Asthma endotype

; toward personalized therapy

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Asthma

- A complex condition

  with differences in severity, natural history, comorbidities, and treatment response.

- Definition

  a common chronic disorder of the airways

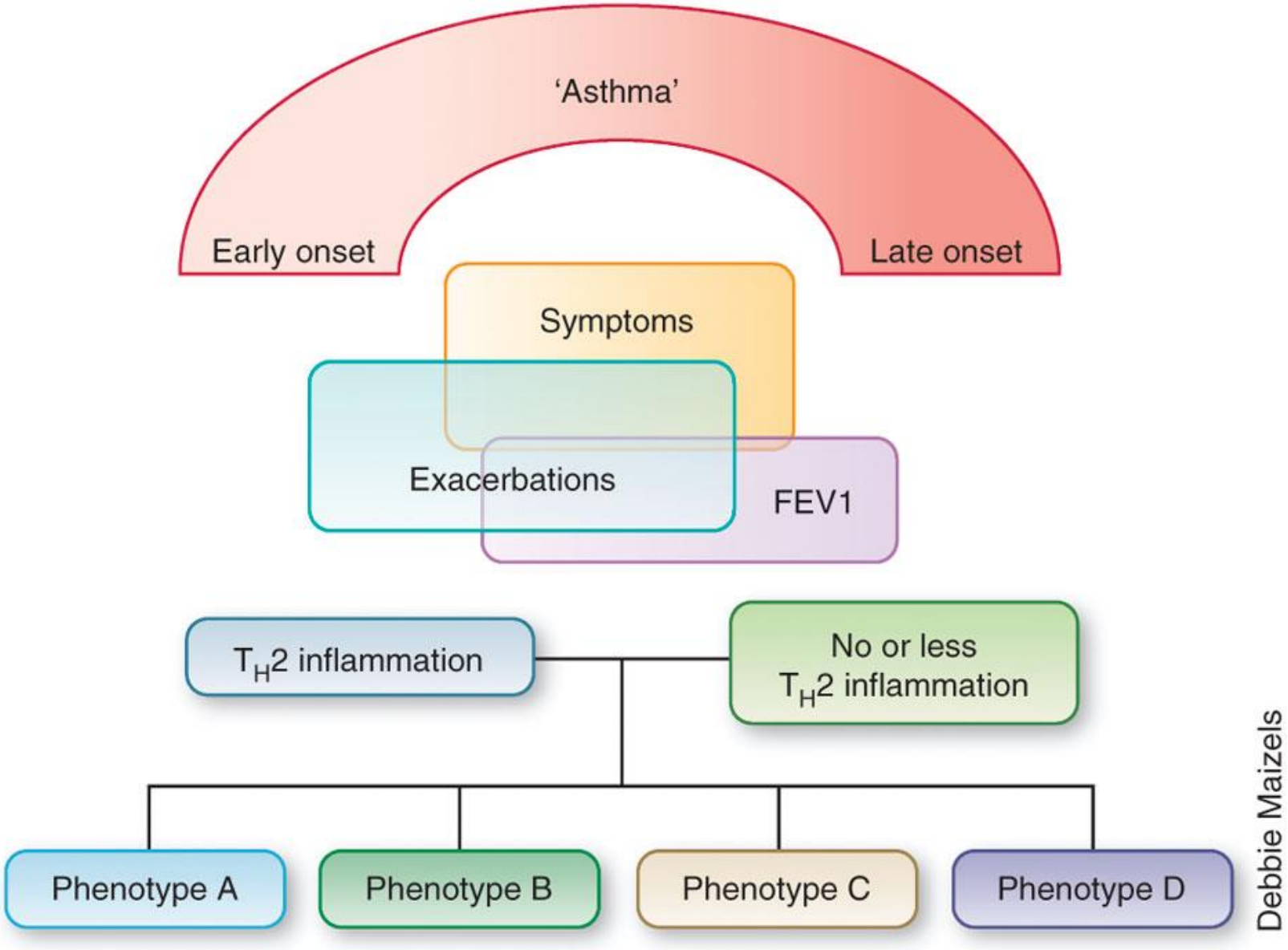
  variable and recurring symptoms, airflow obstruction, AHR, and an underlying inflammation

- Asthma phenotypes are proposed (Wenzel, Lancet, 2006)

Asthma Phenotypes

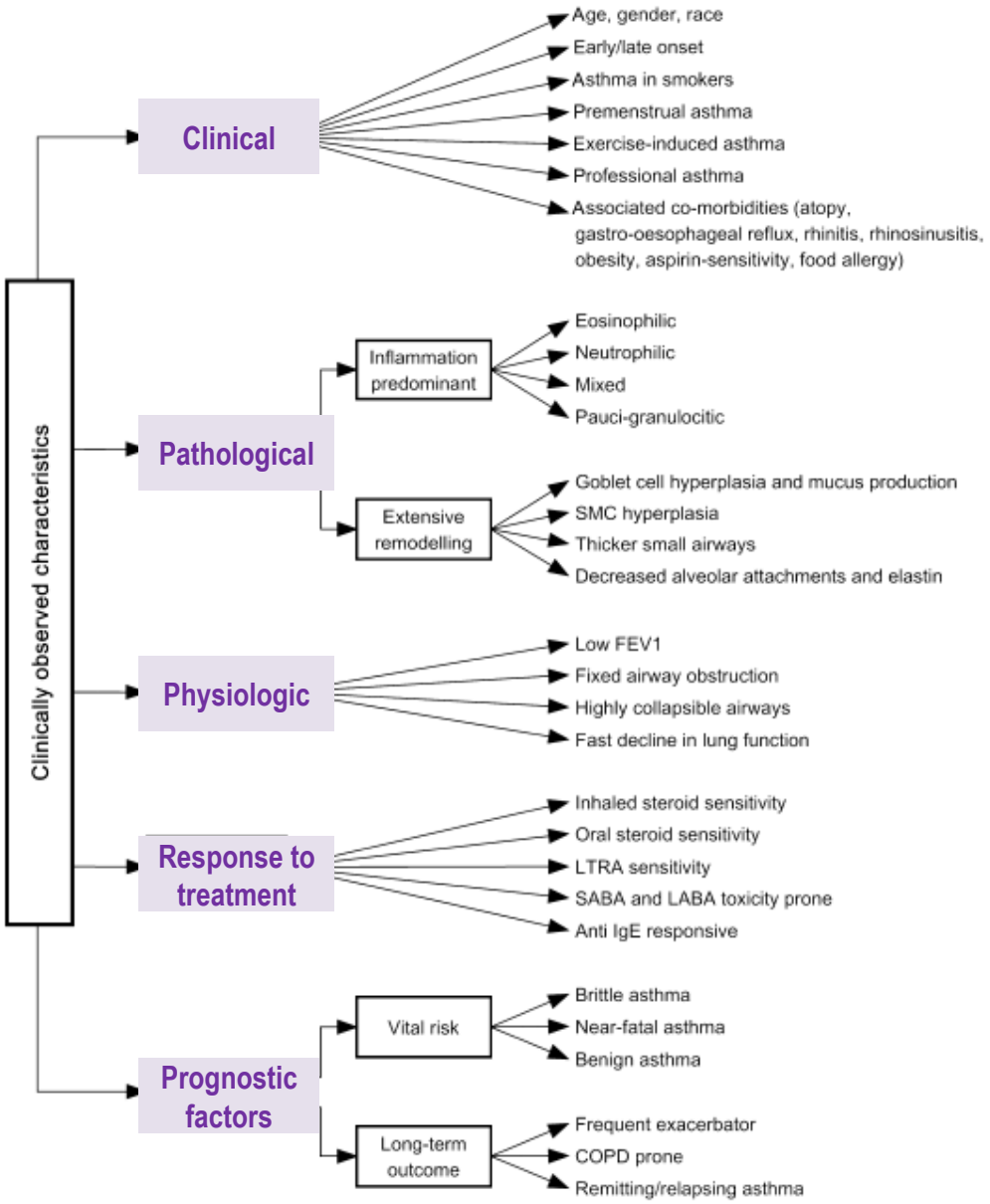
Potential phenotypic categories of asthma by phenotype
Clinical or physiological phenotypes
Severity-defined
Exacerbation-prone
Defined by chronic restriction
Treatment-resistant
Defined by age at onset
Phenotypes related to the following triggers
Aspirin or Non-steroidal anti-inflammatory drugs
Environmental allergens
Occupational allergens or irritants
Menses
Exercises
Inflammatory phenotypes
Eosinophilic
Neutrophilic
Pauci-granulocytic

Wenzel SE, Lancet 2006;368:804-13



Wenzel SE. *Nature Medicine 2012;*18:716–25

Clinically observed asthma phenotypes



Agache I et al, Allergy 2012;67:835-46

Phenotype vs. Endotype

- Phenotype

  describe “observational characteristics”

  ; clinical, physiological, morphologic, and biochemical characteristics

  and responses to different treatments

- Endotype

  introduced by Anderson in 2008

  ; endophenotype

  subtype of disease defined functionally and pathologically

  by a molecular mechanism or by treatment response.

Phenotype vs. Endotype

- Phenotype

  clinically relevant in terms of presentation, triggers,

  and treatment response

  (not related with underlying pathological mechanism)

- Endotype

  subtype based on cellular and molecular mechanisms

  using biomarkers

Moving from phenotypes to endotype

- To link pathobiology to clinical phenotypes

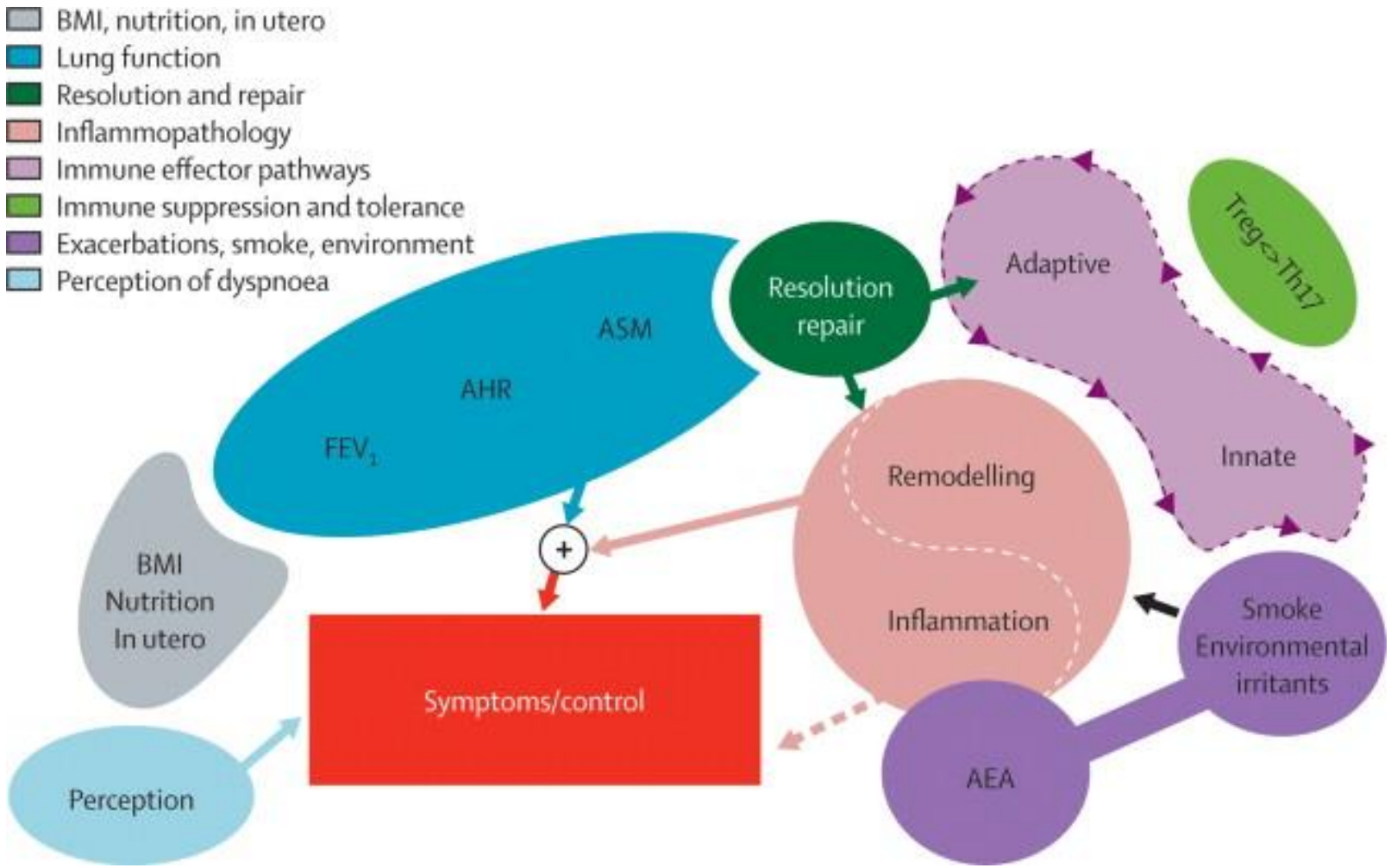
- Pathobiology, biomarker, genetic elements, stability, response to therapy (targeted to the biology)

- Endotype

subtype of a condition which is defined by a distinct functional or pathophysiological mechanism

Wenzel S et al. Clin Exp Allergy 2012; 42:650-8

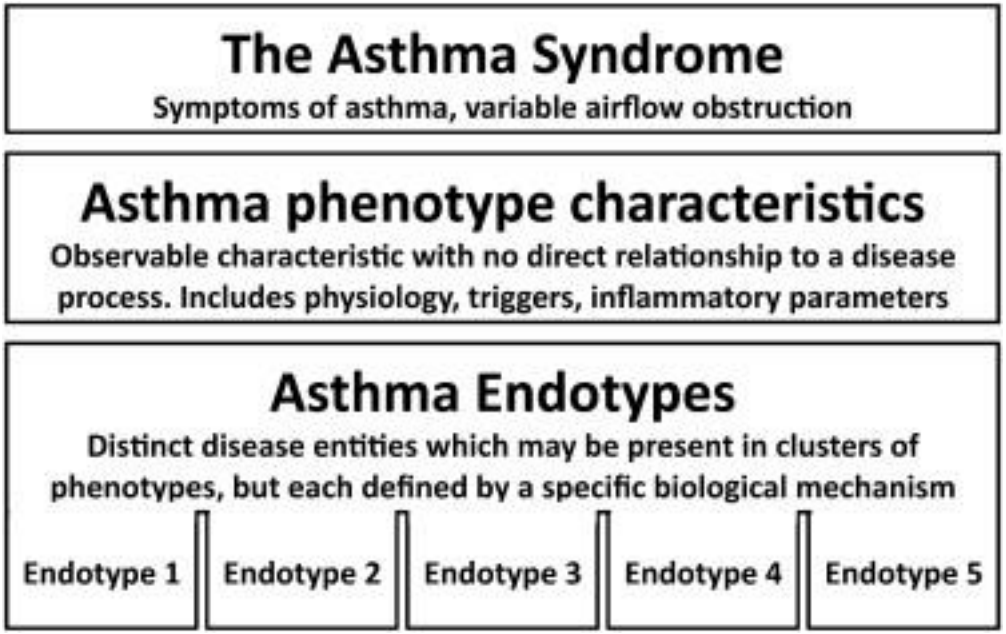
Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease



Anderson GP. Lancet, 2008; 372:1107-19

Endotype

- A subtype of a condition, defined by a distinct functional or pathophysiological mechanism



Lötvall J et al. J Allergy Clin Immunol 2011; 127:355-60

Endotype

- Definitions will enable the identification of novel therapeutic targets and biomarkers
- Defining endotypes

  may help predict the response to treatment

  → facilitate improved management decisions

- Phenotypes

  represent observations of clinical dimensions

- Endotypes

  represent mechanistically coherent disease entity

Proposed relationship between asthma phenotypes and endotypes:

Phenotype:	Eosinophilic asthma
	Endotypes: allergic asthma (adult),* aspirin-sensitive asthma, severe late-onset hypereosinophilic asthma,* ABPM*
Phenotype:	Exacerbation-prone asthma
	Endotypes: allergic asthma (adult),* aspirin-sensitive asthma,* late-onset hypereosinophilic asthma, API-positive preschool wheezer,* ABPM,* viral-exacerbated asthma, premenstrual asthma
Phenotype:	Obesity-related asthma
	Endotypes: airflow obstruction caused by obesity, severe steroid-dependent asthma, severe late-onset hypereosinophilic asthma*
Phenotype:	Exercise-induced asthma
	Endotypes: cross-country skiers' asthma, other forms of elite-athlete asthma, allergic asthma, API-positive preschool wheezer*
Phenotype:	Adult-onset asthma
	Endotypes: aspirin-sensitive asthma,* infection-induced asthma, severe late-onset hypereosinophilic asthma*
Phenotype:	Fixed airflow limitation
	Endotypes: noneosinophilic (neutrophilic) asthma
Phenotype:	Poorly steroid-responsive asthma
	Endotypes: noneosinophilic (neutrophilic) asthma, steroid-insensitive eosinophilic asthma, airflow obstruction caused by obesity

Lötvall J et al. J Allergy Clin Immunol 2011; 127:355-60

Proposed rules for defining asthma endotype

- No generally accepted criteria

- 7 parameters are suggested
  - clinical characteristics
  - biomarkers
  - lung physiology
  - genetics
  - histopathology
  - epidemiology
  - treatment response

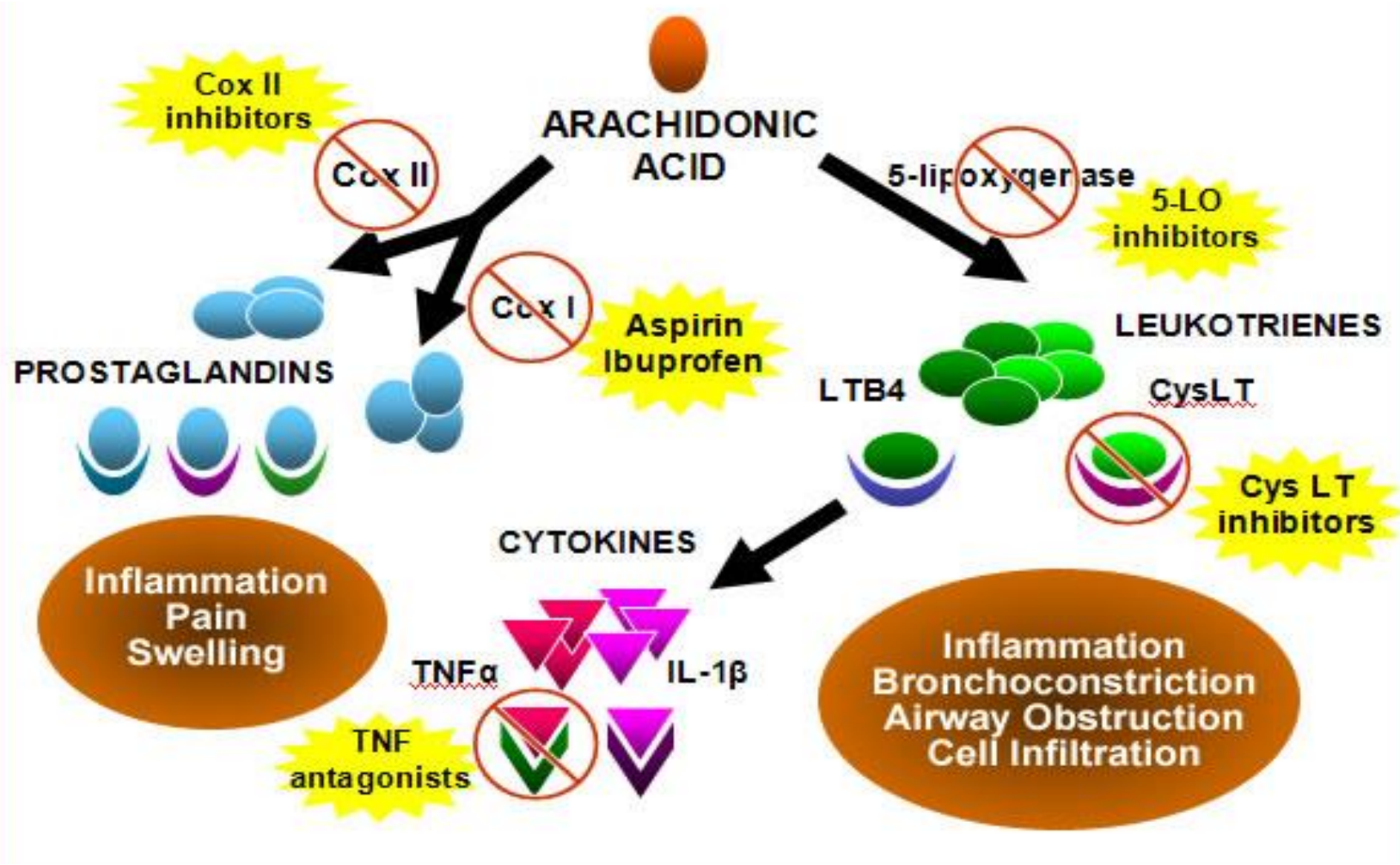
Examples of endotypes that fulfill at least 5 of 7 prespecified disease characteristics

Endotype	Disease characteristics							Proposed mechanism
	Clinical characteristics	Biomarkers	Lung physiology	Genetics	Histopathology	Epidemiology	Treatment response	
Proposed Endotype	History, P/Ex, Comorbidities	Eosinophilia, FeNO, SPT, IgE	BHR, FEV1 reversibility	SNPs and pathways	Tissue/lung Characteristics	Prevalence, risk factors, and natural history	Response or lack of response to a specific treatment	Specific biological pathway or process
Aspirin-sensitive Asthma	Polyposis, often more severe asthma	Often eosinophilic, ↑urinary LTs	aspirin challenge	LT-related gene Polymorphisms	Often eosinophilic	Adult onset, severe disease poor prognosis, prevalence 2% to 5%	Responds to anti-LT, especially 5-LO inhibitors	Likely eicosanoids-related
ABPM	Severe, mucus production, adult/long disease duration	Blood eos, markedly ↑IgE and specific IgE	Less reversible/ fixed airflow Obstruction	HLA and rare CF variants	Bronchiectasis/eosinophils and PMNs, bronchocentric granulomatosis	Long duration/adult onset/poor prognosis	Glucocorticoids, antifungals, possibly omalizumab	Colonization of airways
Allergic asthma (adults)	Allergen associated Sx. /allergic rhinitis	Positive SPT, ↑IgE/↑FeNO	Specific allergic bronchospasm	T_H2 pathway SNPs	Eosinophils, SBM thickening	Childhood onset, history of eczema	Responds to glucocorticoids and omalizumab, possible IL-4/13 pathway inhibition	T_H2–dominant
API-positive preschool Wheezer	>3 episodes / yr, 1 major or 2 minor characteristics	Often >4% eos in blood (minor), aeroallergen-specific IgE	Potential ↑ risk of loss of lung Function	Unknown	Unknown	Mother or father with asthma	Responds well to daily inhaled glucocorticoids	T_H2–dominant
Severe late-onset Hypereosinophilic	Severe exacerbations, late-onset ds	PB eosinophilia	Bronchodilator –resistant, episodic fall in lung function, steroid–sensitive	No evidence	High blood eosinophil count and eosinophils in tissue	Approximately 20 % of severe asthma populations	Glucocorticoid-sensitive, often oral steroid–dependent, responds to anti–IL-5	Nonatopic, otherwise unknown
Asthma in cross-country skiers	Mild to moderate severity, sx mostly related to exercise, URTI commonly reported	FeNO normal, normal PB eos, ↑ LTE_4 in urine	Methacholine and or exercise positive, usually negative to mannitol or AMP challenge	Unknown	SBM thickening with low-grade noneosinophilic inflammation, increased neutrophils in sputum related to training intensity or duration, BALT in airway mucosa	15% to 25% of elite skiers, highest prevalence among those training in a cold, dry environment	Responds poorly to inhaled glucocorticoid treatment, improves when training intensity diminishes	Cold, dry air induces chronic stress to the airways, subclinical viral infections?

Aspirin-sensitive asthma (ASA)

- Chronic/severe rhinosinusitis, nasal polyps (AERD)
- Peripheral blood eosinophilia
- Urinary leukotrienes at baseline and aspirin challenge
- Cysteinyl leukotriene production leukotriene C4 synthase
- SNPs – genes encoding for leukotriene overproduction

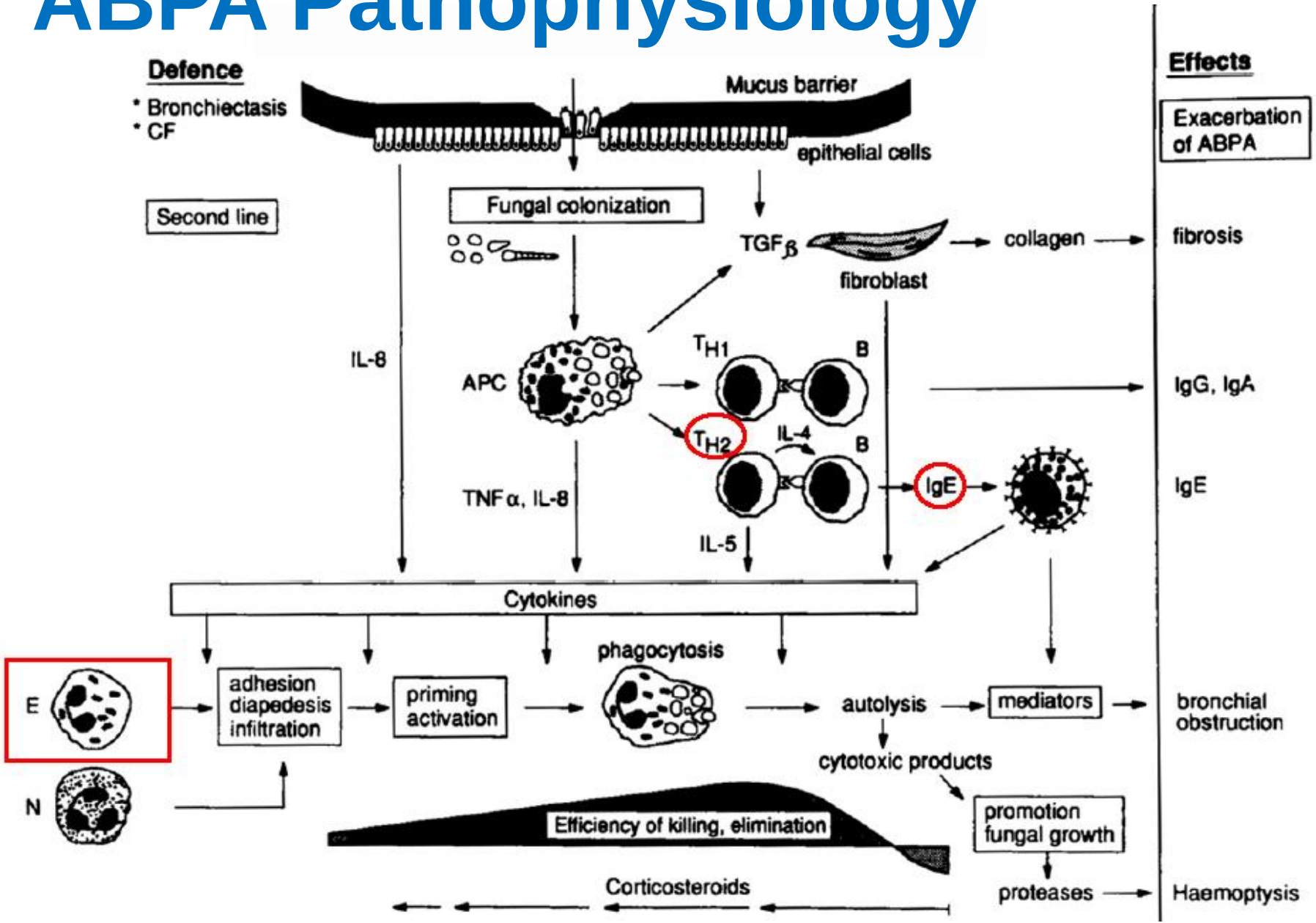
ASA mechanisms



ABPM

- Hypersensitivity reaction to the colonization of the airways by molds, most frequently *Aspergillus fumigatus*.
- mixed pattern of neutrophilic / eosinophilic airway inflammation
- ↑ mold specific IgE and IgG
- Episodic bronchial obstruction and mucoid impaction with the development of bronchiectasis and fixed airflow obstruction
- Considered a complication of the allergic asthma endotype
- Associated with severe disease, recurrent exacerbations and progressive lung damage
- Respond to systemic glucocorticoids, antifungal agent, omalizumab.

ABPA Pathophysiology



Diagnostic features

Main Diagnostic criteria

Bronchial asthma

Pulmonary infiltrates

Peripheral eosinophilia(>1000/uL)

Immediate wheal-and-flare response to A. fumigatus

Serum precipitins to A. fumigatus

Elevated serum IgE

Central bronchiectasis

Other Diagnostic features

History of brownish plugs in sputum

Culture of A. fumigatus from sputum

Elevated IgE(and IgG) class antibodies specific for A. fumigatus

Allergic asthma

- A classic form of persistent asthma
- Typically has a childhood onset
- Accompanied by allergic features, including sensitization to allergens and allergic rhinitis
- Airway eosinophilia
- Th2 dominant inflammatory process

Asthma-predictive index(API) positive preschool wheezer

- Clearly increased risk of developing asthma
- May not encompass the classic allergic asthma endotype
- Repeated wheezing episodes (>3 in first 3 yrs)

Major criteria (1 of 3)

atopic dermatitis

parental asthma

sensitization to an aeroallergen

Minor criteria (2 of 3)

peripheral eosinophils >4%

wheezing unrelated to the common cold

sensitization to a food allergen

Late-onset asthma

- Severe exacerbations
- Hypereosinophilia in blood (>1,000/mm^3), and sputum (>10%)

  who meet the criteria for an asthma endotype
- About 20% of refractory asthma
- Lower prevalence of atopy
- Lower BDR and AHR
- Anti-IL-5 therapy may be clinically useful

Cross-country skier's asthma

- Asthma symptoms

  related to strenuous skiing-related exercise with AHR
- Exposure to cold, dry air → major risk factor
- Seldom associated with allergic sensitization
- ↑ Lymphocytes, macrophages, and neutrophils
- Seldom eosinophils
- Not responsive to ICS alone.

Severe asthma

Characteristics variably associated with severe asthma

Symptoms

Wheeze, shortness of breath, cough, nocturnal awakenings, chest tightness

Airway obstruction

Complete or incomplete bronchodilator responsiveness

Severe exacerbations

Frequent exacerbations

Atopy/allergic responses

Non-steroidal ant-inflammatory reactions

Age at onset

Rhinosinusitis

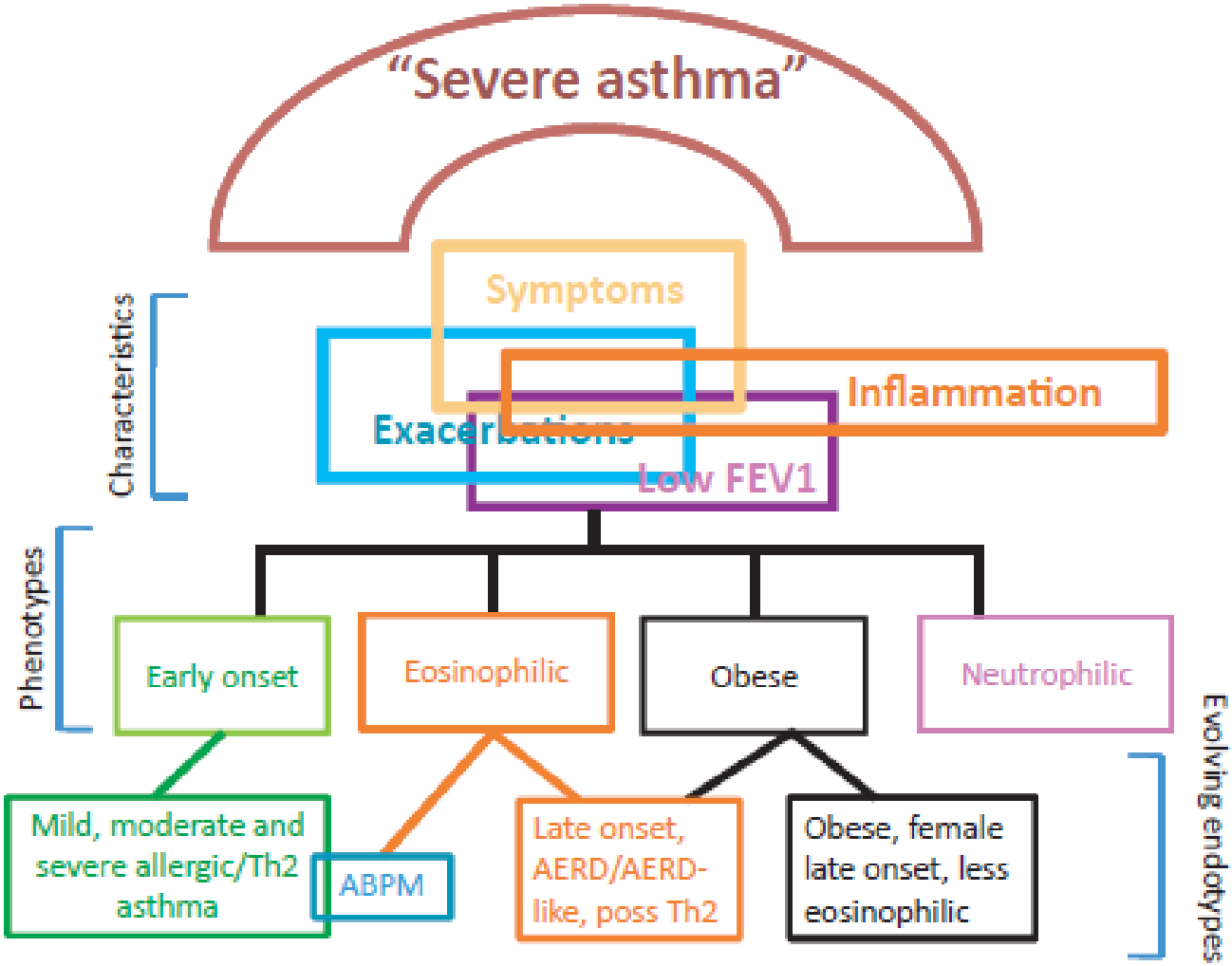
Air trapping

Airway wall thickening

Inflammation

Eosinophilic, neutrophilic, paucigranulocytic

Wenzel S et al. Clin Exp Allergy 2012; 42:650-8



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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 & probably Progressive	Aeroallergen sensitivity other allergic diseases	17q12–21 Th2 pathway	Th2 cytokines, eos–less clear in severe disease	FeNO, increased specific IgE Periostin	Mild responds to CSs/Th2 blockers. less clear in severe
Persistent Eosinophilia	Adult onset, persistence and progression unknown	Often severe sinusitis, nasal polyps Subset with AERD	LT pathway HLA	Blood and lung eos despite CSs IL-5, cLT pathway	Sputum eos (not specific for this endo-type)	Anti-Th2/IL-5 LT Modifiers
ABPM	Usually adult onset persistent, but progression unknown	Increased cough/ mucus central Bronchiectasis	CFTR?	Blood and lung eos, mixed adaptive Immunity	Fungus specific IgE and IgG	CSs, anti-fungals, possibly anti-IgE
Obese -Female	Very late onset persistence and progression unknown	Very symptomatic, but less airway obstruction and few severe exacerbations hormonal ties	Unknown	Inconsistent reports	Unknown	No good studies of targeted Rx, but poorly CS responsive
Neutrophilic	Unknown	Fixed airway obstruction, few other defined clinical characteristics	Unknown	Neutrophils, possibly increased innate immune activation	Unknown	Possible response to macrolide antibiotics

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Phenotypes of asthma and endotypes

Allergic asthma	Intrinsic asthma	Neutrophilic asthma	Aspirin intolerant asthma	Extensive remodeling asthma
• Eosinophilic • Th2 inflammation • Steroid response • Response to ITX • Anti IgE response • Anti IL-5 responsive • Anti IL-4/IL-13 responsive	• Eosinophilic • Neutrophilic • Association with AutoAb/superantigen • Steroid response • Steroid resistant	• Innate immune • HDAC2 recruitment • Neutrophil survival • Steroid resistant • Antioxidant response • Anti TNF-α response • HDAC regulator	• Eosinophilic • LT C4, D4, E4 • Steroid response • LTRA response	• Lack of inflammation • Extensive remodeling • EMTU activation • ASM abnormality • Defective repair mechanism • Steroid resistant • ASM targeted Tx • MMP-targeted Tx • Antiangiogenic response

Agache I et al, Allergy 2012;67:835-46

Genetics of asthma and endotypes

Asthma endotype	Proposed genetic linkage
Allergic asthma	SNP located inside the coding sequence of C5 Other loci regulating immune- or inflammation-mediated mechanisms and airway smooth muscle contraction
	Several Th2 cytokine SNPs Filaggrin ORMDL3
	TSLP promoter gene polymorphism
Nonatopic asthma	Homozygosity for MMP-9 variants
Aspirin-intolerant asthma	SNPs of CEP68 gene
	Galectin-10 gene
	The human EMI domain–containing protein 2 (EMID2) gene
	Solute carrier family 22 member 2 (SLC22A2), DTD1, STK 10, ADAM 33, HLA-DPBI*0301, genes encoding the leucotriene C4 synthase, ALOX5, CYSLT, PGE2, TBXA2R, and TBX21
Extensive remodeling asthma	ADAM 33 and DPP10 polymorphisms
	Hedgehog interacting protein (HHIP) gene Family with sequence similarity 13, member A (FAM13A), Patched homolog 1 (PTCH1)

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Asthma endotypes and response to targeted Treatment

Targeted treatment	Surrogate marker predicting better response	Subphenotype	Strength of association
	Younger age, shorter disease duration, and increased LTE4/FENO ratio	Pediatric asthma	+
Antileukotriene agents	Comorbid allergic rhinitis, younger age, shorter duration of asthma, and treatme nt with only ICS and not ICS + LABA	Adult asthma	+
	Less severe aspirin-induced bronchospa sm Lack of history of aspirin hypersensiti vity or sinusitis	AIA	+/−
Allergen-specific Immunotherapy	Monosensitized and/or in whom a single allergen is predominantly driving asthma symptoms	Mild, well-controlled allergic asth ma	+
Aspirin desensitization	Recurrent nasal polyposis Overdepende nce on systemic corticosteroids	AIA	+
Restoration of HDAC 2 nuclear recruitment with theophylline	?	Neutrophilic asthma?	+/−
	?	Smokers with asthma	+/−

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Asthma endotypes and response to targeted treatment with biologics

Targeted treatment	Surrogate marker predicting better response	Subphenotype	Strength of association
Anti-IgE	Both sensitized and exposed	Severe allergic asthma	+
		Uncontrolled asthma	+/−
		Exacerbation-prone asthma	+/−
	IP-10?	Viral-induced asthma exacerbations (prevention)	+/−
Anti-IL-5	Sputum eosinophils > 3%	Refractory eosinophilic asthma	+
Anti-IL-13	Serum periostin FeNO?	Allergic asthma with dominant IL-13 activation	+
Anti-IL-4/IL-13	IL-4 receptor α polymorphism	Allergic asthma with dominant IL-4/IL-13 activation	+/−
Anti-TNF-α	Increased TNF-α in BAL, bronchial biopsies, PBMC	Severe corticosteroid refractory asthma with up-regulation of TNF-α axis	+/−

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Conclusions

- There is increasing evidence for different pathogenetic mechanisms within the syndrome of asthma
- Different treatment approaches according to different endotypes
- Specific phenotypes and endotypes may be defined by their response to target-specific interventions.
- Novel biomarkers will be developed to identify the pathogenic mechanisms
- More specific, individually tailored treatment will be possible based on more comprehensive approaches to understand the pathogenesis of asthma