Asthma

- ***airflow obstruction that varies markedly, both spontaneously and with treatment.***

- ***inflammation in the airways that makes them more responsive than nonasthmatics to a wide range of triggers***

- ***excessive narrowing with consequent reduced airflow and symptomatic wheezing and dyspnea.***

- **Asthma is a *chronic inflammatory* disorder of the airways**

- **inflammation causes recurrent episodes of**

❖ **Wheezing**

❖ **Breathlessness**

❖ **chest tightness**

❖ **Coughing *particularly at night or in the early morning***

- ✓ ***No feature is unique to asthma***

- ✓ **no feature is universal in patients with the condition**

For example

A. all tests of airway caliber may be normal between attacks

B. Bronchial responsiveness may be normal over most of the year in patients with seasonal asthma

C. bronchial hyperresponsiveness is often found in people with allergic rhinitis but without asthma

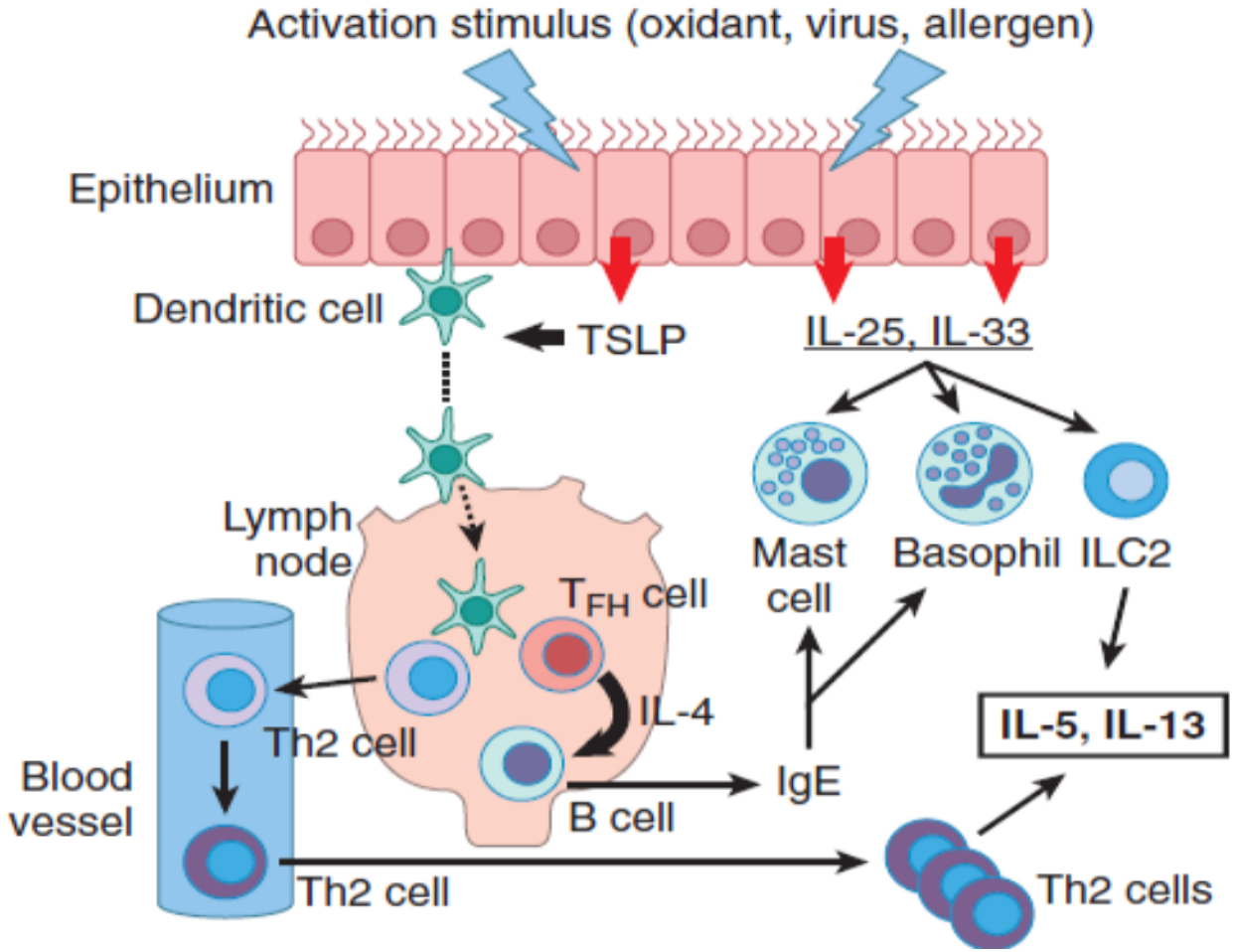
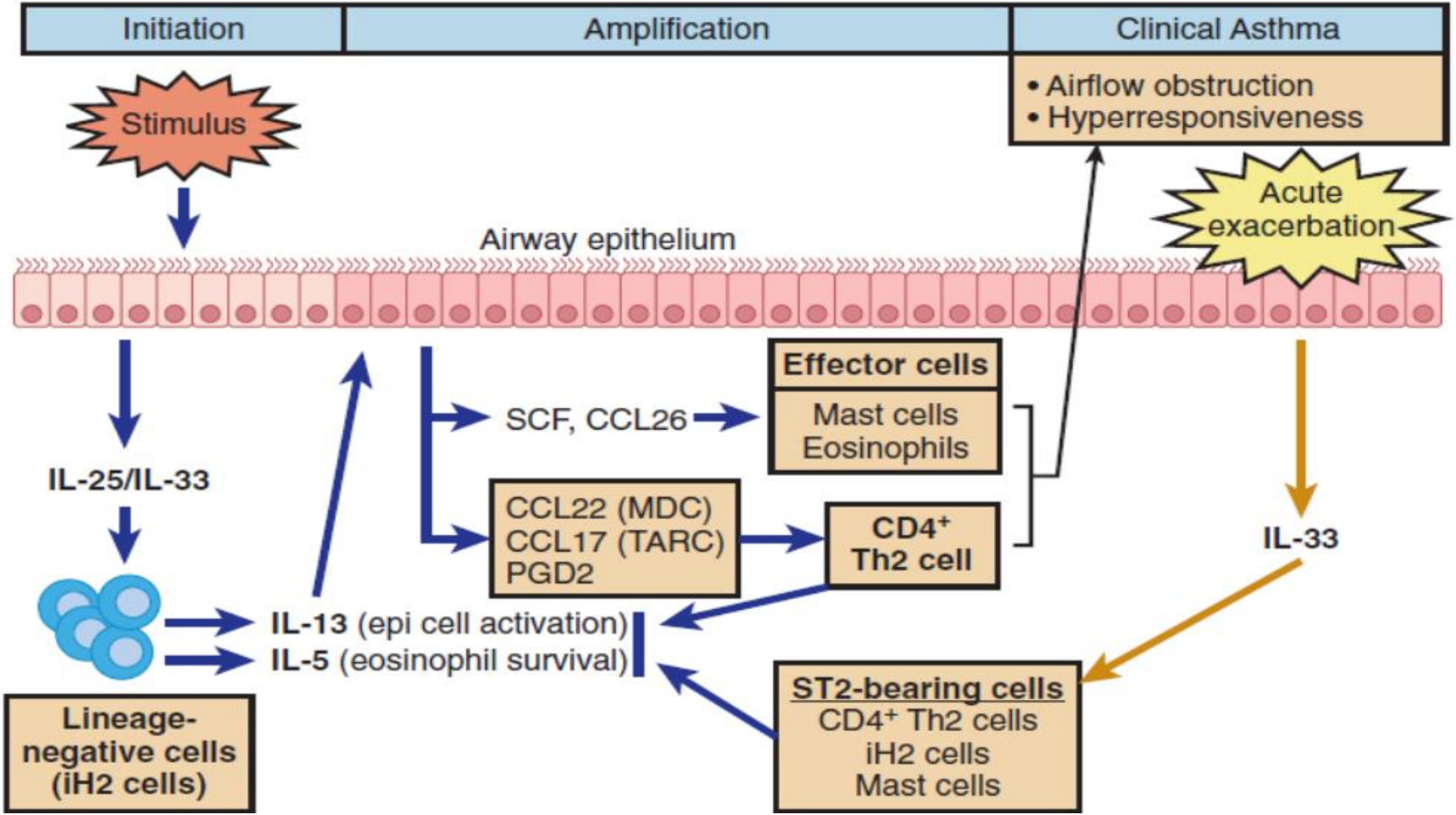


Figure 41-4 Generation of Type 2 immune responses in the lower airway. The airway epithelium is activated to release thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. TSLP mediates maturation and migration of dendritic cells to local lymph nodes, where they have the following effects: (1) generation of Th2 cells from Th0 cells; (2) generation of IL-4– secreting T_{FH} cells; and (3) B cell isotype-switching to IgE, which arms mast cells and basophils for allergen-specific activation. IL-33 promotes IL-4 release from basophils, and IL-25 and IL-33 promote IL-5 and IL-13 release from innate lymphoid type 2 (ILC2) cells and Th2 cells (see text for details). T_{FH}. T follicular helper cells. (From Locksley RM: Asthma and allergic inflammation. Cell 140(6):777–783, 2010.)


Initiation
Amplification
Clinical Asthma
• Airflow obstruction
• Hyperresponsiveness
Stimulus
Acute exacerbation
Airway epithelium
IL-25/IL-33
SCF, CCL26
Effector cells
Mast cells
Eosinophils
CCL22 (MDC)
CCL17 (TARC)
PGD2
CD4+ Th2 cell
IL-33
IL-13 (epi cell activation)
IL-5 (eosinophil survival)
Lineage-negative cells (iH2 cells)
ST2-bearing cells
CD4+ Th2 cells
iH2 cells
Mast cells

ASTHMA HETEROGENEITY

patients with asthma can have a ***great deal of heterogeneity*** with respect to severity of airflow limitation, symptoms, degree of reversibility, and therapeutic response

I. **CELLULAR PHENOTYPES**
II. **CLINICAL PHENOTYPES**
III. **TH2 INFLAMMATION AS A BIOMARKER**
IV. **NON-TH2 ASTHMA PHENOTYPES**

CELLULAR PHENOTYPES

1-Eosinophilic

majority of asthmatics

generally responds to ICSs with reduced eosinophils, improved airway obstruction, and decreased symptoms

2-Neutrophilic

up to 25% of asthmatics not on treatment and in up to 50% of those on

responds poorly to ICSs

lower FEV1, fewer mast cells

3-mixed eosinophilic and neutrophilic

refractory asthma

4-paucigranulocytic

CLINICAL PHENOTYPES

1-mild to moderate asthmatics

- *early-onset atopic asthma and eosinophilia*
- *preponderance of obesity, females, and lack of eosinophilia*
- *mild disease and lack of airway eosinophilia*

2-severe, refractory disease

- *early-onset atopic*
- *obese noneosinophilic*
- *early onset and symptoms in the absence of eosinophilia*
- *late onset, minimal symptoms, and marked sputum eosinophilia*

TH2 INFLAMMATION AS A BIOMARKER

expression level of IL-13–induced genes in epithelial

- ***Th2-high*** responded to inhaled corticosteroids

- ***Th2-low*** did not respond to inhaled corticosteroids

NON-TH2 ASTHMA PHENOTYPES

Th1- and Th17-driven inflammation can lead to airflow obstruction and exacerbate an asthma phenotype

corticosteroid resistance

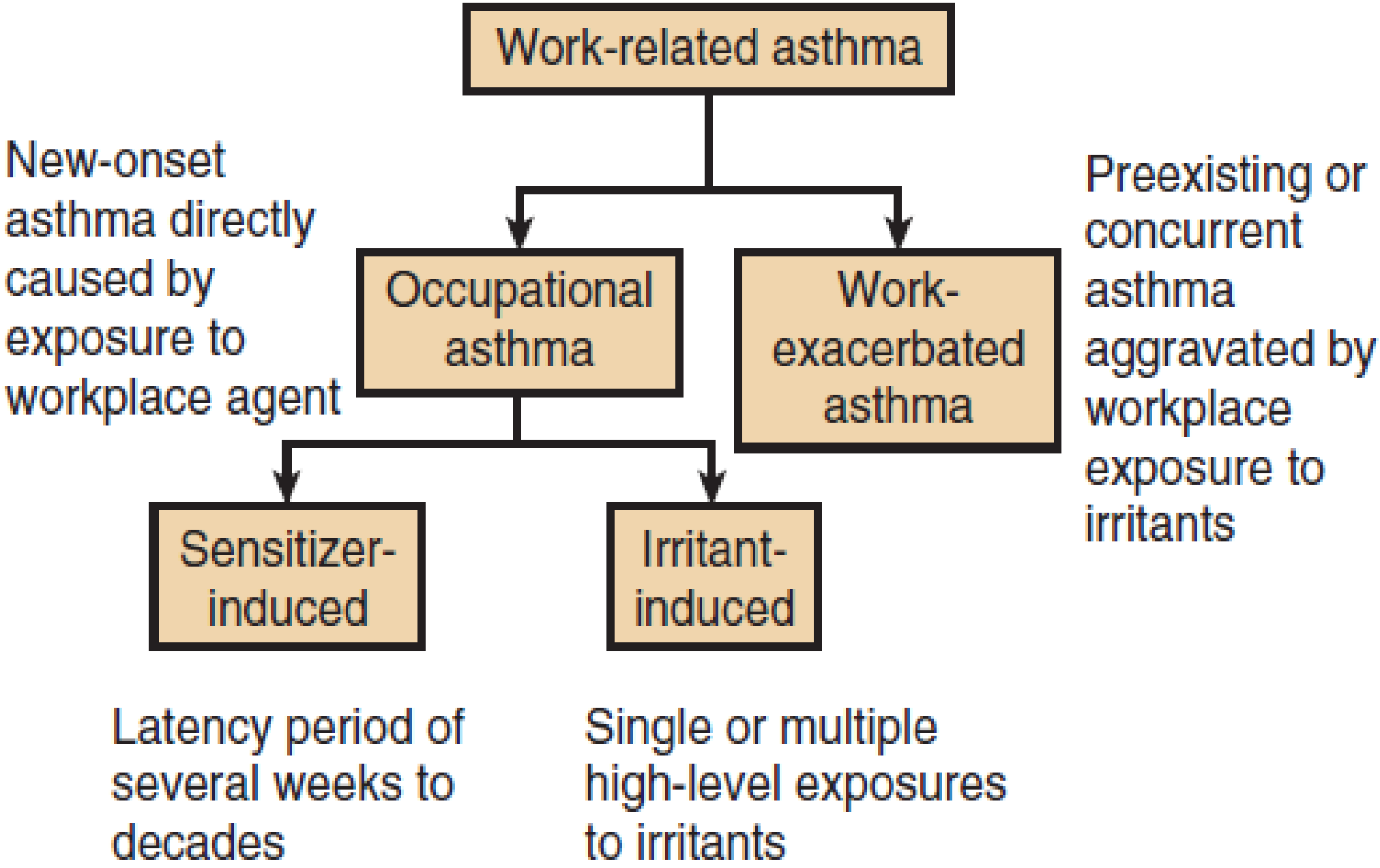
IMMUNE RESPONSES IN THE LOWER AIRWAY

1-Type 1

- ✓Th1 CD4+
- ✓mounted against intracellular bacteria, viruses, and protozoa
- ✓can also be inappropriately mounted against self-antigens, and this is one mechanism of ***autoimmune disease***

2-type 2

- ✓Th2 CD4+ cells and IgE
- ✓usually arise in response to helminth and parasite infections
- ✓can also be inappropriately mounted against innocuous environmental antigens resulting in ***allergy***


Work-related asthma
New-onset asthma directly caused by exposure to workplace agent
Occupational asthma
Work-exacerbated asthma
Preexisting or concurrent asthma aggravated by workplace exposure to irritants
Sensitizer-induced
Irritant-induced
Latency period of several weeks to decades
Single or multiple high-level exposures to irritants

Intrinsic Asthma

- ✓ A minority of asthmatic patients (approximately 10%)
- ✓ negative skin tests to common inhalant allergens
- ✓ normal serum concentrations of IgE.
- ✓ later onset of disease (adult-onset asthma)
- ✓ concomitant nasal polyps
- ✓ may be aspirin-sensitive
- ✓ more severe, persistent asthma

Figure 1 Selected asthma subphenotypes

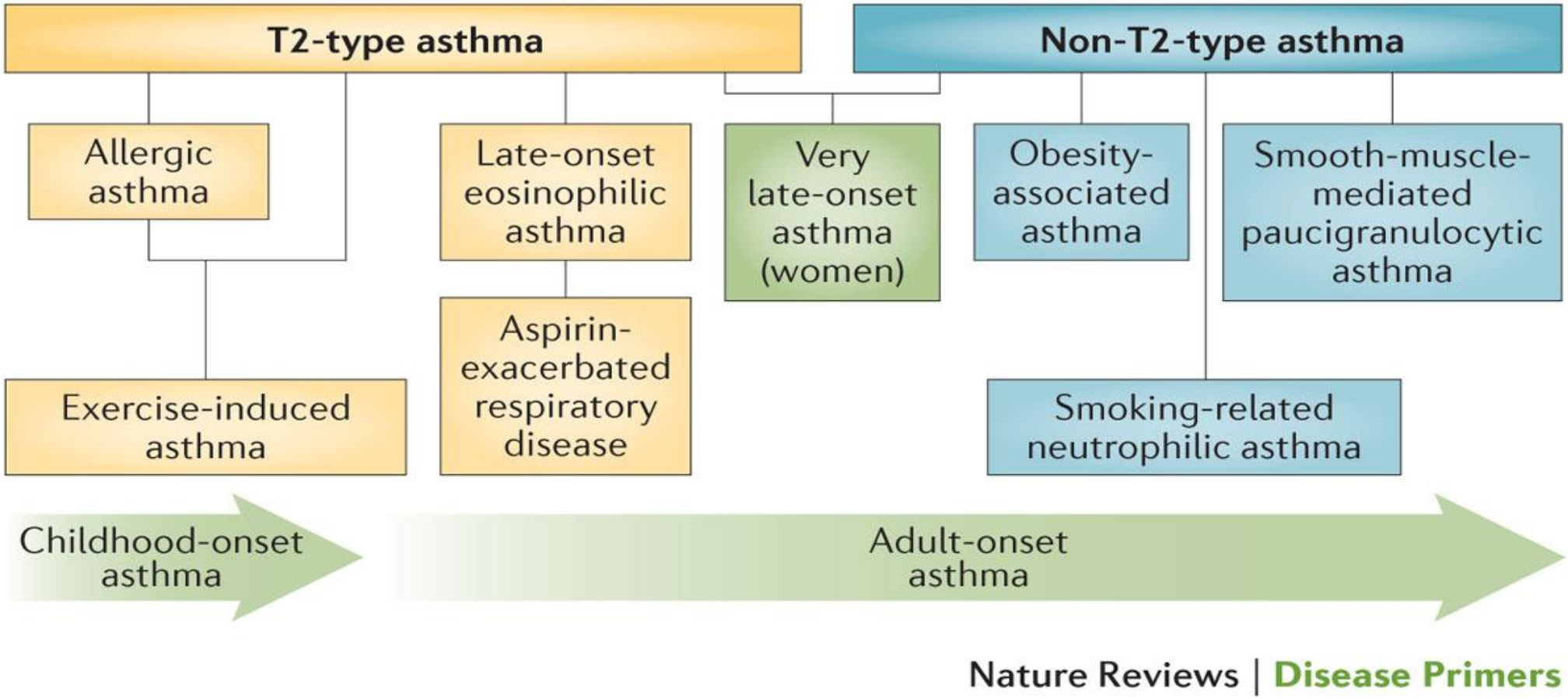


Figure from Wenzel, S. E. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat. Med.* **18**, 716–725 (2012), Nature Publishing Group

Pathology

1. Asthma is associated with a specific ***chronic inflammation*** of the mucosa of the lower airways
2. The airway mucosa is infiltrated with activated eosinophils and T lymphocytes, and there is activation of mucosal mast cells.
3. A characteristic finding is ***thickening of the basement membrane***
4. The epithelium is often shed or friable

- The ***airway wall*** itself may be ***thickened*** and edematous, particularly in fatal asthma
- occlusion of the airway lumen by a mucous plug(common finding in fatal asthma)
- vasodilation and increased numbers of blood vessels
- There is inflammation ***in the respiratory mucosa from the trachea to terminal bronchioles***

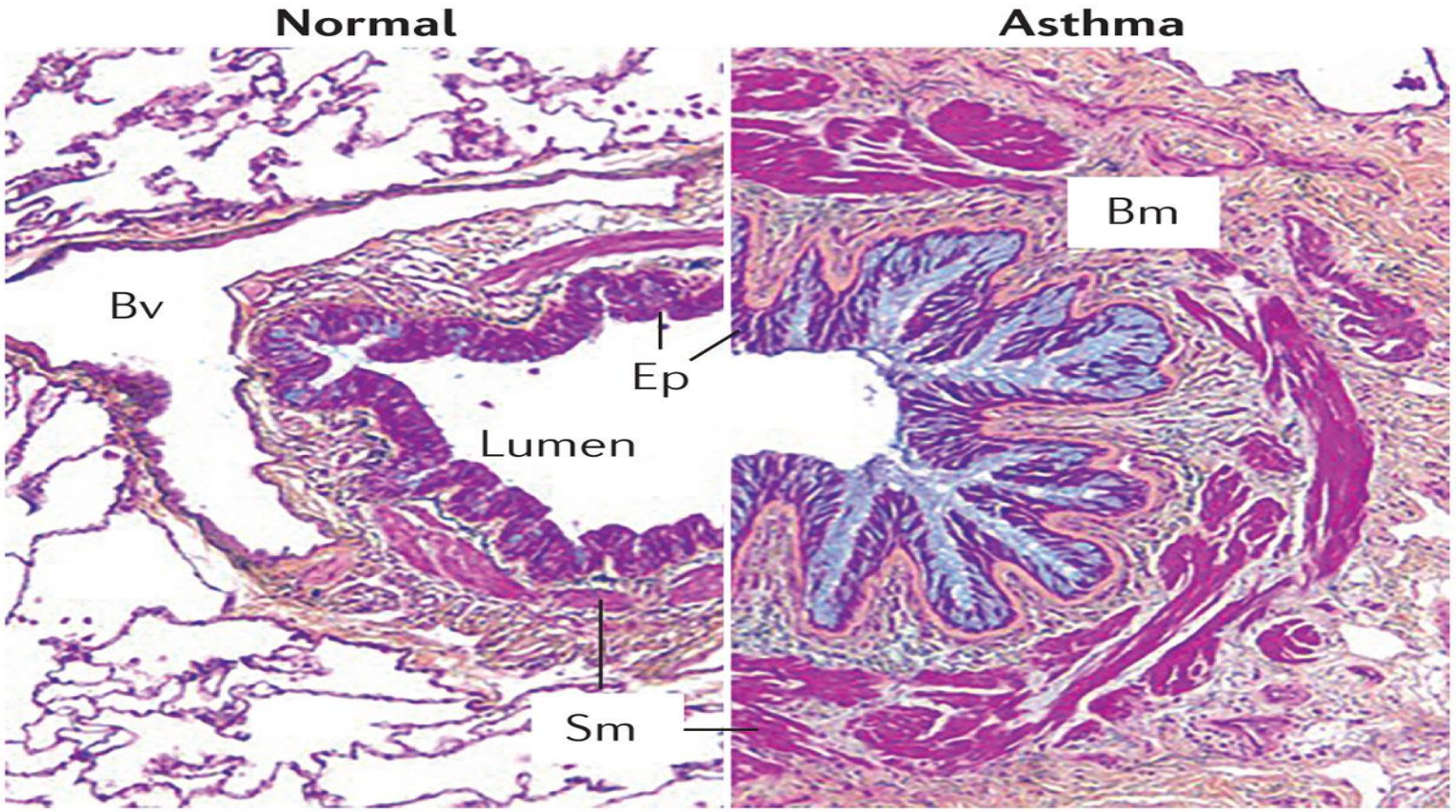
❖**airway inflammation in asthma is associated with airway hyperresponsiveness**

Pathophysiology

Limitation of airflow is due mainly to

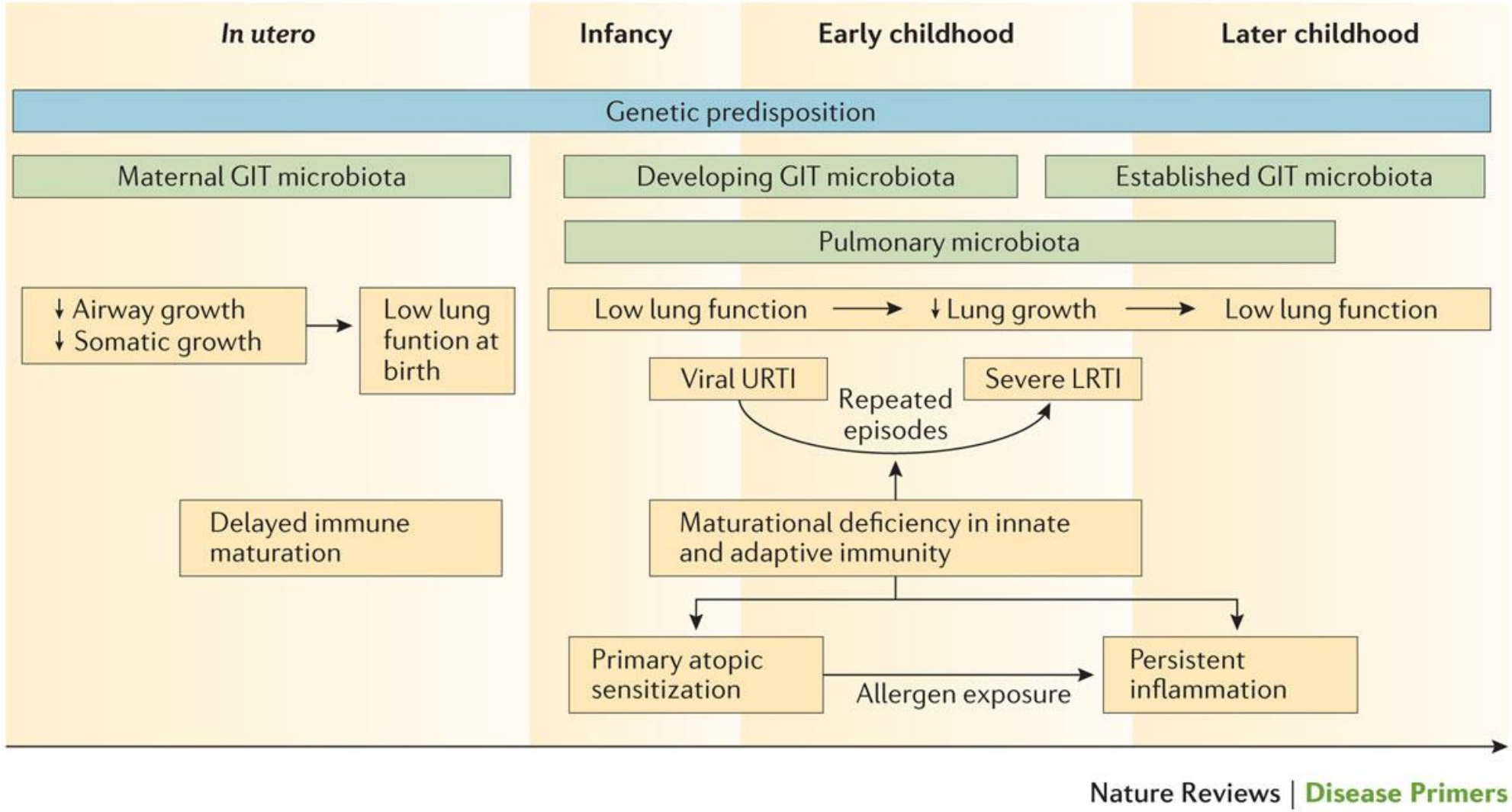
- ❑bronchoconstriction
- ❑airway edema
- ❑ vascular congestion
- ❑ luminal occlusion with exudate

Figure 4 Histopathology of the asthmatic airway



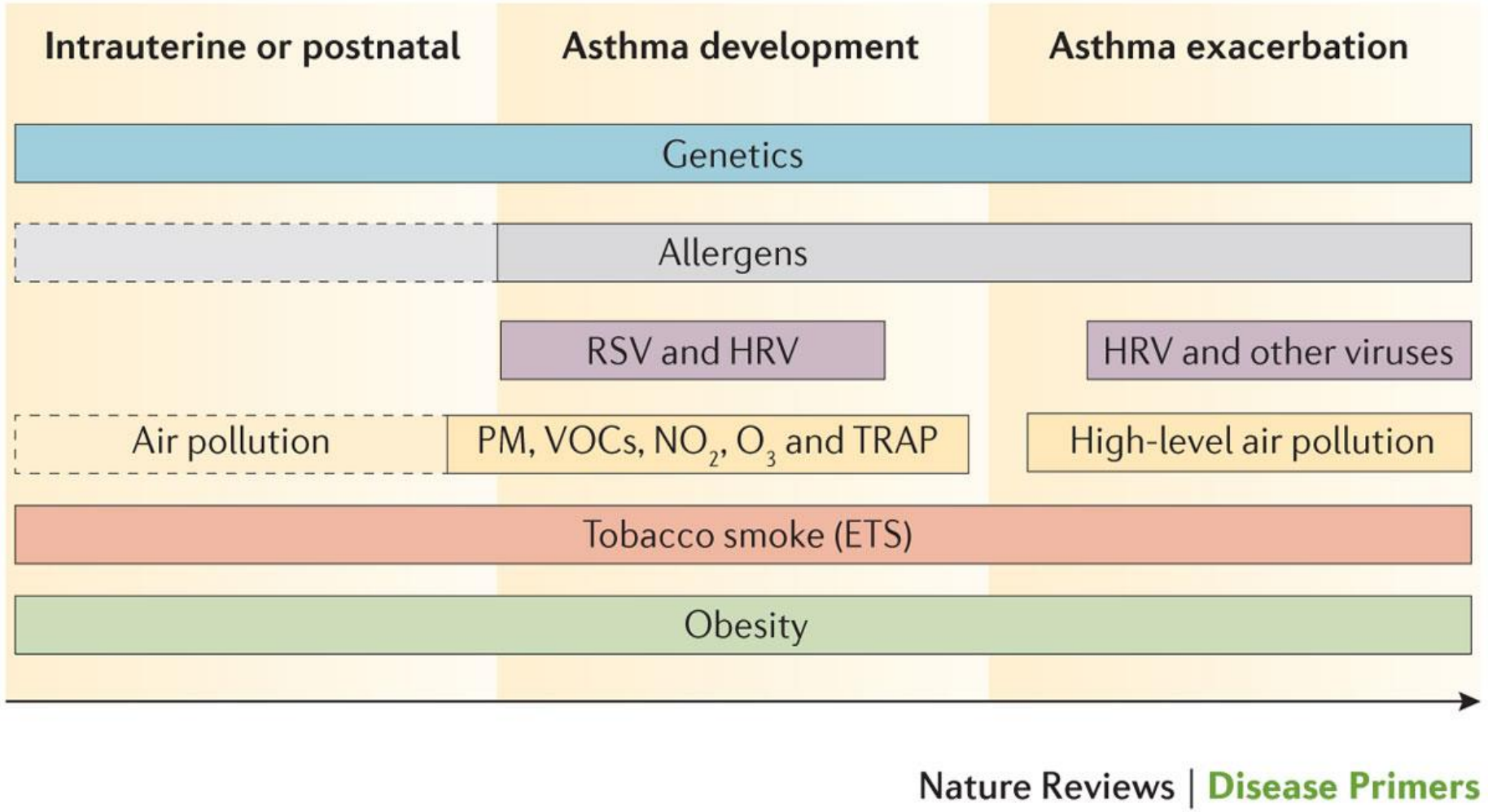
Holgate, S. T. *et al.* (2015) Asthma
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.25

Figure 8 Asthma as a developmental disease



Holgate, S. T. *et al.* (2015) Asthma
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.25

Figure 9 Contribution of risk factors to the development and/or exacerbation of asthma



Holgate, S. T. *et al.* (2015) Asthma
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.25

Etiology

1. *Atopy*

- Atopy is the ***major risk factor*** for asthma,
- nonatopic individuals have a ***very low risk*** of developing asthma.
- Patients with asthma commonly ***suffer from other atopic diseases***, particularly allergic rhinitis, which may be found in over 80% of asthmatic patients, and atopic dermatitis (eczema).

2. *Atypical Bacterial Infections*

atypical bacteria such as *Mycoplasma* and *Chlamydophila,* have been implicated in the mechanism of ***severe asthma***

3-Respiratory Viral Infections

history of ***bronchiolitis or croup*** in early childhood was a predictor of increased bronchial responsiveness and of atopy in later years

upper respiratory infections (URIs) were noted 1 to 2 months before the onset of allergic sensitization

Children who have *lower respiratory tract infections* (LRIs) caused by ***respiratory syncytial virus (RSV)*** are at a threefold to fourfold risk of subsequent wheezing during the early school years

3.Genetic Considerations

- ✓ asthma is ***polygenic***
- ✓ ***familial association*** of asthma
- ✓ high degree of ***concordance*** for asthma in identical twins
- ✓ different genes
- ✓ ***severity of asthma*** is also genetically determined
- ✓ Genetic polymorphisms may also be important in determining the ***response to asthma therapy***
- ✓ the Arg-Gly-16 variant in the $_2$-receptor has been associated with reduced response to $_2$-agonists

4.Hygiene Hypothesis

lack of infections in early childhood preserves the ***T_H2 cell bias*** at birth, whereas exposure to infections and endotoxin results in a shift toward a predominant protective T_H1 immune response.

Children brought up on ***farms*** who are exposed to a high level of endotoxin are ***less likely*** to develop allergic sensitization than children raised on dairy farms.

5.Diet

The role of dietary factors is ***controversial.***

low in antioxidants such as vitamin C and vitamin A, magnesium, selenium, omega-3 polyunsaturated fats (fish oil)

high in sodium and omega-6 polyunsaturates

Obesity is also an independent risk factor for asthma, particularly in women

6.Air Pollution

Most evidence ***argues against*** an important role for air pollution as asthma is no more prevalent in cities with a high ambient level of traffic pollution than in rural areas with low levels of pollution

There is some evidence that ***maternal smoking is a risk factor for asthma***

7.Allergens

triggers of asthma symptoms

implicated in ***allergic sensitization***

Exposure to house dust mites in early childhood is a risk factor ***for allergic sensitization and asthma***

8.Occupational Exposure

relatively common and may affect up to 10% of young adults

Early-Life Factors

exposures in utero

- ✓ growth rates (both high and low)
- ✓ dietary vitamins D and E deficiency
- ✓ exposure to microbial products
- ✓ parental smoking
- ✓ parental stress

Perinatally

- ✓ Prematurity
- ✓ chorioamnionitis

early childhood

- ✓ shorter period of breastfeeding
- ✓ Obesity
- ✓ bacterial colonization of the airways in early childhood
- ✓ antibiotic use
- ✓ acetaminophen use

Asthma Triggers

1.Allergens

Inhaled allergens

- ***early response***

Inhaled allergens ***activate mast cells*** with bound IgE directly leading to the immediate release of bronchoconstrictor mediators, resulting in the early response that is reversed by bronchodilators

- ***late response***

airway edema and an acute inflammatory response with increased eosinophils and neutrophils that are not very reversible with bronchodilators.

2.Virus Infections

rhinovirus, respiratory syncytial virus, and coronavirus are the most common triggers of acute severe exacerbations

3.Pharmacologic Agents

increased cholinergic bronchoconstriction

- ***Beta-adrenergic blockers*** commonly acutely worsen asthma, and their use may be fatal
- ***Angiotensin-converting enzyme inhibitors***
- ***Aspirin*** may worsen asthma in some patients

4..Exercise

hyperventilation

increased osmolality in airway lining fluid

triggers mast cell mediator release

begins after exercise has ***ended***, and recovers spontaneously within about 30 minutes

EIA is worse ***in cold, dry climates*** than in hot, humid conditions.

It may be prevented by ***prior administration of $_2$-agonists and antileukotrienes***, but is best prevented by regular treatment ***with ICS***

5.Physical Factors

Cold air and hyperventilation

Laughter

hot weather

strong smells or perfumes

6.Food

little evidence

7.Air Pollution

sulfur dioxide,

ozone

nitrogen oxides

8.Occupational Factors

Occupational asthma is characteristically associated with symptoms at work with relief on weekends and holidays

9.Hormonal Factors

premenstrual worsening of asthma

fall in progesterone

in severe cases may be improved by treatment with ***high doses of progesterone***

Thyrotoxicosis and hypothyroidism

10.Gastroesophageal Reflux

is common in asthmatic patients

increased by bronchodilators. Although acid reflux might trigger reflex bronchoconstriction,

it rarely causes asthma symptoms,

antireflux therapy fails to reduce asthma symptoms in most patients.

11.Stress

psychological factors can induce bronchoconstriction through ***cholinergic reflex pathways***

Clinical Features

1. Wheezing
2. dyspnea,
3. coughing
4. variable, both spontaneously and with therapy
5. difficulty in filling their lungs with air
6. increased mucus production(typically tenacious mucus that is difficult to expectorate)

➢physical signs

- rhonchi throughout the chest
- hyperinflation

- ✓Some patients, particularly children, may present with a predominant nonproductive cough ***(cough-variant asthma)***

Differential Diagnosis

- Upper airway obstruction
- stridor localized to large airways.
- foreign body
- Left ventricular failure
- Eosinophilic pneumonias
- systemic vasculitis, including Churg-Strauss syndrome and polyarteritis nodosa
- Chronic obstructive pulmonary disease (COPD)

Differential Diagnosis

Extrathoracic upper airway obstruction
Postnasal drip syndrome
Paroxysmal vocal cord motion
Hypertrophied tonsils
Supraglottitis
Laryngeal edema
Laryngostenosis
Postextubation granuloma
Retropharyngeal abscess
Benign airway tumors
Anaphylaxis
Malignancy
Obesity
Klebsiella rhinoscleroma
Mobile supraglottic soft tissue
Relapsing polychondritis
Laryngocele
Abnormal arytenoid movement
Vocal cord hematoma
Bilateral vocal cord paralysis

Intrathoracic upper airway obstruction	Lower airway obstruction
Tracheal stenosis	Asthma
Foreign body aspiration	COPD
Benign airway tumors	Pulmonary edema
Malignancies	Aspiration
Intrathoracic goiter	Pulmonary embolism
Tracheobronchomegaly	Bronchiolitis
Acquired tracheomalacia	Cystic fibrosis
Herpetic tracheobronchitis	Carcinoid syndrome
Right sided aortic arch	Bronchiectasis
	Lymphangitic carcinomatosis
	Parasitic infections