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معاونت آموزشی بیمارستان بهارلو

مبانی و ماتوژنز آسم

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INTRODUCTION

While asthma is readily recognized in its classic presentation, with intermittent cough, wheeze, and shortness of breath brought on by characteristic triggers and relieved by bronchodilating medications, it is difficult to provide a definition that distinguishes asthma from similar and overlapping conditions

asthma is characterized by bronchial hyperresponsiveness, the tendency of airways to narrow excessively in response to a variety of stimuli that provoke little or no bronchoconstriction in persons without airway disease, but bronchial hyperresponsiveness is not unique to asthma. Pathologically, asthma may be described broadly as "a chronic inflammatory disorder of the airways"

INTRODUCTION

However, this description omits the characteristic waxing and waning of airflow obstruction in asthma and fails to distinguish asthma from other inflammatory airways disorders, such as chronic bronchitis or bronchiolitis Many of the features described above for asthma overlap with chronic obstructive pulmonary disease (COPD). Sometimes the distinction between asthma and COPD is clear: chronic exercise limitation and persistent airflow obstruction in a middle-aged or older person with a history of more than 20 pack-years of cigarette smoking point to a diagnosis of COPD. In COPD, pre- and post-bronchodilator pulmonary function testing may confirm little or no reversibility of the airflow obstruction. At other times, however, the distinction is less clear, such as when patients with COPD exhibit episodic symptoms and a large reversible component to their airflow obstruction. Recognition of these overlapping features of both asthma and COPD in some patients has led to description of the condition, asthma-COPD overlap, discussed below.

PREVALENCE

Asthma is one of the most common chronic diseases globally and currently affects ~300 million people worldwide, with 250,000 deaths annually.

The prevalence of asthma has risen in affluent countries over the last 30 years but now appears to have stabilized, with ~10–12% of adults and 15% of children affected by the disease.

In developing countries where the prevalence of asthma had been much lower, there is a rising prevalence, which is associated with increased urbanization.

The prevalence of atopy and other allergic diseases has also increased over the same time, suggesting that the reasons for the increase are likely to be systemic rather than confined to the lungs

Asthma can present at any age, with a peak age of 3 years.
In childhood, twice as many males as females are asthmatic but by adulthood the sex ratio has equalized. Long-term studies that have followed children until they reach the age of 40 years suggest that many with asthma become asymptomatic during adolescence but that asthma returns in some during adult life, particularly in those with persistent symptoms and severe asthma. Adults with asthma, including those with onset during adulthood, rarely become permanently asymptomatic. The severity of asthma does not vary significantly within a given patient; those with mild asthma rarely progress to more severe disease, whereas those with severe asthma usually have severe disease at the onset.

Deaths from asthma are relatively uncommon, and in many affluent countries have been steadily declining over the last decade.
A rise in asthma mortality seen in several countries during the 1960s was associated with increased use of short-acting inhaled β -adrenergic agonists (as rescue therapy), but there is now compelling evidence that the more widespread use of inhaled corticosteroids (ICS) in patients with persistent asthma is responsible for the decrease in mortality in recent years.
Major risk factors for asthma deaths are poorly controlled disease with frequent use of bronchodilator inhalers, lack of or poor compliance with ICS therapy, and previous admissions to hospital with near-fatal asthma.

RISK FACTORS AND TRIGGERS

Asthma is a heterogeneous disease with interplay between genetic and environmental factors

TABLE 281-1

Risk Factors and Triggers Involved in Asthma

ENDOGENOUS FACTORS	ENVIRONMENTAL FACTORS
Genetic predisposition	Indoor allergens
Atopy	Outdoor allergens
Airway hyperresponsiveness	Occupational sensitizers
Gender	Passive smoking
Ethnicity	Respiratory infections
Obesity	Air pollution (diesel particulates, nitrogen oxides)
Early viral infections	Diet
	Dampness and mold exposure
	Acetaminophen (paracetamol)
Triggers	
Allergens	
Upper respiratory tract viral infections	
Exercise and hyperventilation	
Cold air	
Sulfur dioxide and irritant gases	
Drugs (β-blockers, aspirin)	
Stress	
Irritants (household sprays, paint fumes)	

ATOPY

Atopy is the major risk factor for asthma, and non-atopic 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 >80% of asthmatic patients, and atopic dermatitis (eczema).

Atopy may be found in 40–50% of the population in affluent countries, but only a proportion of atopic individuals becoming asthmatic. This observation suggests that some other environmental or genetic factor(s) predispose to the development of asthma in atopic individuals.

GENETIC

predisposition to the disease; however, whether or not the genes predisposing to asthma are similar or in addition to those predisposing to atopy is not yet clear.

It now seems likely that different genes may also contribute to asthma specifically, and there is increasing evidence that the severity of asthma is also genetically determined.

Genetic screens with classical linkage analysis and single-nucleotide polymorphisms of various candidate genes indicate that asthma is polygenic.

The most consistent findings have been associations with polymorphisms of genes on chromosome 5q, including the T helper 2 (T 2) cells interleukin (IL)-4, IL-5, IL-9, and IL-13, which are associated with atopy.

Novel genes that have been associated with asthma, including *ADAM-33*, *DPP-10*, and *ORMDL3*, have also been identified by positional cloning.

Genetic polymorphisms may also be important in determining the response to asthma therapy. For example, the Arg-Gly-16 variant in the β -receptor has been associated with reduced response to β -agonists, and repeats of an Sp1 recognition sequence in the promoter region of 5-lipoxygenase may affect the response to antileukotrienes. However, these effects are small and inconsistent and do not yet have any implications for asthma therapy.

EPIGENETIC MECHANISMS

There is increasing evidence that epigenetic mechanisms may be important, particularly in the early development of asthma.
DNA methylation and histone modification patterns may be influenced by diet, cigarette smoke exposure, and air pollution, and
may affect genes involved in the pathogenesis of asthma. These epigenetic changes may occur in the fetus as a result of
maternal environmental exposure.

INFECTIONS

Although viral infections (especially Rhinovirus) are common as triggers of asthma exacerbations, it is uncertain whether they play a role in etiology.

There is some association between respiratory syncytial virus infection in infancy and the development of asthma, but the specific pathogenesis is difficult to elucidate, as this infection is very common in children.

Atypical bacteria, such as *Mycoplasma* and *Chlamydophila*, have been implicated in the mechanism of severe asthma, but thus far, the evidence is not very convincing of a true association.

Living in damp houses with exposure to mold spores is now recognized to be a risk factor, and removal of these factors may improve asthma.

The observation that allergic sensitization and asthma were less common in children with older siblings first suggested that lower levels of infection may be a factor in affluent societies that increase the risks of asthma.

This “hygiene hypothesis” proposes that lack of infections in early childhood preserves the T 2 cell bias at birth, whereas exposure to infections and endotoxin results in a shift toward a predominant protective T 1 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.

Intestinal parasite infection, such as hookworm, may also be associated with a reduced risk of asthma.

While there is considerable epidemiologic support for the hygiene hypothesis, it cannot account for the parallel increase in T 1-driven diseases such as diabetes mellitus over the same period.

DIET

The role of dietary factors is controversial. Observational studies have shown that diets low in antioxidants such as vitamin C and vitamin A, magnesium, selenium, and omega-3 polyunsaturated fats (fish oil) or high in sodium and omega-6 polyunsaturates are associated with an increased risk of asthma.

Vitamin D deficiency may also predispose to the development of asthma.

However, interventional studies with supplementary diets have not supported an important role for these dietary factors.

AIR POLLUTION

Air pollutants such as sulfur dioxide, ozone, and diesel particulates may trigger asthma symptoms, but the role of different air pollutants in the etiology of the disease is not yet clear.

There is increasing evidence that exposure to road traffic pollution is associated with increased asthma symptoms, with the main culprits being diesel particulates and nitrogen dioxide. Indoor air pollution is also important with exposure to nitrogen oxides from cooking stoves and exposure to passive cigarette smoke.

There is some evidence that maternal smoking is a risk factor for asthma, but it is difficult to dissociate this association from an increased risk of respiratory infections.

ALLERGENS

Inhaled allergens are common triggers of asthma symptoms and have also been implicated in allergic sensitization.

Exposure to house dust mites in early childhood is a risk factor for allergic sensitization and asthma, but rigorous allergen avoidance has not shown any evidence for a reduced risk of developing asthma.

The increase in house dust mites in centrally heated poorly ventilated homes with fitted carpets has been implicated in the increasing prevalence of asthma in affluent countries.

Domestic pets, particularly cats, have also been associated with allergic sensitization, but early exposure to cats in the home may be protective through the induction of tolerance.

OCCUPATIONAL EXPOSURE

Occupational asthma is relatively common and may affect up to 10% of young adults. Over 300 sensitizing agents have been identified.

Occupational asthma may be suspected when symptoms improve during weekends and holidays.

OBESITY

Obesity is also an independent risk factor for asthma, particularly in women, but the mechanisms are not yet clear.

Asthma occurs more frequently in obese people (BMI >30 kg/m) and is often more difficult to control.

Although mechanical factors may contribute, it may also be linked to the pro-inflammatory adipokines and reduced anti-inflammatory adipokines that are released from fat cells.

OTHER FACTORS

Several other factors have been implicated in the etiology of asthma, including lower maternal age, duration of breast-feeding, prematurity and low birthweight, and inactivity, but are unlikely to contribute to the recent global increase in asthma prevalence.

There is also an association with acetaminophen (paracetamol) consumption in childhood, which may be linked to increased oxidative stress.

INTRINSIC ASTHMA

A minority of asthmatic patients (~10%) have negative skin tests to common inhalant allergens and normal serum concentrations of IgE.

These patients, with non-atopic or intrinsic asthma, usually show later onset of disease (adult-onset asthma), commonly have concomitant nasal polyps, and may be aspirin-sensitive. They usually have more severe, persistent asthma.

Little is understood about mechanism, but the immunopathology in bronchial biopsies and sputum appears to be identical to that found in atopic asthma.

There is recent evidence for increased local production of IgE in the airways, suggesting that there may be common IgE-mediated mechanisms; staphylococcal enterotoxins, which serve as “superantigens,” have been implicated. Type-2 innate lymphoid cells (ILC2) may drive the eosinophilic inflammation in these non-allergic patients.

ASTHMA TRIGGERS

Several stimuli trigger airway narrowing, wheezing, and dyspnea in asthmatic patients.

While the previous view held that these should be avoided, it is now seen as evidence for poor control and an indicator of the need to increase controller (preventive) therapy.

ALLERGENS

VIRUS INFECTIONS

Upper respiratory tract virus infections such as rhinovirus, respiratory syncytial virus, and coronavirus are the most common triggers of acute severe exacerbations and may invade epithelial cells of the lower as well as the upper airways.

PHARMACOLOGIC AGENTS

Several drugs may trigger asthma. Beta-adrenergic blockers commonly acutely worsen asthma, and their use may be fatal.
The mechanisms are not clear but are likely mediated through increased cholinergic bronchoconstriction. All beta blockers need to be avoided and even selective β, β blockers, or topical application (e.g., timolol eye drops) may be dangerous.

Angiotensinconverting enzyme inhibitors are theoretically detrimental as they inhibit breakdown of kinins, which are bronchoconstrictors; however, they rarely worsen asthma, and the characteristic cough is no more frequent in asthmatics than in non-asthmatics.

Aspirin may worsen asthma in some patients (aspirin-sensitive asthma is discussed under “Special Considerations”).

EXERCISE

Exercise is a common trigger of asthma, particularly in children. The mechanism is linked to hyperventilation, which results in increased osmolality in airway lining fluid and triggers mast cell mediator release, resulting in bronchoconstriction.

Exerciseinduced asthma (EIA) typically begins after exercise has ended, and recovers spontaneously within about 30 min.

EIA is worse in cold, dry climates than in hot, humid conditions. It is, therefore, more common in sports such as cross-country running in cold weather, overland skiing, and ice hockey than in swimming.

It may be prevented by prior administration of β –agonists and antileukotrienes, but is best prevented by regular treatment with ICS, which reduce the population of surface mast cells required for this response.

FOOD AND DIET

Exclusion diets are usually unsuccessful at reducing the frequency of episodes. Some foods such as shellfish and nuts may induce anaphylactic reactions that may include wheezing.

Patients with aspirin-induced asthma may benefit from a salicylate-free diet, but these are difficult to maintain.

Certain foodadditives may trigger asthma.

AIR POLLUTION

Increased ambient levels of sulfur dioxide, ozone, diesel particulates and nitrogen oxides are associated with increased asthma symptoms.

OCCUPATIONAL FACTORS

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

If removed from exposure within the first 6 months of symptoms, there is usually complete recovery.

More persistent symptoms lead to irreversible airway changes, and, thus, early detection and avoidance are important.

HORMONES

Some women show premenstrual worsening of asthma, which can occasionally be very severe.

The mechanisms are not completely understood, but are related to a fall in progesterone and in severe cases may be improved by treatment with high doses of progesterone or gonadotropin-releasing factors.

Thyrotoxicosis and hypothyroidism can both worsen asthma, although the mechanisms are uncertain.

GASTROESOPHAGEAL REFLUX

Gastroesophageal reflux is common in asthmatic patients as it is increased by bronchodilators.

Although acid reflux might trigger reflex bronchoconstriction, it rarely causes asthma symptoms, and antireflux therapy usually fails to reduce asthma symptoms in most patients.

STRESS

Many asthmatics report worsening of symptoms with stress.

Psychological factors can induce bronchoconstriction through cholinergic reflex pathways.

Paradoxically, very severe stress such as bereavement usually does not worsen, and may even improve, asthma symptoms.

PATHOLOGY

The airway mucosa is infiltrated with activated eosinophils and T lymphocytes, and there is activation of mucosal mast cells.

The degree of inflammation is poorly related to disease severity and may even be found in atopic patients without asthma symptoms.

A characteristic finding is thickening of the basement membrane due to subepithelial collagen deposition. This feature is also found in patients with eosinophilic bronchitis presenting as cough who do not have asthma and is, therefore, likely to be a marker of eosinophilic inflammation in the airway as eosinophils release fibrogenic mediators.

PATHOLOGY

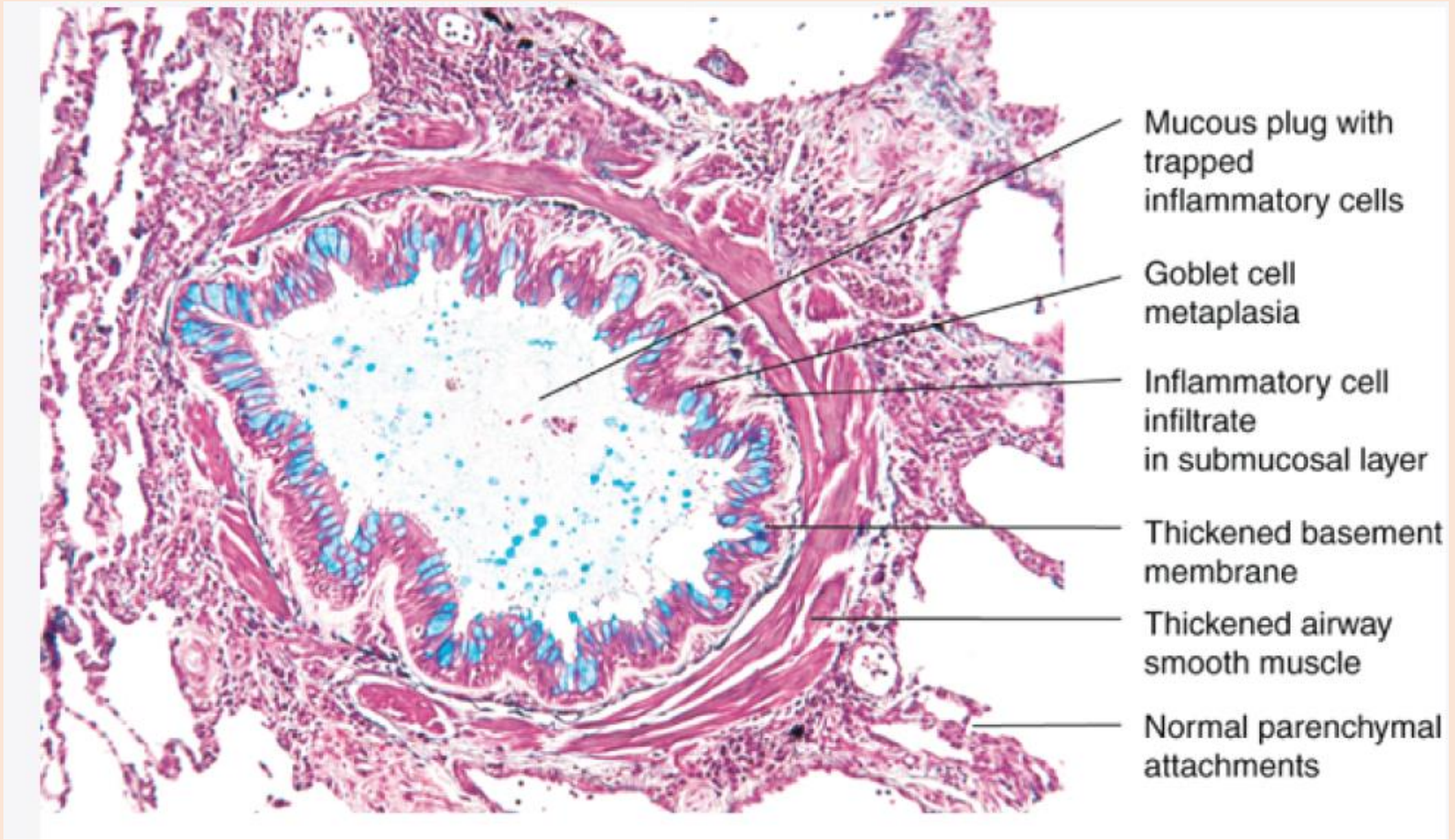
The epithelium is often shed or friable, with reduced attachments to the airway wall and increased numbers of epithelial cells in the lumen. The airway wall itself may be thickened and edematous, particularly in fatal asthma.

Another common finding in fatal asthma is occlusion of the airway lumen by a mucous plug, which is comprised of mucous glycoproteins secreted from goblet cells and plasma proteins from leaky bronchial vessels

There is also vasodilation and increased numbers of blood vessels (angiogenesis).

The pathology of asthma is remarkably uniform in different phenotypes of asthma, including atopic (extrinsic), non-atopic (intrinsic), occupational, aspirin-sensitive, and pediatric asthma.

These pathologic changes are found in all airways, but do not extend to the lung parenchyma; peripheral airway inflammation is found particularly in patients with severe asthma. The involvement of airways may be patchy and this is consistent withbronchographic findings of uneven narrowing of the airways.


Mucous plug with trapped inflammatory cells
Goblet cell metaplasia
Inflammatory cell infiltrate in submucosal layer
Thickened basement membrane
Thickened airway smooth muscle
Normal parenchymal attachments

AIRWAY INFLAMMATION

There is good evidence that the specific pattern of airway inflammation in asthma is associated with airway hyperresponsiveness (AHR), the physiologic abnormality of asthma, which is correlated with variable airflow obstruction.

The pattern of inflammation in asthma is characteristic of allergic diseases, with similar inflammatory cells seen in the nasal mucosa in rhinitis.

the common pattern of inflammation in asthma is characterized by eosinophil infiltration, some patients with severe asthma show a neutrophilic pattern of inflammation that is less sensitive to corticosteroids.

LYMPHOCYTES

T lymphocytes play a very important role in coordinating the inflammatory response in asthma through the release of specific patterns of cytokines, resulting in the recruitment and survival of eosinophils and in the maintenance of a mast cell population in the airways.

The naïve immune system and the immune system of asthmatics are skewed to express the T 2 phenotype, whereas in normal airways T 1 cells predominate.

T 2 cells, through the release of IL-5, are associated with eosinophilic inflammation and, through the release of IL-4 and IL-13, are associated with increased IgE formation.

Natural killer CD4 T lymphocytes that express high levels of IL-4 have been described in some studies. Regulatory T cells (Treg) play an important role in determining the expression of other T cells, and there is evidence for a reduction in a certain subset of Tregs (CD4 CD25) that express the transcription factor FOXP3 in asthma that is associated with increased T 2 cells.

Recently innate T cells (ILC2) without T cell receptors have been identified that release T 2 cytokines and are regulated by epithelial cytokines such as IL-25 and IL-33 and may be predominant in non-allergic asthma.

INFLAMMATORY MEDIATORS

Multiple inflammatory mediators have been implicated in asthma, and they may have a variety of effects on the airways that account for the pathologic features of asthma **(**Fig. 281-4**)**. Mast cell-derived mediators, such as histamine, prostaglandin D , and cysteinyl-leukotrienes, contract airway smooth muscle, increase microvascular leakage, increase airway mucus secretion, and attract other inflammatory cells. Because each mediator has many effects, the role of individual mediators in the pathophysiology of asthma is not yet clear. Although the multiplicity of mediators makes it unlikely that preventing the synthesis or action of a single mediator will have a major impact in clinical asthma, recent clinical studies with antileukotrienes suggest that cysteinyl-leukotrienes have clinically important effects.

Many cells and mediators are involved in asthma and lead to several effects on the airways. AHR, airway hyperresponsiveness; PAF, platelet-activating factor.

CYTOKINES

Multiple cytokines regulate the chronic inflammation of asthma. The T 2 cytokines IL-4, IL-5, IL-9, and IL-13 mediate allergic inflammation, whereas proinflammatory cytokines such as TNF-α and IL-1β amplify the inflammatory response and play a role in more severe disease. TSLP is an upstream cytokine released from epithelial cells of asthmatics that orchestrates the release of chemokines that selectively attract T 2 cells. Some cytokines such as IL-10 and IL-12 are anti-inflammatory and may be deficient in asthma.

CHEMOKINES

Chemokines are involved in attracting inflammatory cells from the bronchial circulation into the airways. Eotaxin (CCL11) is selectively attractant to eosinophils via CCR3 and is expressed by epithelial

AIRWAY EPITHELIUM

Airway epithelial shedding may be important in contributing to AHR and may explain how several mechanisms, such as ozone exposure, virus infections, chemical sensitizers, and allergens (usually proteases), can lead to its development, as all of these stimuli may lead to epithelial disruption.

VASCULAR RESPONSES

There is increased airway mucosal blood flow in asthma, which may contribute to airway narrowing.

There is an increase in the number of blood vessels in asthmatic airways as a result of angiogenesis in response to growth factors, particularly vascularendothelial growth factor.

با تشکر