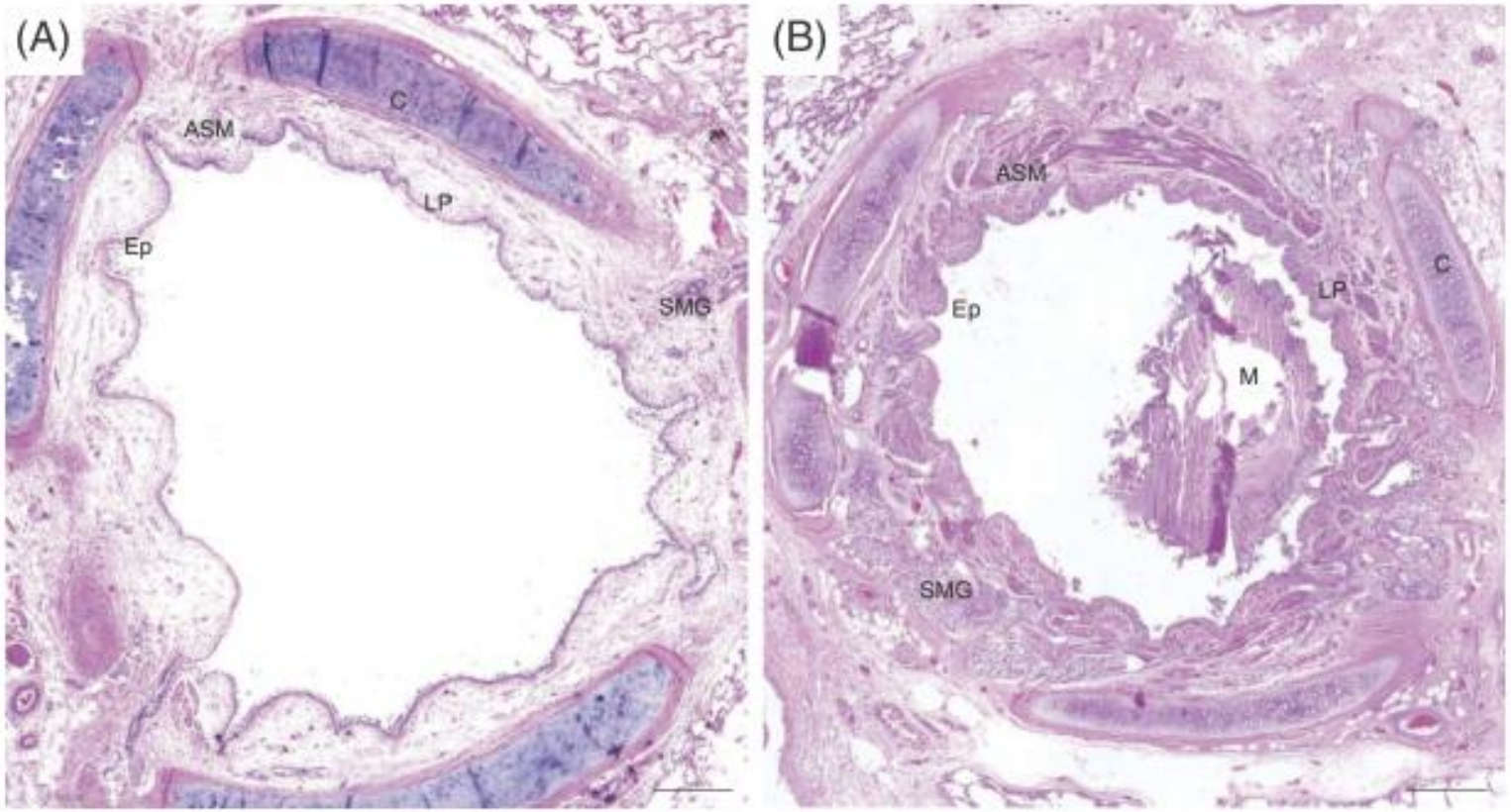
2018 GINA

Uncontrolled asthma

- Poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma)

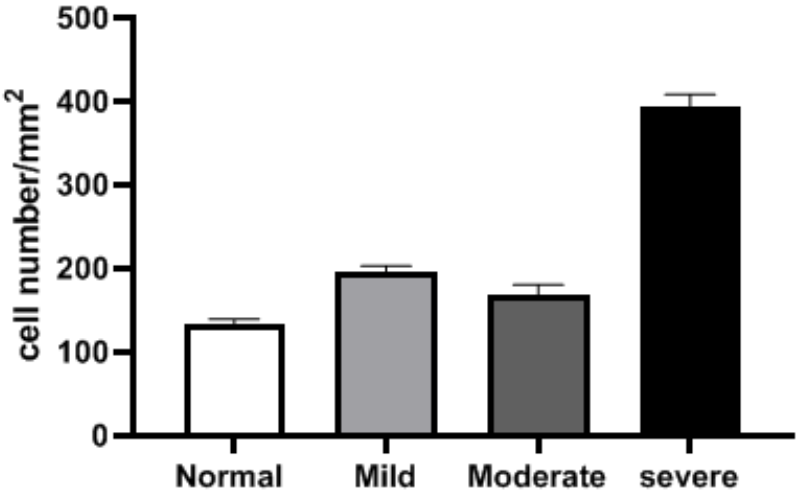
- Frequent exacerbations (≥2/year) requiring oral corticosteroid, or serious exacerbations (≥1/year) requiring hospitalization

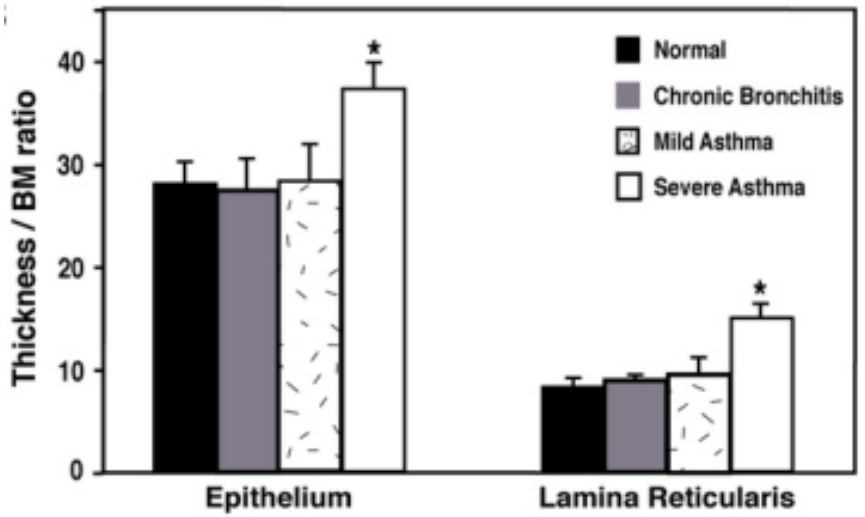
Severe asthma_Histology



Respirology (2018) 23, 262 – 271

Structural difference of Severe asthma





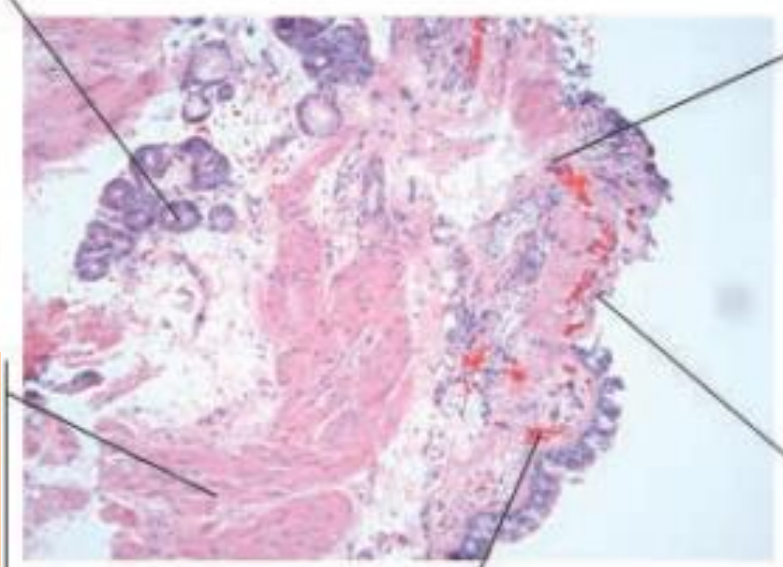
(Modified from) Am J Respir Crit Care Med. 1999;160:1001–1008.
Am J Respir Crit Care Med. 2007;176(2):138–45.

Cardinal features of Severe asthma

- Airway remodeling
- Airway inflammation (TH_2/ non-TH_2)
- Steroid resistance

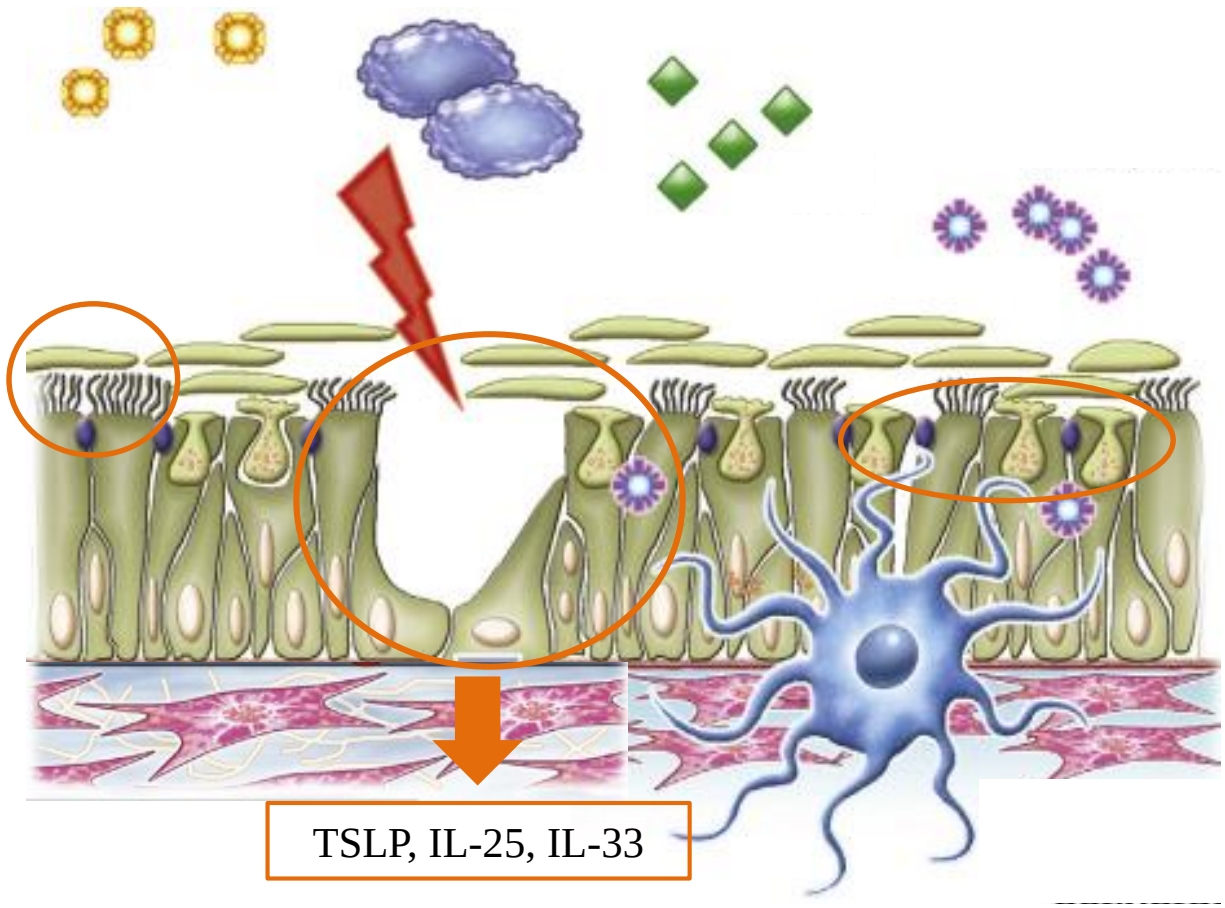
Airway remodeling

Airway remodeling



Can Respir J. 2010 Jul-Aug;17(4):e85-93

Epithelial alteration

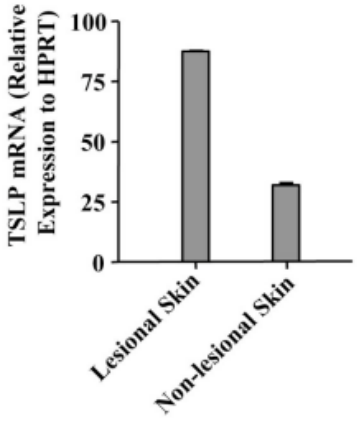


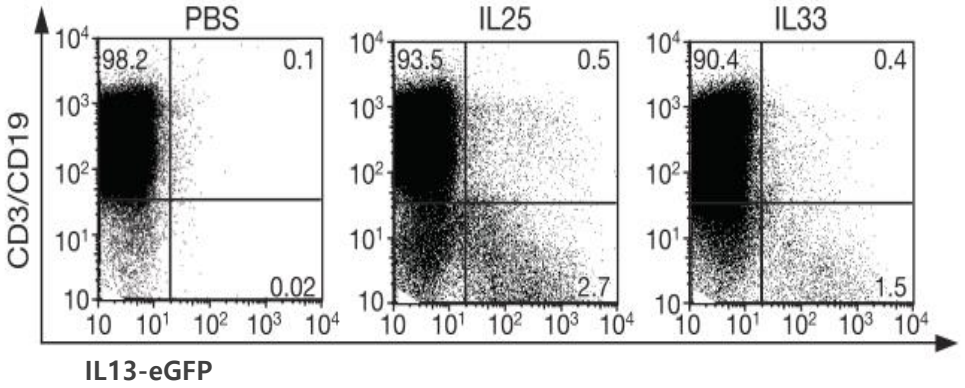
- Loss of epithelial integrity, disruption of cell tight junction
- Decrease of ciliary function
- Goblet cell hyperplasia
- Source of pro-inflammatory cytokine

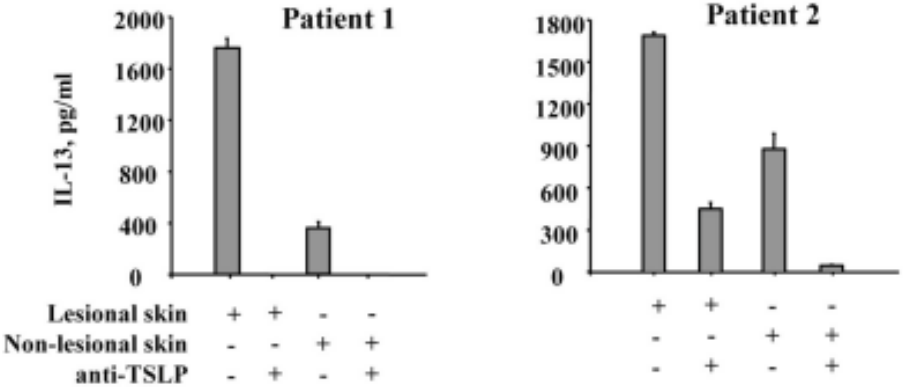
J Allergy Clin Immunol 2017;139:1736-51

Epithelial alteration

- Thymic stromal lymphopoietin (TSLP), IL-25, IL-33
  - Recruit and activate dendritic cell, mast cell, eosinophil
  - Provoke type2 innate lymphoid cell (ILC2)



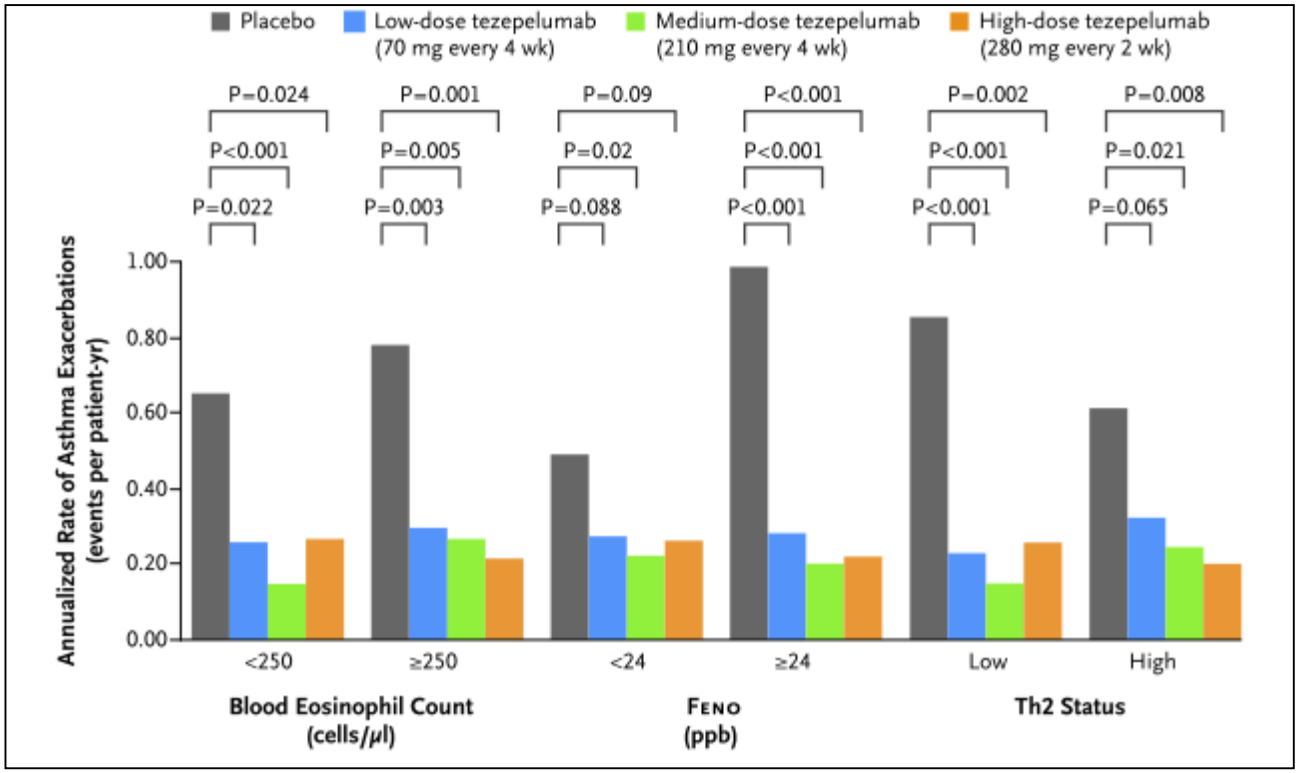




J. Exp. Med. 204, 253–258.
J Allergy Clin Immunol 2013;132:933-41

Anti-TSLP monoclonal Ab

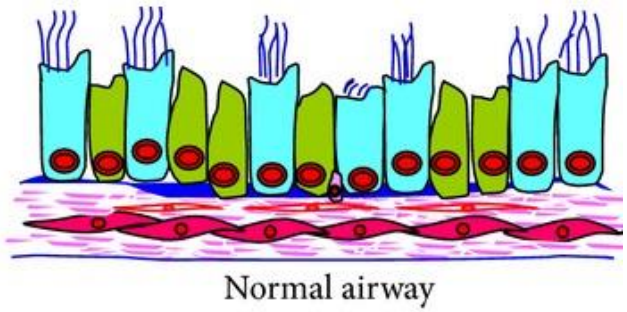
- Tezepelumab
- Uncontrolled asthma despite to step 4-5 treatment
- Reduces the rate of asthma exacerbation by 60-70%

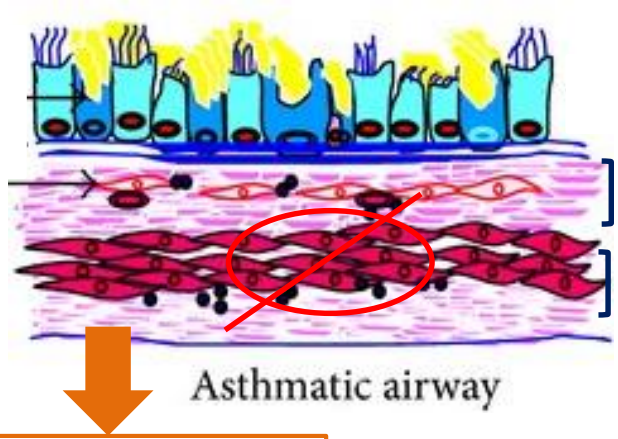


N Engl J Med 2017;377:936-46.

ASM hypertrophy & Subepithelial fibrosis

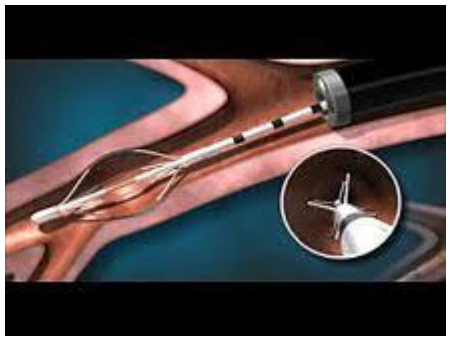
- Thickening & stiffening
  - Airway narrowing due to ASM thickening itself
  - Increase airway contractility
  - Loss of protective mechanism against ASM contraction
- Increase airway hyperresponsiveness (AHR)
- Augments airway inflammation by pro-inflammatory cytokines/ chemokines





IL-5, IL-6, TSLP,
TGF-β, MMP-9

Bronchial thermoplasty



Altered airway contractility by disrupting Actin-Myosin interaction

Reduction of ASM mass - Decrease of Airway responsiveness

Reduction of inflammatory mediators from ASM

Eur Respir J 2008; 32:265–274

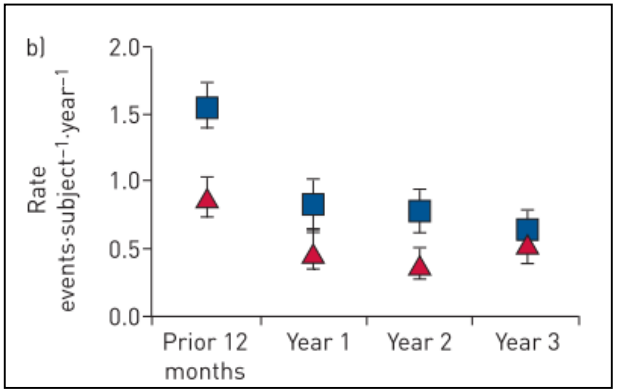
Chest 2005; 127:1999–2006

Am J Respir Cell Mol Biol 2011; 44:213–221.

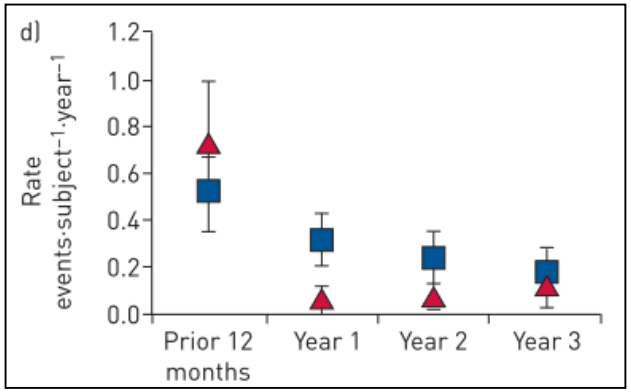
Long-term outcomes

- **AIR2** (Asthma Intervention Research 2) vs. **PAS2** (Post-FDA Approval Clinical Trial Evaluation Bronchial Thermoplasty)
- 3-year follow up
- Reduces the rate of asthma exacerbation

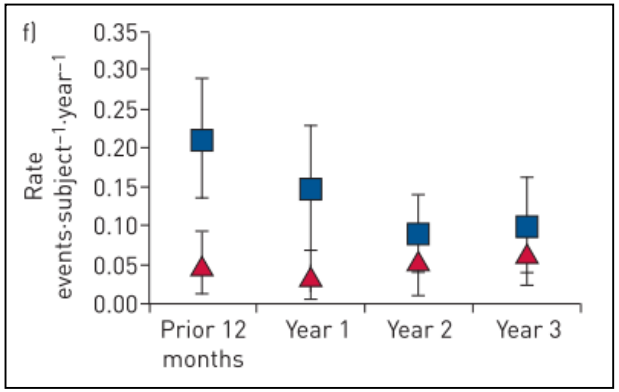
severe exacerbation



ER visits



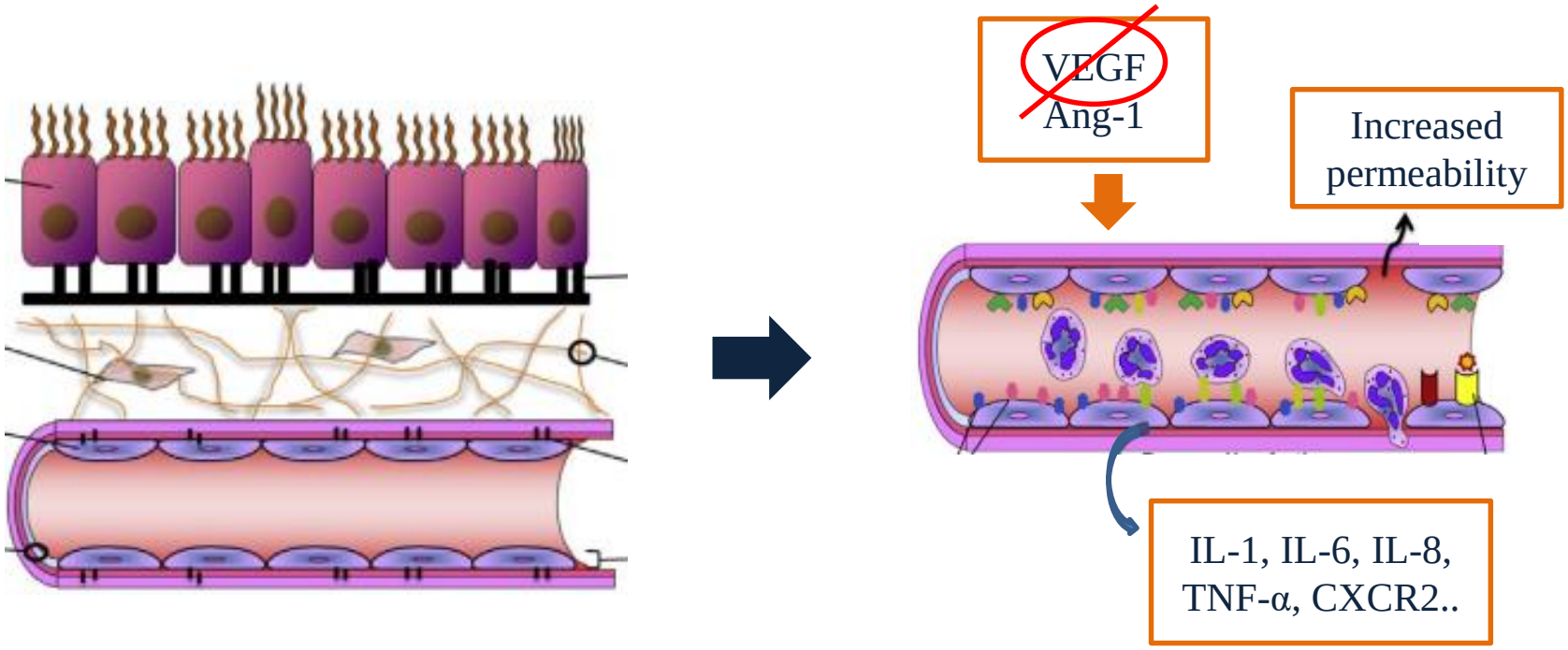
Hospitalizations



Eur Respir J 2017; 50: 1700017

Angiogenesis & vascular permeability

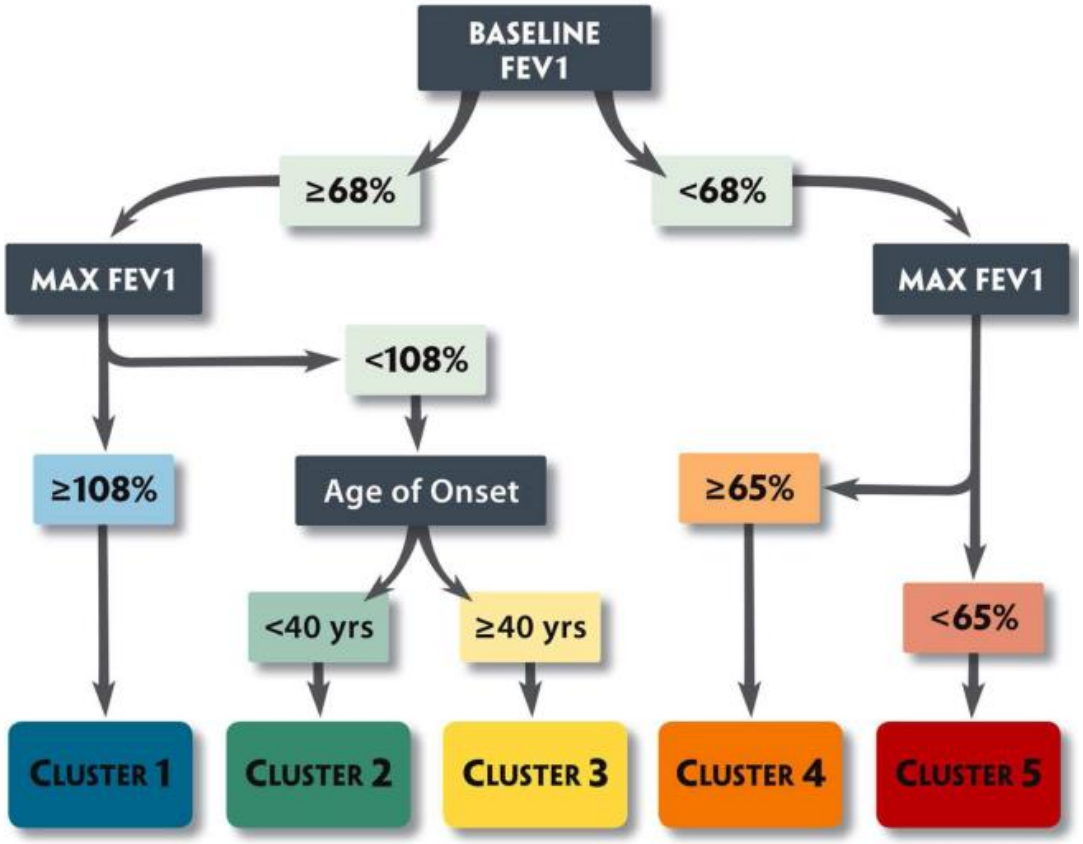
- Amplifies inflammatory response
- Contribute airway wall thickening



Allergology International 65 (2016) 21-29

Airway Inflammation

Phenotype in Severe asthma



- **2010 SARP Cohort**
- **34 of core variables**
  - Onset age
  - Gender
  - Atopy
  - Lung function & reversibility
  - Medication use
  - Health care utilization

Am J Respir Crit Care Med 2010;181:315–323

Phenotype in Severe asthma

Cluster 1
Mild atopic asthma

- early onset, female predominant, atopic, normal lung function, minimal HCU , ≤ 2 controller medication, Highest serum eosinophil & IgE

Cluster 2
Mild to moderate atopic asthma

- largest group, early onset, female predominant, atopic, borderline lung function, low HCU, ≤ 2 controller medication

Cluster 3
Late onset, (obese) non-atopic asthma

- Smallest group
- Adulthood
- F > M
- Less-atopic
- Moderate FEV1 & reversibility
- Highest BMI
- ≥ 3 controller medication
- More HCU use

Cluster 4
Severe atopic asthma

- Early onset
- F = M
- Atopic
- Low pre-FEV1 & reversibility
- ≥ 3 controller medication
- High HCU use

Cluster 5
Severe asthma with fixed airflow

- Later-onset
- F > M
- Less-atopic
- Poor FEV1 & reversibility
- Frequent OCS use
- High HCU use

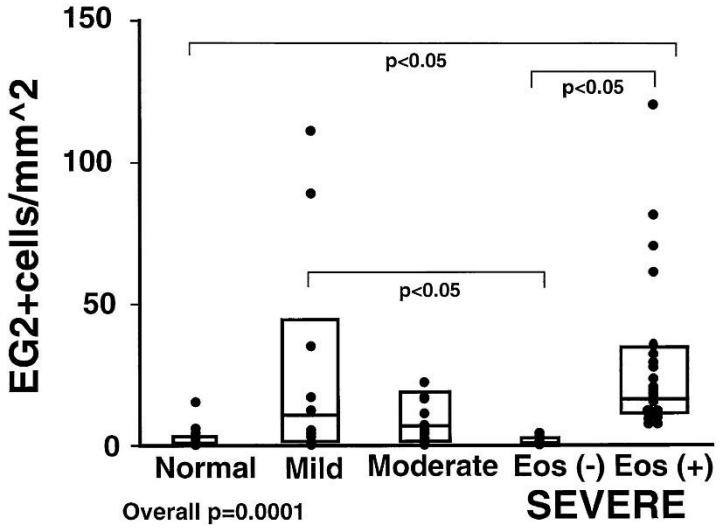
Evolving endotypes in relation to severe asthma

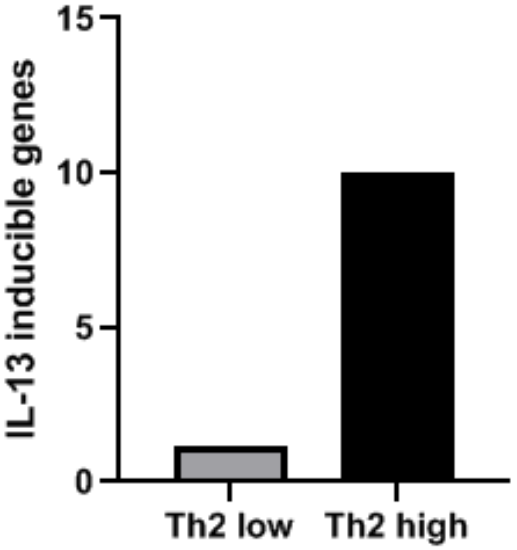
	Natural history	Clinical	Genetics	Pathobiology	Biomarkers	Response to Rx
Early onset allergic	Childhood onset severe disease is persistent & progressive	Aeroallergen sensitivity other allergic diseases	17q12-21 Th2 pathway	Th2 cytokines, eos-less clear in severe disease	FeNO, increased sIgE periostin	Mild responds to CSs/Th2 blockers.
Persistent eosinophilia	Adult onset persistence and progr ession unknown	Severe sinusitis, nasal polyps subset with AERD	LT pathway HLA	Blood and lung eos despite CSs IL-5, cLT pathway	Sputum eos	Anti-Th2/IL-5 LT modifiers
ABPM	Usually adult onset persistent	Increased cough/ m ucus central bronchiectasis	CFTR?	Blood and lung eos, mixed adapt ive immunity	Fungus sIgE and IgG	CSs, anti-fungals, possibly anti-IgE
Obese-Female	Very late onset persistence	Very symptomatic, but less airway obstruction and few severe exacerba tions hormonal ties	Unknown	Inconsistent reports	Unknown	No good studies of targeted Rx
Neutrophilic	Unknown	Fixed airway obstru ction, few other defined clinical characteristics	Unknown	Neutrophils, possibly increas ed innate immun e activation	Unknown	Response to macrolide

Clin Exp Allergy. 2012;42:650-8

Subphenotypes of Severe asthma

- Severe asthma with vs. without airway eosinophils
- Th2 low vs. Th2 high severe asthma





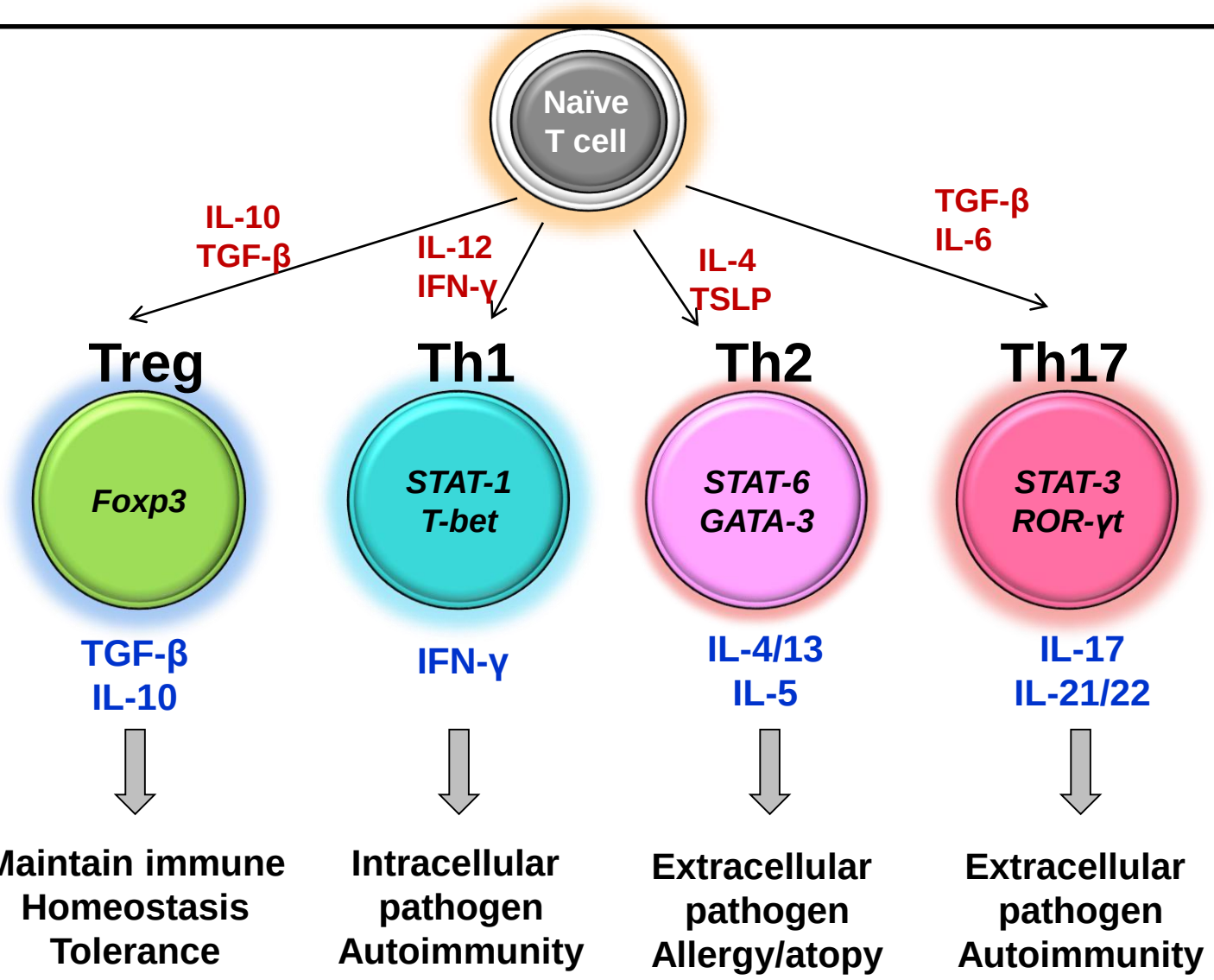
Am. J. Respir. Crit. Care Med. 160:1001–8
Am. J. Respir. Crit. Care Med. 180:388–95

Th2 inflammation in Severe asthma

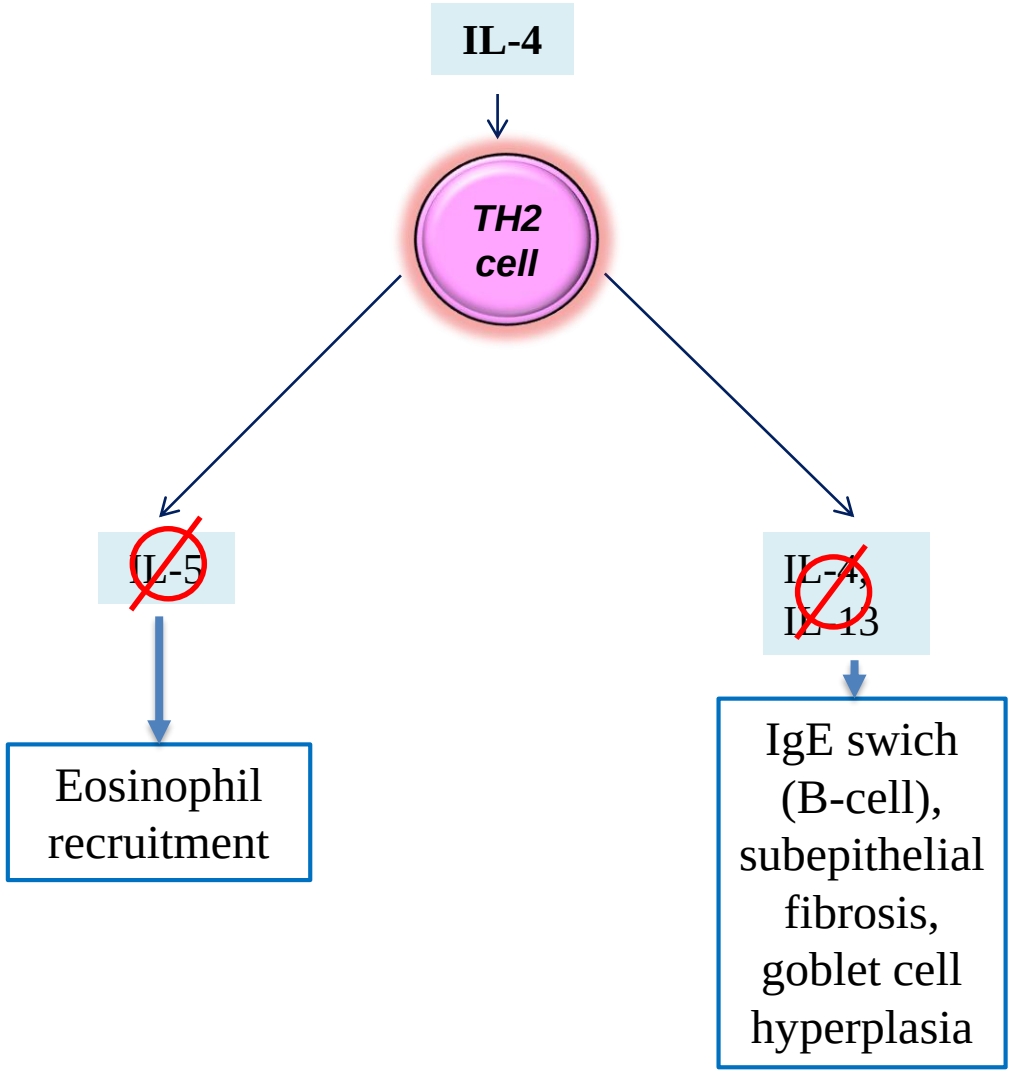
- Cardinal cells
  - Type 2 helper T-cell (Th2 cell), eosinophil, mast cell, Innate lymphoid cell2 (ILC2), basophil

- Cardinal mediators
  - IgE, IL-4, IL-5, IL-13

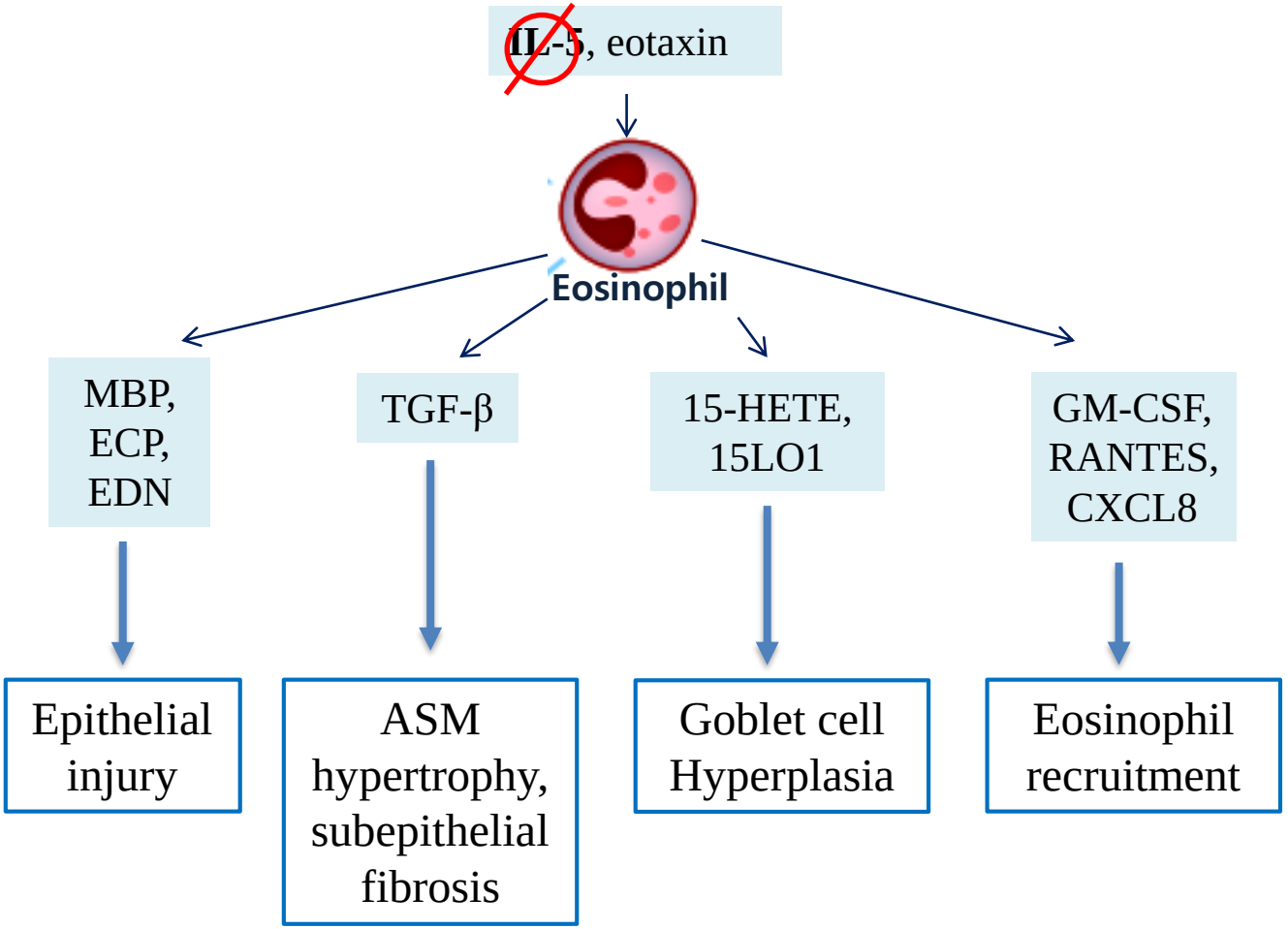
Diversification of CD4+ T cell lineages



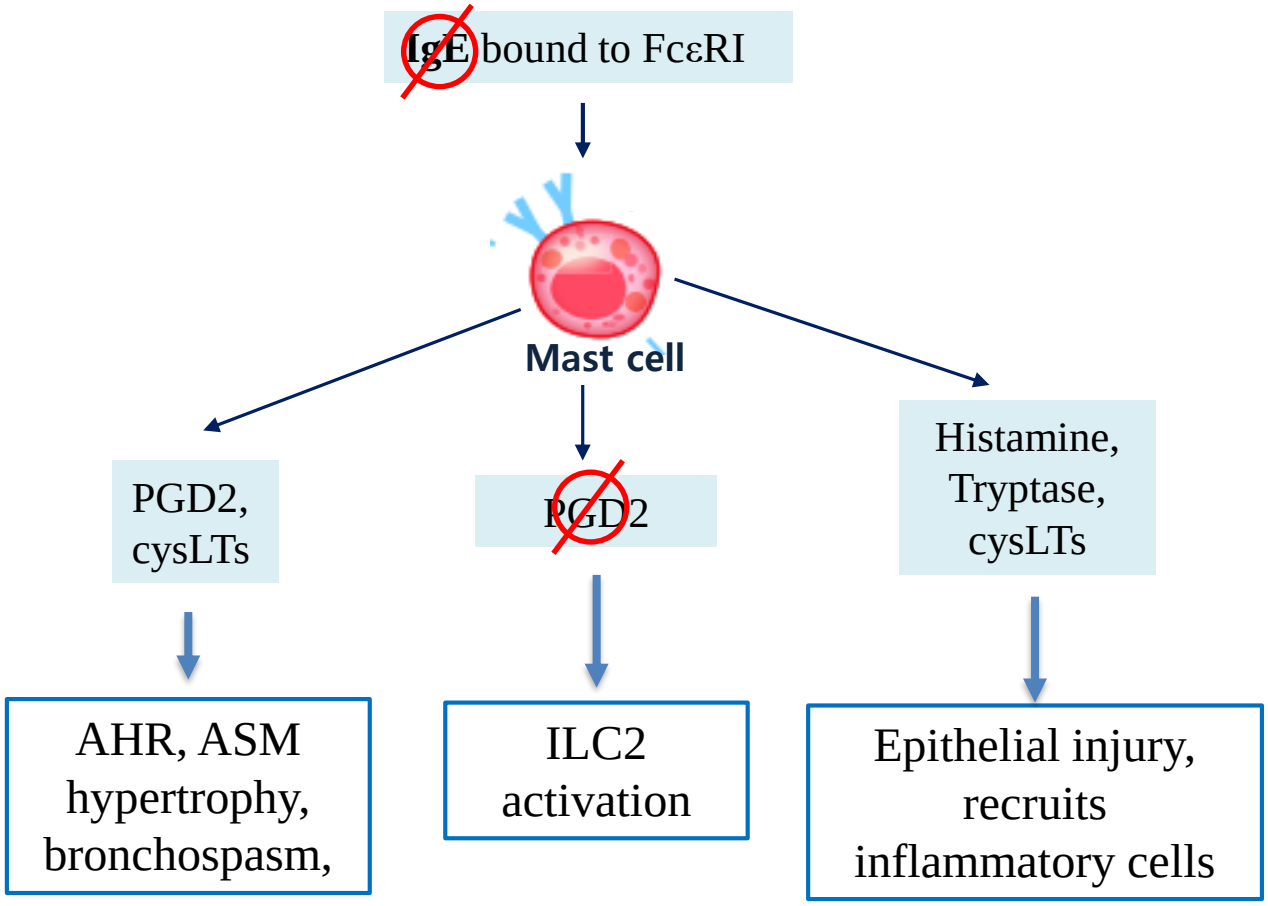
Type2 helper T-cell



Eosinophil

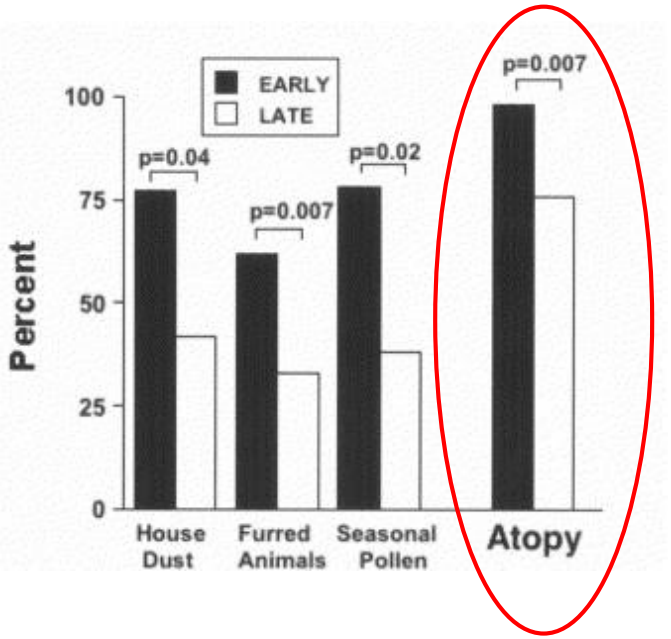

IL-5, eotaxin
Eosinophil
MBP, ECP, EDN
TGF-β
15-HETE, 15LO1
GM-CSF, RANTES, CXCL8
Epithelial injury
ASM hypertrophy, subepithelial fibrosis
Goblet cell Hyperplasia
Eosinophil recruitment

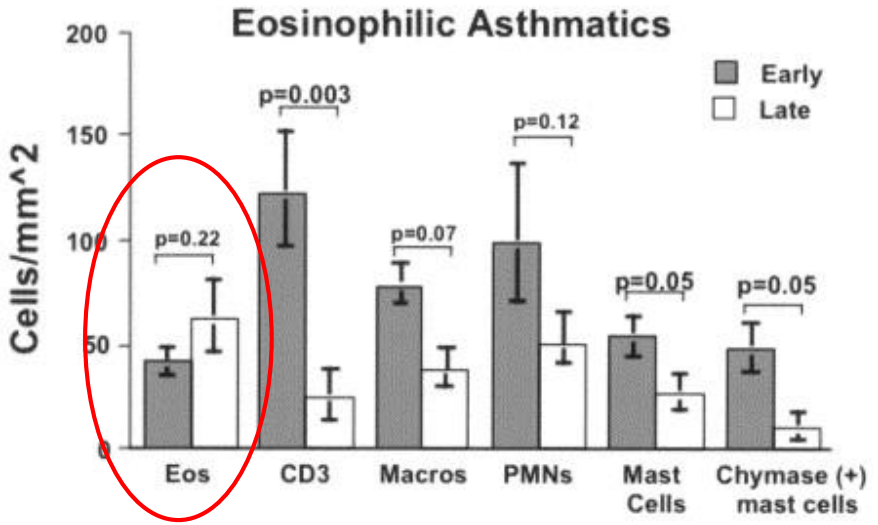
Mast cell


IgE bound to FcεRI
Mast cell
PGD2, cysLTs
PGD2
Histamine, Tryptase, cysLTs
AHR, ASM hypertrophy, bronchospasm,
ILC2 activation
Epithelial injury, recruits inflammatory cells

Atopic vs. Eosinophilic asthma

- Atopic, but less eosinophils vs.
- Non- or less atopic, but highly eosinophilic

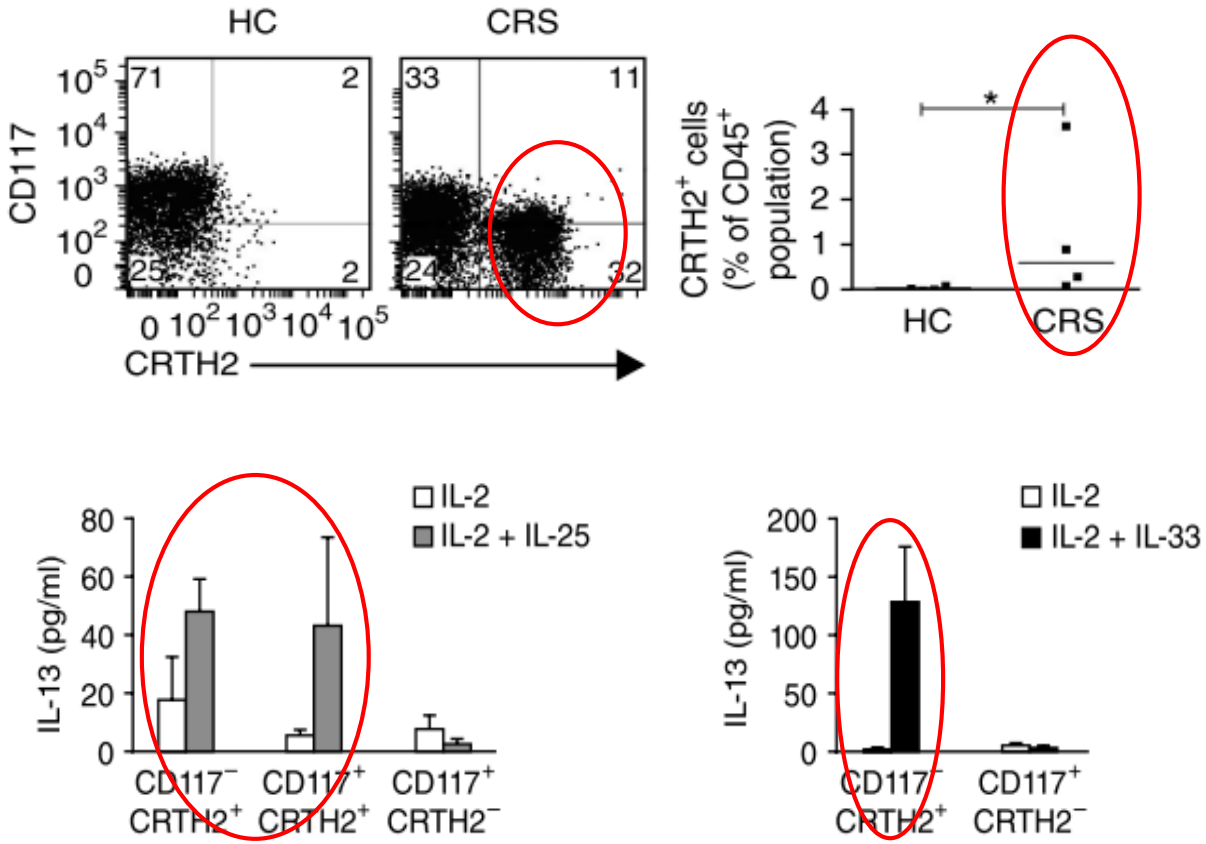




J Allergy Clin Immunol 2004;113;101-8.

Innate lymphoid cell type2 (ILC2)

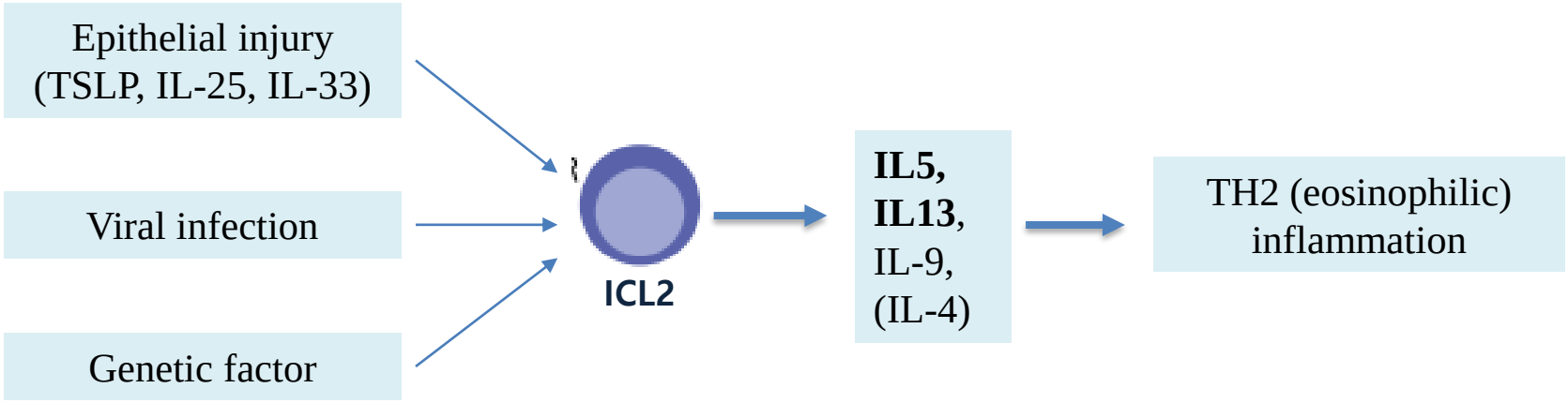
- Human ILC2 from chronic rhinosinusitis
- Lin^{-}CD117$^{+/-}$CD127^{+}CTRH2^{+} cell line



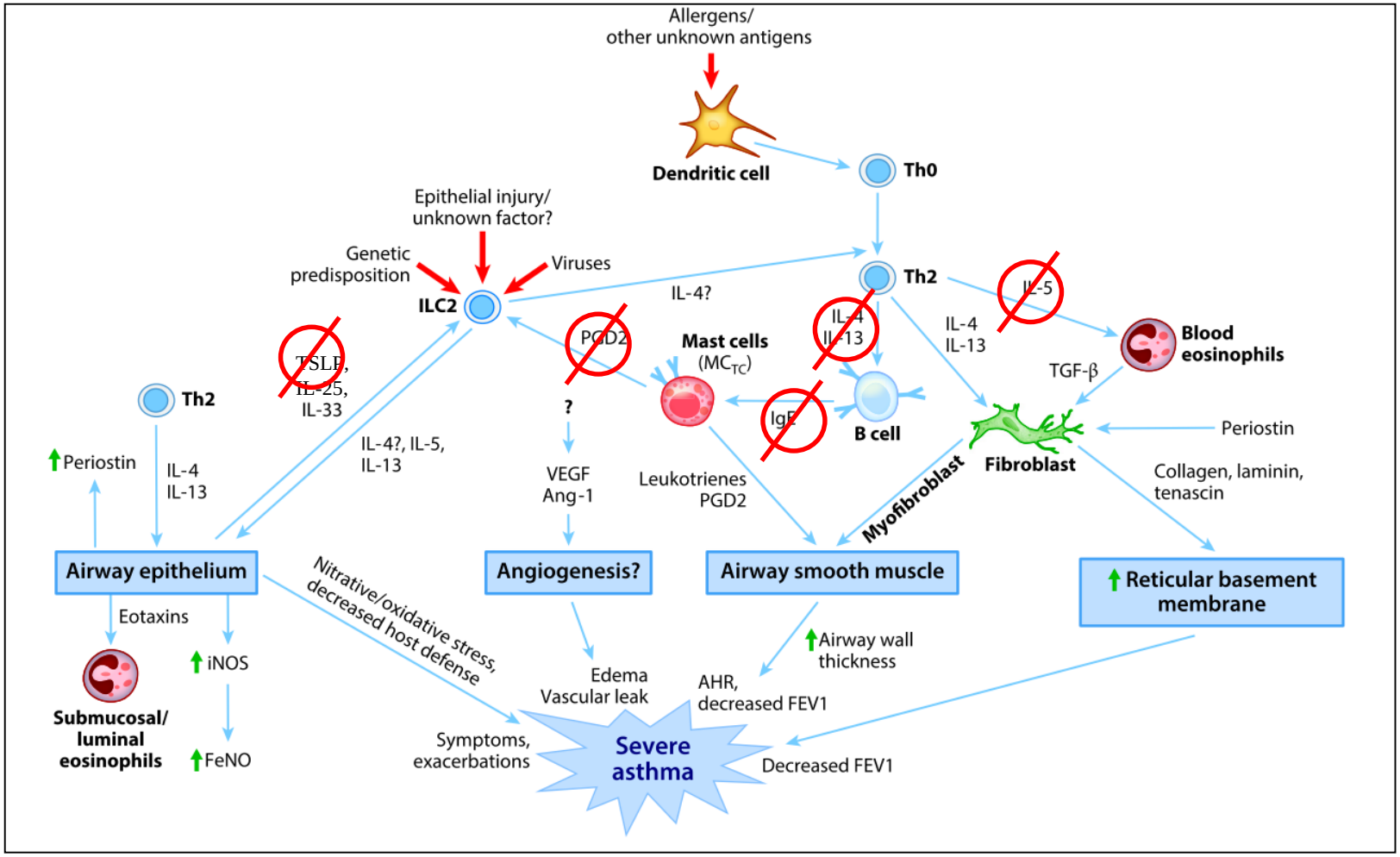
Nat Immunol 2011, 12:1055-1062.

Innate lymphoid cell type2

- Derived from common lymphoid progenitor cells
- Non-B/ Non-T nature
- Major source of IL-5, IL-13

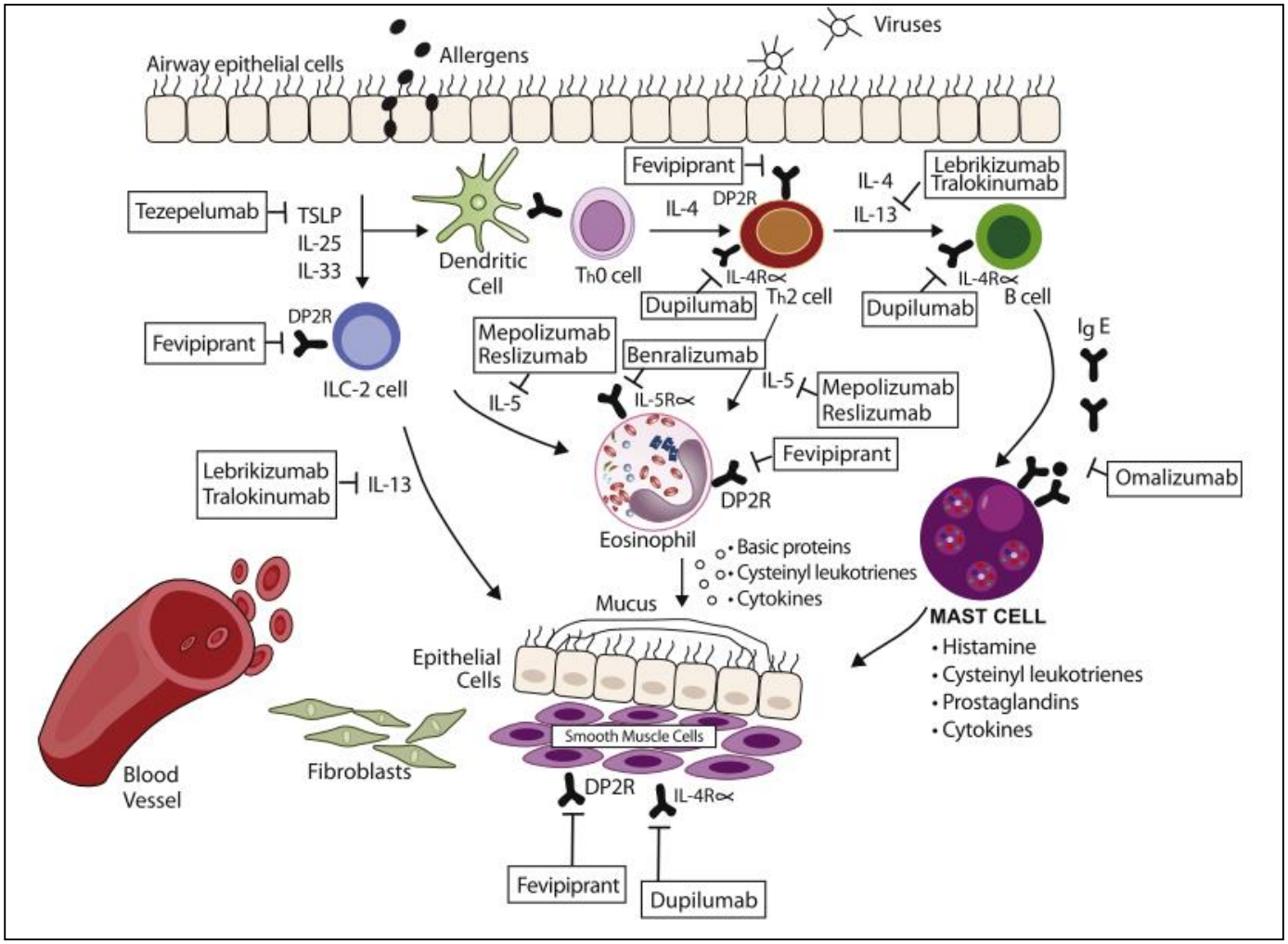


Th2 inflammation



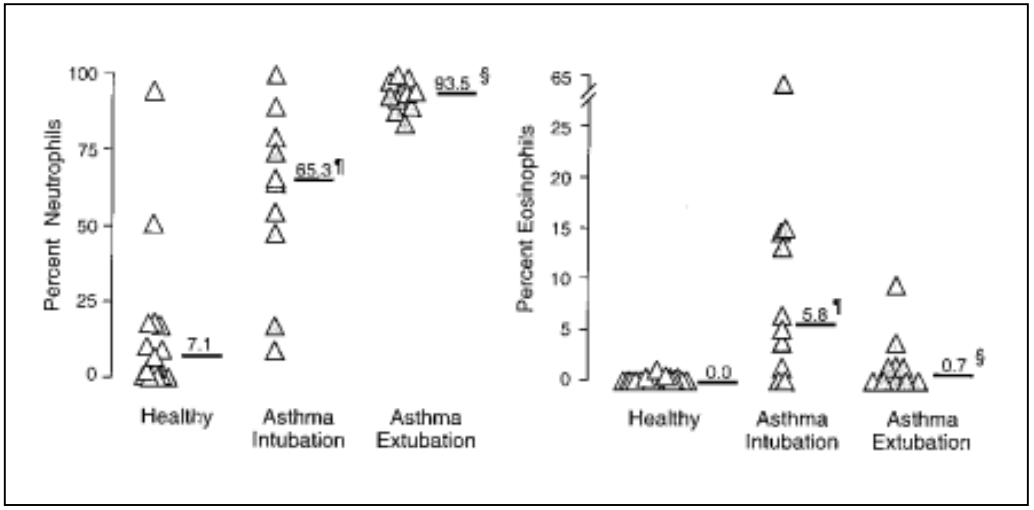
Annu. Rev. Pathol. Mech. Dis. 2015. 10:511–45

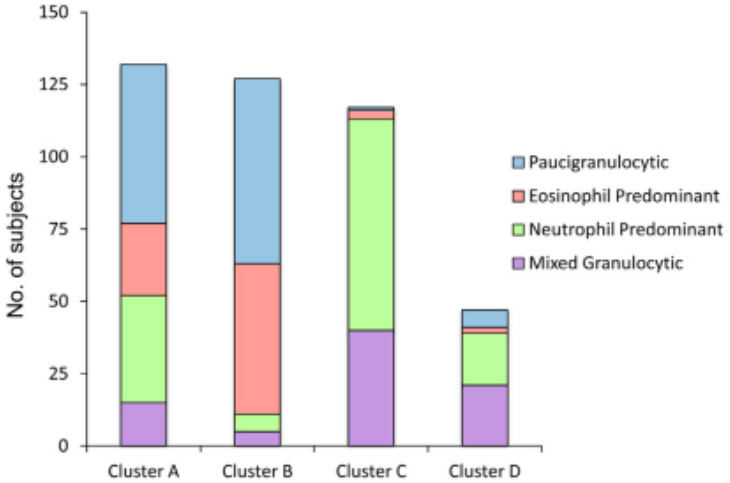
Biologics for Th2 high severe asthma

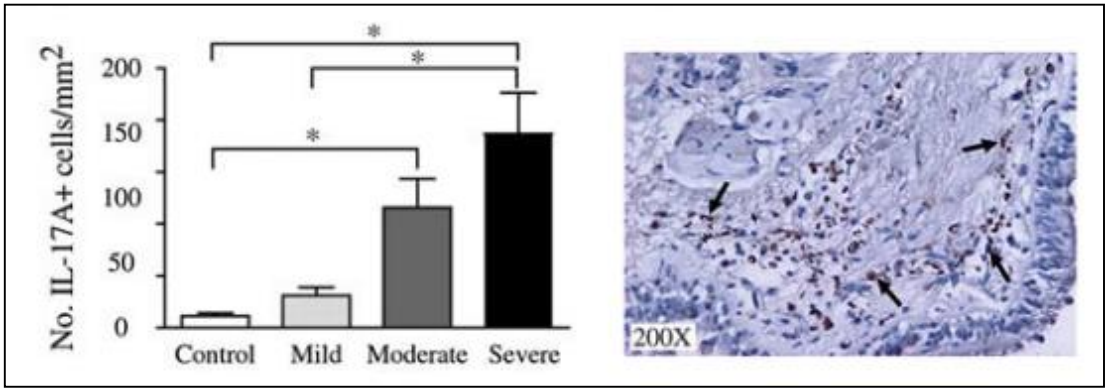


J Allergy Clin Immunol Pract 2019;7:1379-92.

Non-Th2 inflammation in Severe asthma







Am J Respir Crit Care Med 2000; 161: 1185–1190
J Allergy Clin Immunol 2009;123;1185-1187
J Allergy Clin Immunol 2014;133:1557-63

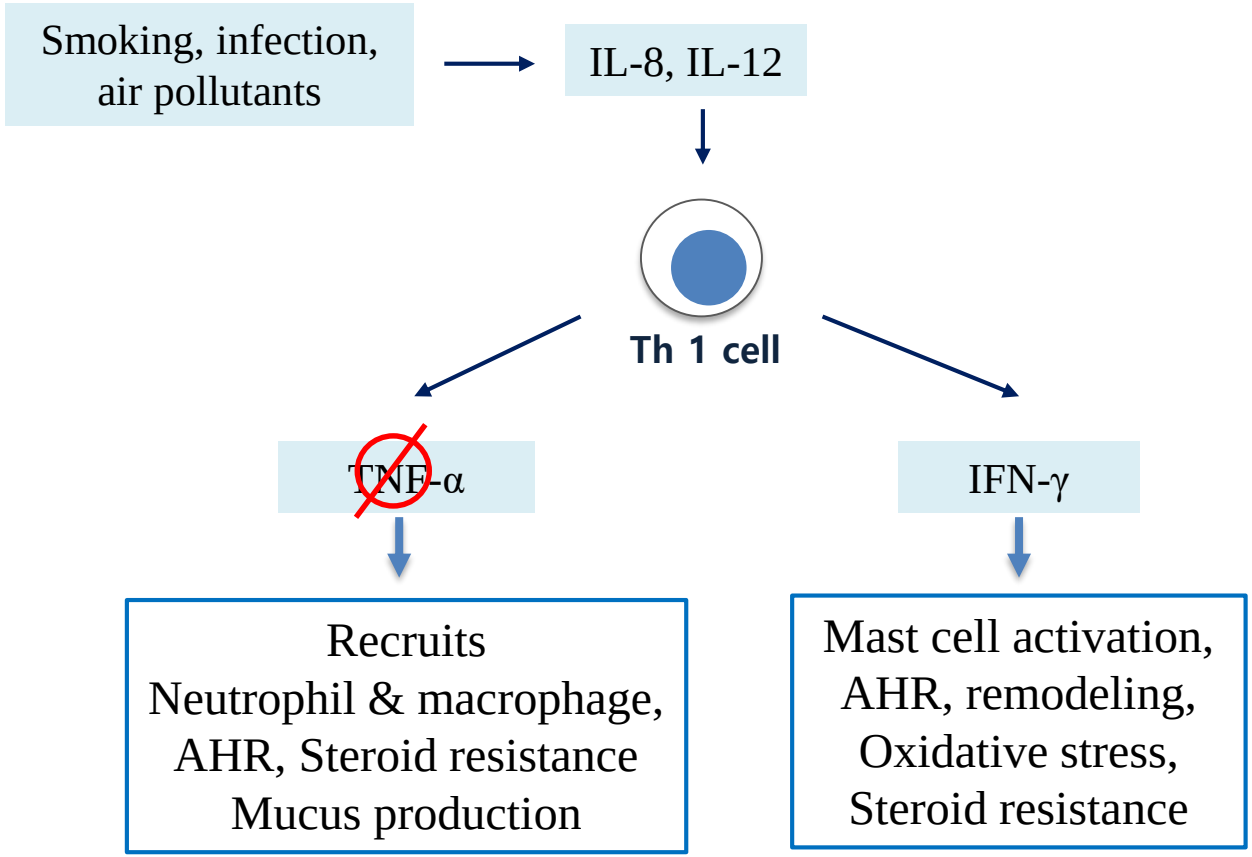
Non-Th2 inflammation in Severe asthma

- Involved cells

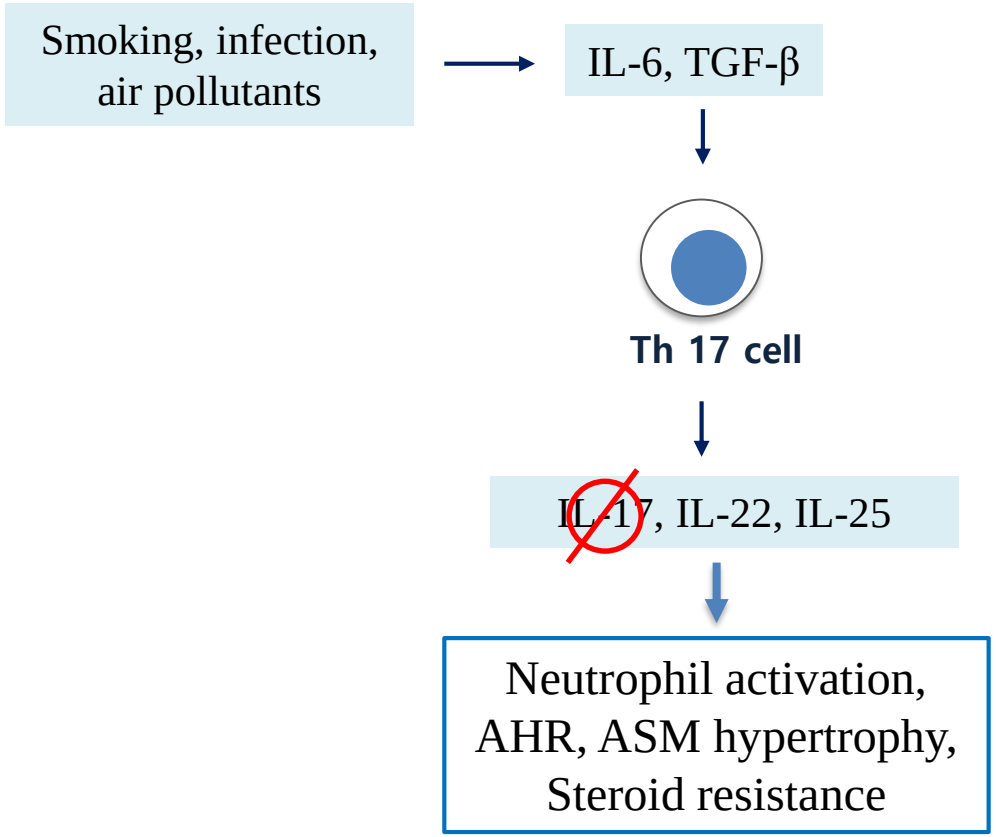
  Type1 helper T-cell (Th1 cell), Type17 helper T-cell (Th17 cell)

- Associate mediators
  - IFN-γ, IL-17, IL-22, IL-25, TNF-α

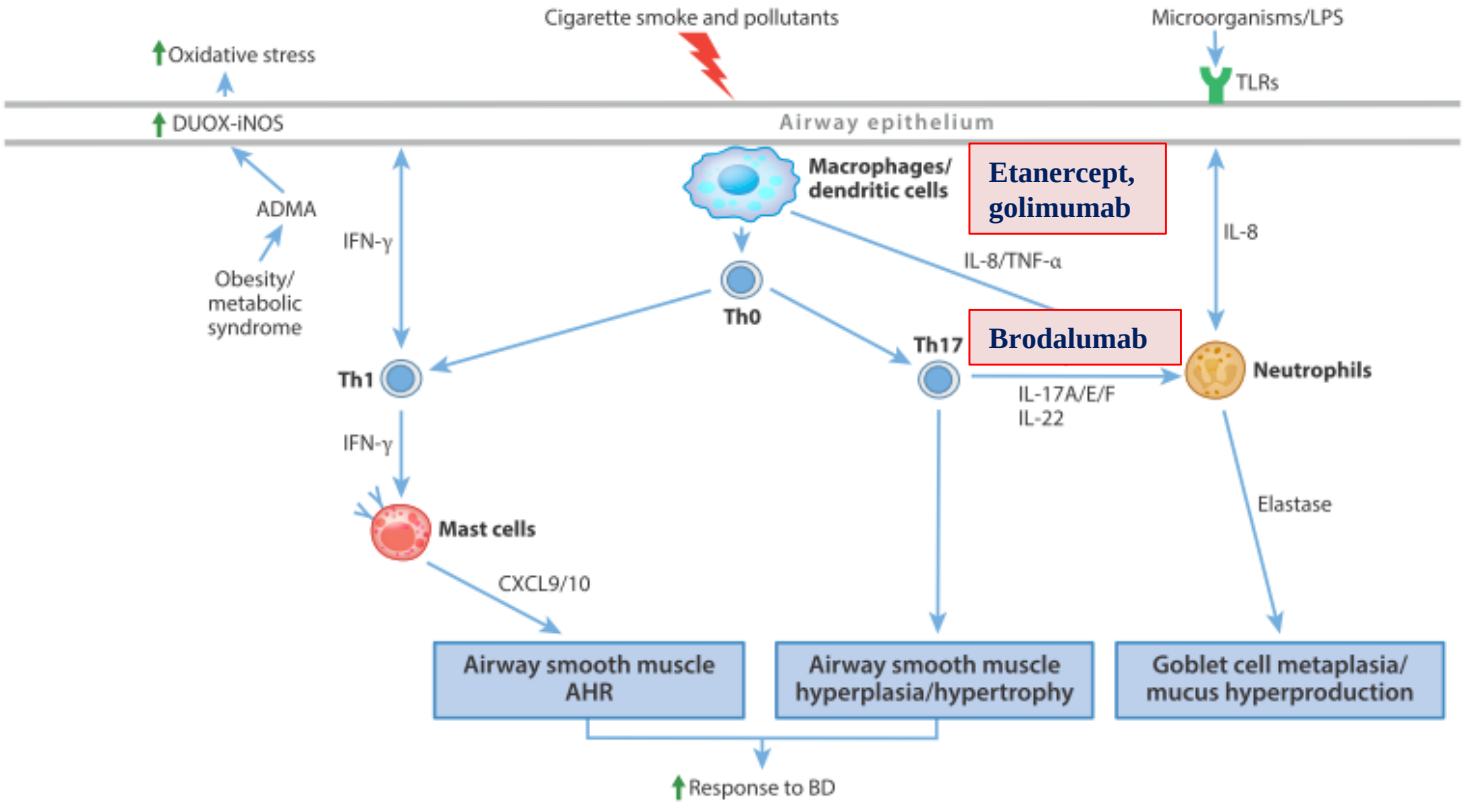
Type1 helper T-cell



Type17 helper T-cell



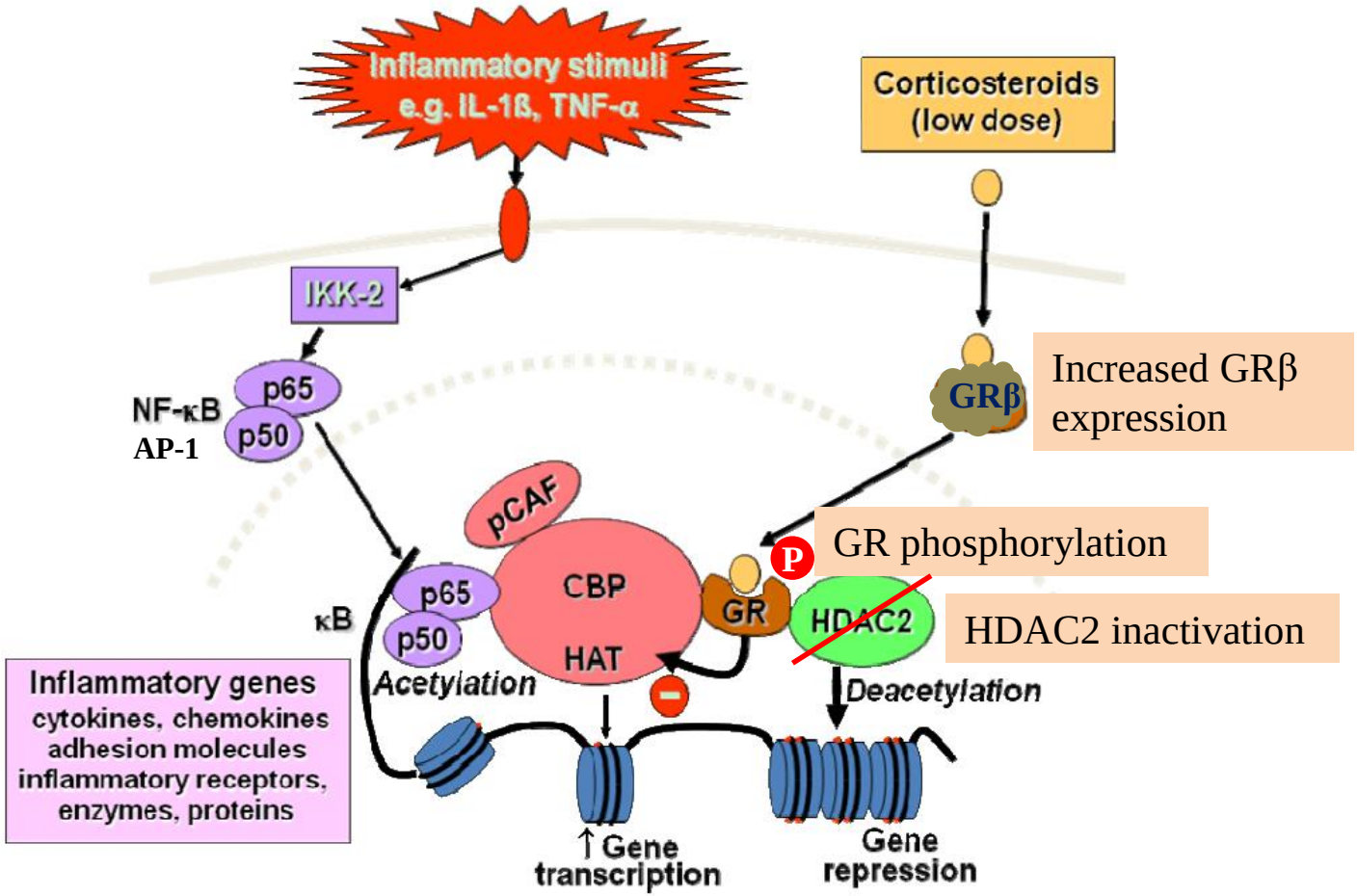
Non-Th2 inflammation



Annu. Rev. Pathol. Mech. Dis. 2015. 10:511–45

Corticosteroid resistance

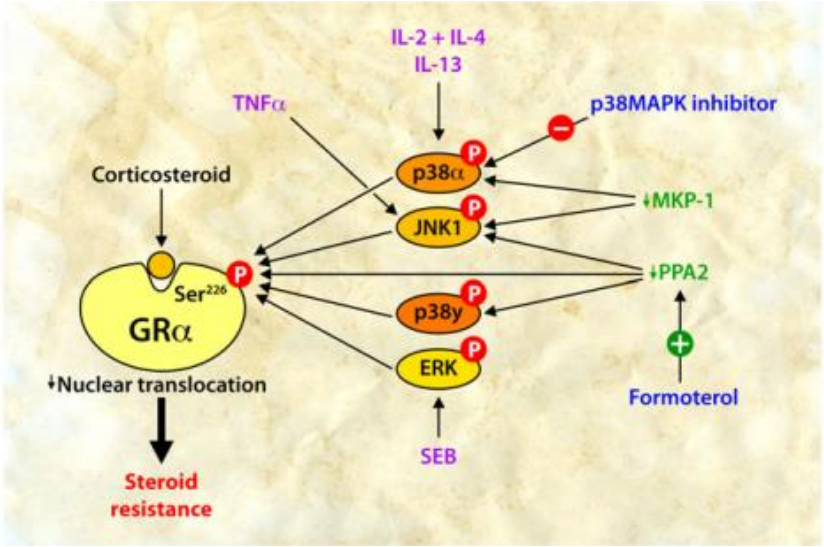
Molecular mechanism of CS resistance

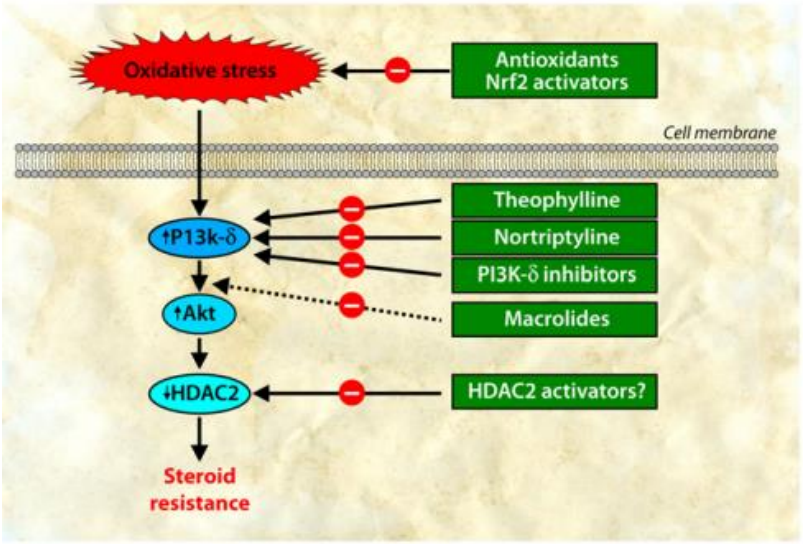


Pharmaceuticals 2010, 3, 514-540

Therapeutic implications

- Promote GR dephosphorylation
  - p38MAPK inhibitor, β-agonist
- Restoring HDAC2 activity
  - Antioxidants, theophylline, nortriptyline, macrolides, PI3Kδ inhibitor, HDAC2 activator





J Allergy Clin Immunol 2013;131:636-45.

Take home message

- The major pathogenesis of severe asthma are **airway remodeling, chronic airway inflammation** and **steroid resistance.**

- Various structures are involved in airway remodeling, especially **bronchial epithelium** and **airway smooth muscle** are considering potential therapeutic target for severe asthma.

- Airway inflammation can be largely divided into **TH2/ non-TH2 subtypes**, and development of customized treatment for non-TH2 inflammation is urgent.

- Several molecular mechanisms of corticosteroid resistance have been unveiled, researches are in progress as a potential treatment target.

경청해주셔서 감사합니다.